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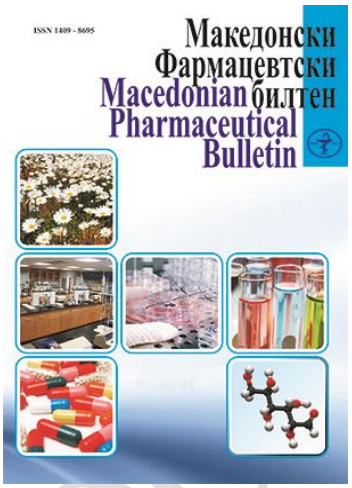

Title: Relevance of fungi for cystic fibrosis patients

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Relevance of fungi for cystic fibrosis patients

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Abstract

Fungal respiratory infections represent a significant and underappreciated challenge in the management of cystic fibrosis. Cystic fibrosis is a genetic disorder characterized by chronic respiratory infections and inflammation. While bacterial pathogens have been extensively studied, fungal infections are increasingly recognized as significant contributors to increased morbidity in cystic fibrosis patients. This review article aims to give a basic overview on fungal infections in respiratory tract of cystic fibrosis patients and to raise awareness of the importance of fungal presence in the respiratory tract of these patients. The research will focus on the most commonly detected fungi in the respiratory tract of cystic fibrosis patients, like *Aspergillus fumigatus*, *Candida* species, *Scedosporium apiospermum* complex, *Lomentospora* species and *Exophiala dermatitidis*, and challenges regarding management of fungal infections, from a physician's point of view, to make appropriate decisions in their everyday practice, and therefore, better overcome fungal infections.

Key words: Fungal respiratory infections, Cystic fibrosis, CF airway, CF patients

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Background

Cystic fibrosis (CF) is a life-limiting autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene (Myer et al., 2023) and is reported to be the most common rare genetic disease in in Caucasian individuals with an incidence of 1/2,500-3,500 live births (Farrell, 2008).

The genetic disease leads to dysfunction of the CF CFTR-protein in epithelial cells (in sweat glands, respiratory system and digestive system). The CFTR protein regulates the transport

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of chloride and bicarbonate ions across epithelial membranes. Dysfunctional CFTR in the secretory epithelial cells results in obstructions in the lung airways and pancreatic ducts as a major pathological consequence. The obstructions result in the accumulation of abnormally thick, sticky mucus in the respiratory tract, which impairs bacterial mucociliary clearance and allows colonization of the airways by various opportunistic microorganisms (Bhagirath et al., 2016). This leads to chronic inflammation and infections, which are the hallmarks of CF.

Over time, recurrent bacterial infections and the inflammatory response cause progressive lung damage and bronchiectasis. Progressive decline in lung function and irreversible structural changes of the lungs culminate in end stage lung disease with chronic respiratory failure, which are the primary causes of morbidity and mortality in CF patients (Yankaskas et al., 2004).

This review article aims to give a basic overview on fungal infections in respiratory tract of cystic fibrosis patients and to raise awareness of the importance of fungal presence in the respiratory tract of these patients. The review should also support healthcare providers involved in CF care and management, to make firm decisions in their everyday practice, to better overcome fungal infections.

Microorganisms as agents of infections in CF

The main focus in bronchopulmonary infections has always been on bacterial pathogens, as they significantly influence lung function and the exacerbation rate. At younger age serious infections are primarily caused by *Staphylococcus aureus* and non-capsulate *Haemophilus influenzae*. As CF progresses, bronchiectasis develops, and CF patients become more susceptible to many Gram-negative bacteria, especially *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*.

As a result of improved health-care systems and prolonged life expectancy due to advances in CF care and treatment with new antibiotics that disrupt the gut microbiome, fungi are increasingly recognized as significant contributors to disease progression (Yu et al., 2023). Improved life expectancy also offers new challenges and clinical dilemmas regarding treatment, as the numbers of patients with filamentous fungi in their respiratory samples continuously grow (Poore et al., 2021). A deeper understanding of fungal infections, coupled with advances in

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diagnostics and therapeutics, has the potential to significantly enhance patient outcomes and quality of life.

Risk factors for fungal infection

Exposure to environments with high fungal loads, such as soil, decaying vegetation, or construction places, increases the risk of fungal colonization in CF patients. Genetics is also a risk factor. Many studies have confirmed that CF patients with specific CFTR mutations may be at higher risk for fungal infections due to prolonged exposure to pathogens and cumulative lung damage. A retrospective study investigating the epidemiologic trend of fungal infections in CF patients found that advanced age was a risk factor for fungal colonization/infection.

This study showed that adults over 18 years were 51% more likely to grow filamentous fungi (Sudfeld et al., 2010). Advanced lung disease is another risk factor for fungal colonization in cystic fibrosis patients. Patients with severe lung disease or bronchiectasis are more likely to harbor fungal pathogens due to impaired mucociliary clearance and structural lung damage (Hong, 2022).

Prolonged or frequent use of antibiotics for treatment of bacterial infections is very important risk factor, which disturbs the microbiome, creating an environment favorable for fungal overgrowth. Sudfeld et al. (2010) also found that the use of inhaled antibiotics is another risk factor for development of fungal infection. The use of inhaled tobramycin as an intermittent regimen for chronic maintenance therapy in CF patients has been linked to increased isolation of fungal species, such as *C. albicans* and *Aspergillus* species (Burns et al., 1998).

Risk factors that also predispose CF patients to fungal colonization and infection are immunosuppression (chronic inflammation and recurrent infections), use of corticosteroids, commonly prescribed for ABPA or asthma-like symptoms (Lattanzi et al., 2020). In a retrospective review of 16,095 patients from 2006 to 2012 Cystic Fibrosis Foundation (CFF) registry data, 9.6% of patients (n=1541) persistently grew *Aspergillus* (Hong et al., 2018). *Aspergillus* spp. can coexist with many bacteria. *Stenotrophomonas maltophilia* and *Aspergillus* species coexistence is actually very common (Amin et al., 2010). *A. fumigatus* and *P. aeruginosa* are the most common pathogens in respiratory tract of CF patients and coexistence with these pathogens is associated with poorer

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FEV_1 scores (Keown et al., 2020). Patients with co-colonization are also associated with increased risk of exacerbations and hospitalizations (Saunders et al., 2016).

Fungi in respiratory tract of CF patients

Fungal colonization and infection are increasingly recognized as significant issues in cystic fibrosis patients. Studies indicate that fungal colonization is very common, with prevalence rates ranging from 30% to 60% in CF populations. When fungi are agents of fungal infections, and cause more serious clinical symptoms, then they are associated with significant morbidity.

The most common fungal pathogens associated with CF respiratory infections include *Aspergillus fumigatus* and *Candida albicans.* Emerging fungi such as *Scedosporium apiospermum* and *Exophiala dermatitidis* are increasingly reported in CF patients, particularly in those with advanced disease. All of them have been associated with accelerated decline in lung function (Al Shakirchi et al., 2020; Breuer et al., 2020). *Aspergillus fumigatus* has been identified in approximately 25% specimens of patients with CF, and is most often connected to a complex hypersensitivity reaction—allergic bronchopulmonary aspergillosis (ABPA). *Candida* species are often colonizing the airways. They both have been linked to increased frequency of pulmonary exacerbations, increased hospitalization rates, higher healthcare costs and reduced quality of life (Navarro et al., 2001). *Scedosporium* species and *Exophiala dermatitidis* have been reported recently in sputum samples of patients with cystic fibrosis (de Jong et al., 2020). Saunders et al. (2016) have also confirmed that detected fungi by culture, in airway secretions of CF patients may be correlated with worse clinical outcomes and the progression of structural lung disease (Breuer et al., 2020). Some CF patients may require screening for fungal infections, especially in case of imaging abnormalities, new fever, change in sputum features, and hemoptysis. While the negative impact of fungi on lung health has already been observed in CF, accurate detection and identification of fungi by culture in airway secretions are limited by the lack of a standardized techniques across clinical laboratories, slow growth rates, and difficult identification (O'Connor et al., 2023).

More recently, the development of a culture-independent and more accurate next generation sequencing approach to detect and identify lower airway fungal communities, or the mycobiome, have clarified our understanding of the CF airway, so now it is accepted that it

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includes more complex and dynamic polymicrobial bacterial communities (Huang et al., 2016; LiPuma, 2015, O'Connor et al., 2021).

Due to the complex ecology in the lower CF respiratory tract, investigation of the contributing role of fungi to the progression of CF lung disease has now emerged as a priority objective, and is crucial to inform our future understanding of the clinical impact of fungi in the lower airways of CF patients (Blanchard et al., 2019).

Despite their growing significance, fungal infections in patients with cystic fibrosis still remain underdiagnosed and poorly understood in many laboratories, because differentiation of a truly pathogenic fungus from the commensal microbiota remains a challenge, both for clinicians and laboratory workers. Consecutive positive cultures of a fungus from a CF specimen, associations with respiratory symptoms and/or radiological findings, as well as critical evaluation of therapeutic response to specific antimicrobial treatment, could probably help in this differentiation (Hong, 2022). The challenges in differentiation are probably a result of the fact that current diagnostic methods in many laboratories are often inappropriate, leading to delayed or missed diagnoses.

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Prevalence of fungal colonization and infection in patients with CF

The rising prevalence of fungal infections in patients with CF is likely due to several factors, including improved survival rates, increased awareness, and more sensitive diagnostic techniques. However, the true burden of fungal infections may be underestimated due to challenges in diagnosis and the overlap of symptoms with bacterial infections.

A retrospective analysis of over 25,000 samples from more than 600 CF patients by the German National Reference Center revealed that around 75% of CF patients were colonized by yeasts, mainly *Candida* species, with a majority of *Candida albicans*, and about 35% were positive for *Aspergillus* species. Other filamentous fungi such as *Exophiala dermatitidis* and *Scedosporium/Lomentospora* complex isolates were found in around 4% of patients, with up to 10% in some CF centers. Authors have reported that between 2009 and 2013, the epidemiology of fungal species remained largely unchanged over the study period (Ziesing et al., 2016). In contrast, an analysis of the United Kingdom CF Registry showed a rise in the prevalence of *Aspergillus* species from 6.5% in 2007 to 13.6% in 2012. Additionally, *Scedosporium* species were detected

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slightly more often in 2012 (0.68%) than in 2007 (0.07%) (Felton et al., 2015). But it is worth noticing that direct comparison of data across many UK centers had been complicated due to the use of different culture protocols in studies and non-uniform diagnostic techniques.

A prospective study from the Netherlands has confirmed that the introduction of modified fungal culture protocols led to an increase in detection rates and diversity of fungal species (Engel et al., 2020). Also a prospective study from the United States using selective mycological media for CF sputa including Sabouraud dextrose agar with gentamicin, inhibitory mold agar and brain heart infusion agar with chloramphenicol and gentamicin revealed prevalence rates of 40.8% for *Aspergillus* species, 5.2% for *Scedosporium*, and 4.7% for *Exophiala* (Hong, 2017).

In a retrospective cross-center analysis across nine European CF centers, Schwarz supported the findings from the USA, Germany, and Netherlands with regard to the prevalence rates. They confirmed the large differences between different centers regarding the fungal diversity and prevalence of specific fungi, further confirming the influence of different culture conditions and diagnostic protocols (Schwarz et al., 2018). An effort from the working group on fungal respiratory infections in cystic fibrosis within the International Society for Human and Animal Mycology (ISHAM) since 2006, to improve the detection and the clinical knowledge of fungal infections in patients with CF, resulted on developing and standardizing mycological culture protocols and nonculture-based diagnostics (Schwarz et al., 2018).

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Aspergillus species

Aspergillus species are among the most widespread filamentous fungi in the environment, especially in areas with high humidity (Paulussen et al., 2017). In CF patients, the most frequently isolated species is *Aspergillus fumigatus*, accounting for 67-73% of *Aspergillus*-positive sputum cultures. Schwartz performed a retrospective analysis of 66,616 samples from 3235 CF patients in 9 European CF centers. They reported *A. fumigatus* was dominant in most of the participating centers. The prevalence rates ranged from 3.9%-42.4% (Schwarz et al., 2018). Beside *A. fumigatus*, other aspergilli were also detected (*A. flavus* - 4%, *A. niger* - 4% and *A. terreus* - 2%). As mentioned previously, the prevalence of isolation of *Aspergillus* species from sputum cultures in CF patients increases with age, possibly reaching 46-78% in adult CF patients (Bakare et al., 2003).

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In several studies, colonization with *A. fumigatus* has been demonstrated that results in declining pulmonary function (Noni et al., 2015). A characterization of microbial organisms in adolescent CF patients has demonstrated that patients colonized with *A. fumigatus* had impaired lung function as demonstrated by a decline in FEV_1 compared to non-colonized patients ($p<0.0001$) and an increased risk of colonization with *P. aeruginosa* (Hector et al., 2016). However, findings for a decline in pulmonary function are conflicting in the literature. In an evaluation of 259 CF patients, colonization with *A. fumigatus* was not associated with lower lung function nor more severe lung function decline over a 5-year period (de Vrankrijker et al., 2011). These conflicting findings raise dilemmas if eradication therapy for chronic colonization with *Aspergillus* species is really necessary.

Aspergillus species have been described in the literature in various classifications: ABPA, colonization, sensitization, bronchitis, and invasive aspergillosis (especially in lung transplant recipients). In this regard, Baxter have proposed a classification based not only on sputum cultures but also on real-time polymerase chain reaction (RT-PCR) for *Aspergillus*, sputum level of galactomannan (a cell-wall component of *Aspergillus*), total IgE, specific *A. fumigatus* IgE, and specific *A. fumigatus* IgG (Baxter et al., 2013). According to Baxter's classification, adult CF patients may be divided into 4 classes with respect to *Aspergillus*-related diseases: (Class 1) non-diseased patients; (Class 2) allergic bronchopulmonary aspergillosis (ABPA); (Class 3) IgE-sensitized patients; (Class 4) *Aspergillus* airway infection or "bronchitis."
A simplified representation of Baxter's classification is displayed in Table 1.

Scedosporium apiospermium complex

The prevalence of non-*Aspergillus* moulds may be underestimated due to overgrowth of bacteria or some fast growing aspergilli on routine media (Pihet et al., 2009). Fungi of the *Scedosporium apiospermum* complex and *Scedosporium prolificans*, recently renamed as *Lomentospora prolificans* (*Sac-Lp*), are the second most frequent colonizing, allergenic or invasive fungal pathogens in patients with CF, with the prevalence ranging from 0.7 to 9% (Schwarz et al., 2017). Prevalence rates from patients with CF has also been previously reported for single centres in Europe and Australia, ranging from 3.4 to 17.4% (Blyth et al., 2010; Paugam et al., 2010). Infections by these species can be dramatic due to a high resistance to

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antifungal agents. The *Scedosporium apiospermium* complex are ubiquitous filamentous fungi mainly found in soil, polluted waters, and sewage.

However, the clinical significance of isolating *S. apiospermium* complex from the respiratory tract of CF patients is still a matter of debate. Colonization of the airways by *S. apiospermium* complex occurs more frequently in adolescents and adults than in children with CF, and often later than colonization by *Aspergillus* species. Cimon reported on two cases of allergic bronchopulmonary mycoses linked to this organism, resolved after combination treatment with itraconazole and oral corticosteroids (Cimon et al., 2000).

S. apiospermium complex has also been reported to possibly cause invasive, disseminated disease in immunocompromised CF patients after lung transplantation. Symoens reported a patient colonized in the pretransplant phase, who later developed an infection with *S. apiospermium,* postoperatively, characterized by moderate fever, subcutaneous nodules, and bilateral chorioretinitis, with subsequent complete loss of vision, meningeal involvement and unfavorable outcome. *S. apiospermium* was isolated from both vitreous humor and cerebrospinal fluid (Symoens et al., 2006).

Lomentospora prolificans

Formerly known as *Scedosporium prolificans*, this mold has a certain geographical distribution. It has been reported as an isolate found in Australia, Northern Spain, and in the United States, although isolation from the respiratory tract of CF patients has also been reported in Germany (Tintelnot et al., 2009). As observed for other molds, *Lomentospora prolificans* usually causes transient or permanent colonization of the respiratory tract of CF patients, but an invasive disease with high mortality (>65%) may develop if severe immunosuppression develops.

Therefore, some experts consider isolation of *L. prolificans* as a possible contraindication to transplantation, due to its multidrug antifungal resistance (Rammaert et al., 2018).

Exophiala dermatitidis

Exophiala dermatitidis is a melanized, thermophilic, dimorphic, dematiaceous and hyphal growth state fungus with multiple conidial forms, and it can be found in hot, moist artificial environments, that are rich in toxic hydrocarbons, such as steam baths and bathrooms; in decaying

organic matter; in creosote-treated oak railway ties in regions near sea level; and in dishwashers (Zupančič et al., 2016). It is a polyextremophilic opportunistic human pathogen, which has frequently been isolated in tropical regions of the world. Its growth characteristics include a polymorphic life cycle, its ability to grow in both high and low temperatures in broadly varying pH environments, its ability to survive high sodium chloride concentrations, and its ability to survive UV and radioactive radiation (Usuda et al., 2021).

The most common forms of deep infections are respiratory system infections, due to inhalation of this fungus. This pathogen is regularly found in the lungs of CF patients, but only very rarely is it found in respiratory specimens from patients who do not suffer from CF. The prevalence of *E. dermatitidis* varies significantly around the world. A German study reported prevalence rates of 4% in comparison to 17% in Sweden (Williams et al., 2016).

Its clinical significance remains uncertain, although recently Kondori demonstrated the presence of serum IgG specific for *E. dermatitidis* in colonized CF patients, with inflammation markers being higher than those observed in patients without specific serum IgG (Kondori et al., 2014). In colonized CF patients with severe respiratory symptoms not responding to antibiotic therapy, some authors have suggested that treatment with antifungals and clearance of *E. dermatitidis* from the sputum may be associated with an improvement in clinical conditions, but this possibility has yet to be confirmed.

Candida species

Candida species may cause transient or permanent colonization of the respiratory tract of CF patients, but can also cause oral and/or genital candidiasis. Prolonged or chronic use of antibiotics and steroids probably are the main factors associated with *Candida* presence in the respiratory tract. They are only rarely detected in bronchoalveolar lavage samples, which raises doubts about their clinical importance as pathogenic microbes versus simple colonizers of the oral cavity (Liu et al., 2021). Therefore, the clinical decision for antifungal treatment is tailored individually, guided by the criteria for "highly probable" pulmonary fungal infection. Evaluation of nearly 26,000 sputum samples of CF patients over a 5-year period, *Candida* species was detected in nearly 75% of samples with the most prevalent species being *C. albicans* (38%) (Ziesing et al., 2016). A prospective observational study in 89 CF patients (3916 sputum samples were analyzed over 11 years) showed that 49.4% of patients were colonized with *C. albicans*.

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Furthermore, colonization with *C. albicans* was associated with significantly increased rates of hospital-treated pulmonary exacerbations (*p=0.004*) and FEV_1 decline (*p<0.001*) (Chotirmall et al., 2010).

A study from Israel, conducted on 91 CF patients (4244 sputum samples over 7 years). Patients were stratified into chronic, intermittent or no *C. albicans* colonization group. Patients in the chronic *C. albicans* colonization group (n=34) had lower FEV_1% predicted (74.3±23.1% vs. 93.9±22.2%) and a higher annual rate of FEV_1 decline (−1.9±4.2% vs. 0.7±4.5%) compared to the non-colonized group (n=27) (Gileles-Hillel et al., 2015).

A retrospective analysis of 3235 patients from nine European CF centers found geographic variations in the prevalence of *Candida* species, *C. albicans* was reportedly the most prevalent yeast in every center with prevalence rates ranging from 33.8% up to 77.9%. Other *Candida* species, like *C. dubliniensis, C. glabrata, C. parapsilosis* and *C. tropicalis*, were also detected at lower frequencies across each center (Schwarz et al., 2018). However, their pathogenicity or ability to cause infection, and their effect on CF disease progression, is not well understood, and remains a matter of debate. A 16-year retrospective study on fungal prevalence in Sweden, on 133 CF patients, revealed that colonization with *C. albicans* or *A. fumigatus*, but particularly *C. dubliniensis* in sputum, was associated with a decline in lung function over time. CF patients with positive *C. dubliniensis* cultures for three consecutive years experienced a 7.6% reduction in percent predicted forced expiratory volume in the first second ($ppFEV_1$; p=0.001) (Al Shakirchi et al., 2020). *C. albicans* also plays a role in severely ill CF patients who need central venous catheter for IV antibiotic treatment. These patients are at risk of *Candida* sepsis, which not only requires systemic antifungal treatment to prevent complications such as endocarditis, but often means the loss of central venous access for treatment. In 2019, *Candida auris*, was first detected in the sputum of a CF patient who has received posaconazole treatment for *Aspergillus* colonization (Stathi et al., 2019). According to Stathi, *Candida auris* may be worth considering in patients with unexplained lung function decline under long-term anti-fungal treatment.

Still, not all studies demonstrate that *Candida* colonization results in decline in lung function over time. Analysis of microbial colonization and corresponding lung function were shown for 770 adolescent CF patients in Europe. These results were conflicting with previous studies, since patients colonized with C. *albicans* demonstrated a protective effect on lung function

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compared to patients colonized with *C. glabrata* who demonstrated an overall decline in FEV_1 from baseline (Hector et al., 2016).

Given the high prevalence rates and conflicting clinical findings in different studies, distinguishing between colonization and active infection with *Candida* species, can be quite challenging.

Conclusion

CF airways have complex microbial environments predominantly occupied by bacteria. With implementation of newer and updated mycological culture techniques and protocols, as well as non-culture based, molecular techniques, scientists now recognize that filamentous fungi and yeasts are increasingly common in the respiratory tract in both adults and children with cystic fibrosis. Although CF treatment has been always focused on treating the bacterial agents, there is emerging evidence that filamentous fungi like *Aspergillus* and yeasts, may play an active role in the progression of the disease.

In the absence of definite consensus criteria for most respiratory fungal conditions and treatment protocols, clinicians are in dilemma how to differentiate harmless airway colonization from damaging fungal disease. This is important if treatment is applied in the case of colonization, since it might pose unnecessary adverse drug effects to the patient, but even more important if antifungal treatment is not applied in case of fungal infection, since negligence might result in irreversible lung damage. This is especially important in case of colonization with *Lomentospora* and *Scedosporium*, which implicates exclusion of the patient from lung transplantation. Therefore, there is an urgent need to better define clinical manifestations of respiratory fungal diseases and identify those patients who will benefit from antifungal treatment. There is also a need to harmonize prophylactic and treatment strategies for high risk populations, like end stage CF lung disease and CF patients after lung transplantation.

Future research should focus on elucidating the mechanisms of fungal colonization and infection in CF, as well as the impact of emerging pathogens and novel therapies on disease outcomes.

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Doi: *Review paper*

Резиме

Значење на фунгите за пациенти со цистична фиброза

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Клучни зборови: фунгални респираторни инфекции, цистична фиброза, ЦФ дишни патишта, ЦФ пациенти.

Фунгалните респираторни инфекции претставуваат значаен и потценет предизвик во лекувањето на цистичната фиброза. Цистичната фиброза (ЦФ) е генетско нарушување кое што се карактеризира со хронични респираторни инфекции и воспаление. Додека бактериските патогени се најмногу проучувани, фунгалните инфекции сè повеќе се препознаваат како значајни придонесувачи за зголемен морбидитет кај пациентите со ЦФ. Овој ревијален труд има за цел да даде основна претстава за фунгалните инфекции на дишните патишта кај пациентите со цистична фиброза, и да ја подигне свеста за важноста на присуството на фунгите во респираторниот тракт на овие пациенти. Фокусот на истражувањето ќе биде ставен на најчестите фунги во дишните патишта на пациентите со цистична фиброза, како *Aspergillus fumigatus*, различни видови на *Candida*, *Scedosporium apiospermum* комплекс, *Lomentospora* species и *Exophiala dermatitidis*, како и на предизвиците во однос на терапијата на фунгалните инфекции, од гледна точка на лекарот, со цел носење на соодветни одлуки во секојдневната пракса, за подобро надминување на фунгалните инфекции.

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Table 1. Classification of *Aspergillus* spp. diseases in adult cystic fibrosis patients, based on the categories proposed by Baxter et al.

Class	RT-PCR *Aspergillus* (sputum)	Total IgE	Specific IgE for *A. fumigatus*	Specific IgG for *A. fumigatus*	GM level (sputum)
Class 1: No disease	+/−	Normal	Normal	Normal	−
Class 2: ABPA	+	Increased	Increased	Increased	+
Class 3: *Aspergillus* sensitized	+/−	Increased (less than in ABPA)	Increased (less than in ABPA)	Normal	−
Class 4: *Aspergillus* bronchitis	+	Normal	Normal	Increased	+

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