



# Fungal Respiratory Colonization and Infections in Cystic Fibrosis Patients in the Middle East

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## Abstract

**Purpose of Review** Cystic fibrosis (CF) is an inherited disease that can progressively affect multiple organs including respiratory tract. CF has been believed to occur infrequently in the Middle East (ME). However, it seems that CF maybe more common in ME countries than expected before. Despite the fact that surveillance of fungal infections is essential, data in the ME region remain scarce. This narrative review aims to evaluate the previously published data on the prevalence of fungal respiratory colonization and infections, spectrum of isolated fungi from the respiratory tract, and antifungal treatment in CF patients across ME countries.

**Recent Findings** Among different opportunistic fungal pathogens, *Aspergillus fumigatus* and *Candida* species were reported as the most prevalent mold and yeast like fungi isolated from respiratory tract of CF patients from ME countries. *A. fumigatus* was reported as the common filamentous colonizing fungi of the respiratory tract of CF patients from Turkey in the range 10.4–76.3%. Colonization due to *Aspergillus* also showed the highest frequency for *A. fumigatus* (50.0%) in CF patients from Qatar. However, in a more comprehensive study from Iran, *A. flavus* was the most common. *Scedosporium* spp. has not been reported in CF patients from ME countries except for one study in Iran.

**Summary** Future efforts should focus on improving laboratory capacities in ME for detection of common and rare fungal pathogens. National CF registries could help to collect more systematic data on fungal colonization and infection in patients in the ME.

**Keywords** Cystic fibrosis · Respiratory fungal infections · Colonization · *Aspergillus* species · *Scedosporium* species

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## Introduction

Cystic fibrosis (CF) is a fatal autosomal recessive genetic disease that systemically affects multiple organs and affects patients from different aspects of life throughout their lives [1]. Although the disease is considered a multi-organ disorder, respiratory involvement represents the most important cause of morbidity and mortality in CF patients [2]. Mutation in cystic fibrosis transmembrane conductance regulator (*CFTR*) gene which encodes CFTR protein, leads to dysfunction of the chloride ion ( $\text{Cl}^-$ ) transporter, followed by dehydration of the organs and production of thick and sticky mucus secretions, and susceptibility to pulmonary infections [3, 4]. *CFTR* mutations at position of  $\Delta\text{F508}$ , N1303K, G542X, 1717-1G > A, R553X, W1282X, G551D, 621 + 1G > T,  $\Delta\text{I507}$ , and R560 becoming important as clinical aspect [1]. European Cystic Fibrosis Society Patient Registry reports F508del substitution accounts for the most frequent mutation in CF patients, more than 80% of all mutations occurred [5]. Mutation at F508del was also reported in the Lebanese (35%), Turkish (24%), and Iranian (17.5–23%) populations [6–10]. In Qatar substitution at the pIle1234Val (I1234V) position is known as the most prevalent mutation in *CFTR* gene [11]. Traditionally, CF has been known as a prevalent disease in Europe, North America, and Australasia affecting the Caucasian population, exclusively [12, 13]. However, recent reports show that the disorder is also present in other areas such as the Middle East (ME), Asia, and Latin America at lower rates [14, 15]. Although actual incidence rates of CF may be lower in these regions, the overall disease burden can be substantial given the high population density. Measures such as national CF registries or proper reporting systems, newborn screening programs, and accuracy and timeliness in diagnosis of CF contribute to a higher incidence of diagnosed disease in high-income countries [16–18]. For the ME, registry data are only available for Iran [19], Turkey [20], and Israel [21] as ME countries. Estimates for the ME indicate a CF incidence of one in every 2560 to 15,876 live births [22]. Epidemiological studies have shown considerable variation in the incidence of CF in different ME countries, with only one CF patient in Bahrain within the last 15 years, compared to 11 CF infants in 1 year in Lebanon [23, 24]. The reported rate for Iran was 1 in 100,000 [25]. According to the report of Health Ministry's Management center for Transplantation and Special Diseases of Iran in 2020, there were 1100 CF patients in Iran [26]. Nevertheless, in a recent study, Guo et al. [17] estimated 162,428 individuals with CF across 94 countries, with 47,650 of these cases located in 40 European countries, 37,002 in seven North American countries, 10,034 in eight South American countries, 3652 in two

Australasian countries, 5349 in 28 Asian countries, and 1665 in nine African countries. However, despite different studies, the exact number of CF patients worldwide is unclear [16, 17].

People with CF (pwCF) exhibit significant variability in the clinical course of their disease. Disparities of race, ethnicity, socioeconomic status (SES), and gender likely contribute to this variability due to increased family stress, exposure to pollution, and tobacco smoke, differences in medication beliefs, and illness management. Studies have shown individuals from racial and ethnic minorities, low SES, and women all face worse health outcomes when diagnosed with CF [27, 28]. PwCF are at high risk for developing severe pulmonary infections caused by a variety of microorganisms including bacteria, viruses and fungi [29]. Bacterial pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common cause of respiratory infection in CF patients [30–32]. Besides bacteria, fungi are often isolated from airway samples [33]. Different fungal species are able to colonize and develop an acute or chronic disease in the respiratory tract of CF patients depending on fungal characteristics and host immune response [34, 35]. Frequent bacterial infections and as a result long-term use of antibacterial agents in CF patients may also predispose to fungal colonization and fungal infection in the lungs. Studies have shown that fungal colonization is associated with worse clinical outcomes in some CF patients; however, whether chronic fungal colonization independently leads to poor outcomes or reflects decreased lung function is not clear [36]. Airways fungal colonization and/or infection in CF patients is commonly diagnosed with broad opportunistic fungal pathogens including *Aspergillus*, *Candida*, *Scedosporium* species, *Exophiala dermatitidis*, *Rasamsonia argillacea* complex, and *Lomentospora prolificans* [37–41]. On the other hand, the spread of resistance to currently available antifungals challenges therapeutic options against these opportunistic pathogens and consequently endangers the lives of CF patients [40, 42–46].

Fungal respiratory infections in pwCF represent a wide spectrum of clinical presentations including sensitization (an immune-mediated response to a fungus that is clinically documented by elevated titers of fungal-specific immunoglobulin E (IgE) or a positive skin test) and allergic bronchopulmonary mycosis, bronchitis and invasive pulmonary form, mostly caused by *Aspergillus* spp. [33, 47–50]. Studies have demonstrated that pwCF are prone to sensitivity to several environmental fungal allergens and represent higher rates of atopy and asthma [51–53]. Allergic bronchopulmonary aspergillosis (ABPA) is a severe disease affecting 8.9% of the CF population which causes mucus impaction and blockage of the airways [47, 54]. However, it is not completely understood how ABPA is developed and who is exactly susceptible [55].

Based on the different definition for classifications of ME countries, we considered the countries that are classified as always ME countries including Iran, Cyprus, Lebanon, Syria, Iraq, Israel, Jordan, Saudi Arabia, Kuwait, Qatar, Bahrain, United Arab Emirates, Oman, and Yemen (Fig. 1) [26].

According to these realities, we aimed to evaluate the previously published data between 1990 and 2022 on the prevalence of fungal respiratory colonization and infections, spectrum of isolated fungi from the respiratory tract, and antifungal treatment in pwCF across ME countries.

## Search Strategy

Data were collected using available sources including PubMed, Google Scholar, Web of Science, Scopus, and several Persian databases (Iran Medex, Iran Doc, and Scientific Information Database) to find all published papers from 1990 to 2022 using the following terms: (Cystic fibrosis OR CF) AND (Fungal infection OR *Aspergill*\* OR *Candida* OR candidemia OR candidiasis OR mucormyc\* OR *Rhizopus* OR *Scedosporiosis*\* OR *Scedosporium*) AND (invasive OR putative OR probable OR infection OR case OR patient OR report) AND (ME countries OR Middle East OR Cyprus OR Lebanon OR Syria OR Iraq OR Iran OR Jordan OR

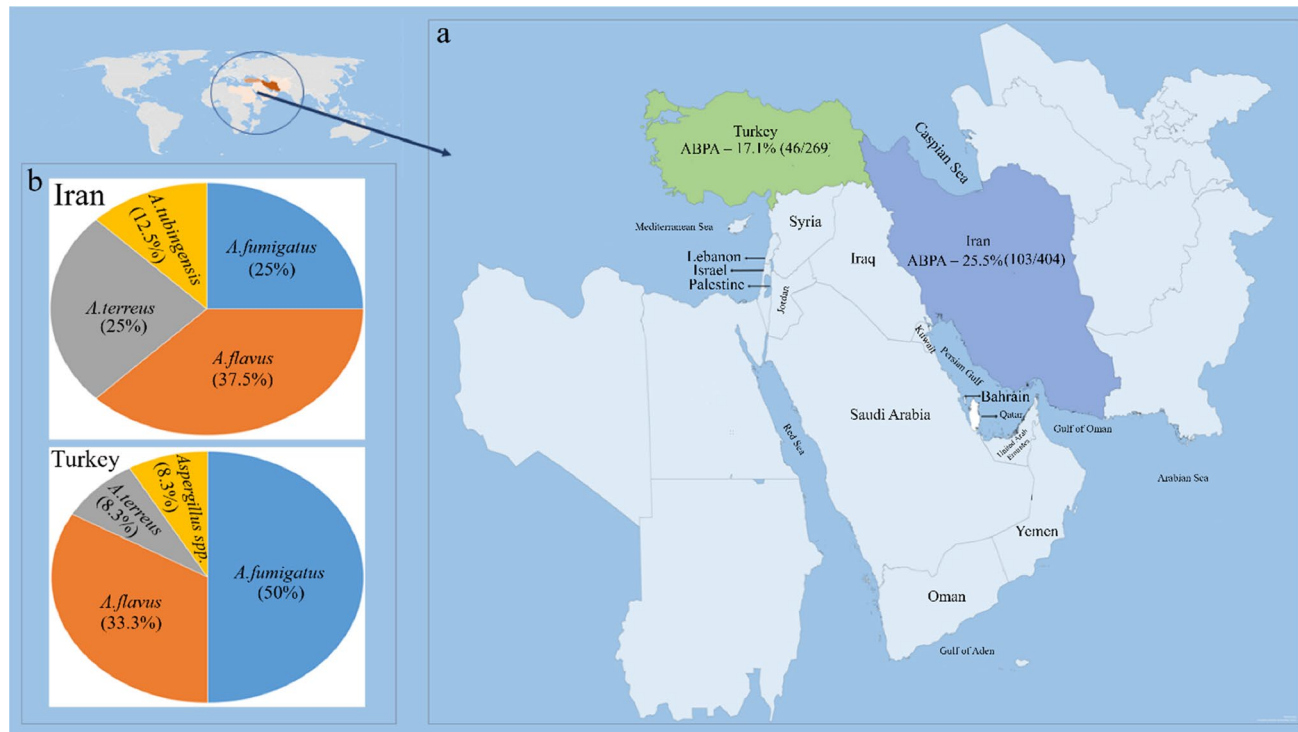
Saudi Arabia OR Kuwait OR Qatar OR Bahrain OR United Arab Emirates OR Oman OR Yemen). Then, we specified all of the potentially relevant studies and included them if appropriate. In the last step, we used EndNote to search the currently selected references for duplicates.

## Respiratory Clinical Entities

According to published data from ME countries, the main reported respiratory clinical entities associated with fungal pathogens were ABPA and fungal sensitization. However, it has been reported in several studies that respiratory fungal colonization is associated with different complications [56–61].

## Allergic Bronchopulmonary Aspergillosis (ABPA)

ABPA is a non-invasive inflammatory lung disease as a common event in immunocompetent individuals, usually with a diagnosis of asthma or CF that manifests as an abnormal pulmonary hypersensitivity reaction, generally caused by *Aspergillus fumigatus* [62]. The prevalence rate of ABPA was



**Fig. 1** (a) Overall incidence of allergic bronchopulmonary aspergillosis in cystic fibrosis patients in Middle East countries. (b) Distribution of isolated *Aspergillus* species in cystic fibrosis with allergic

bronchopulmonary aspergillosis who screened for mycological culture findings according to the extraction of relevant results obtained from the studies conducted in Iran [56, 57, 63] and Turkey [64, 65]

reported between 2.1 and 13.6% in CF patients, globally [61]. There are limited published data from ME countries including Iran [57, 58, 63] and Turkey [64, 65] which reported the prevalence rate of ABPA in CF patients. In addition, there are also some case reports [60, 61, 66]. Two studies from Turkey showed differing prevalence rates of ABPA in CF patients as 9.6% [65] and 2.4% [64]. The reported rate from Iran was 7.1–10.5% according to different studies [56, 57, 63]. Overall, of the 404 and 269 CF patients screened for ABPA from Iran and Turkey, 103 (25.5%) and 46 (17.1%) had proven ABPA, respectively (Fig. 1).

The species of *Aspergillus* involved in CF patients with ABPA was considered only in one study from Iran [57] where *A. flavus* (37.5%) was the most common followed by *A. fumigatus* (25%), *A. terreus* (25%), and *A. tubingensis* (12.5%). Interestingly, Hassanzad et al. [56] from Iran reported a case of recurrent ABPA caused by two species of *Aspergillus*, *A. terreus*, and *A. ochraceus*. However, according to a study conducted by Emiralioglu et al. [65] in Turkey, *A. fumigatus* was the most common (76.3%) species from CF patients including those with ABPA (Fig. 1). It seems that the lack of CF registry in most ME countries and the need for a precise approach and following the different clinical and laboratory practices to identify ABPA are the main reasons for the absence ABPA reporting from most ME countries.

## Fungal Sensitization

CF patients have been reported to have higher rates of atopy and asthma, indicating greater sensitivity to environmental allergens [60]. Among molds, *Aspergillus fumigatus* was the most commonly reported allergen in CF patients [57, 61]. Studies have also shown that adults with CF are more sensitive to several environmental fungal allergens, leading to asthma-like phenotypes, these fungi may not even have been isolated from the sputum of these people [67].

A study by Atay et al. [68] showed a higher rate of sensitivity (33.3%) to aeroallergens in Turkish CF children compared to healthy children. Fungi (19.6%) was identified as the most prevalent allergen followed by pollen (15.7%), animals (9.8%), and house dust mites (7.8%). Among fungi, *Aspergillus fumigatus* was the most frequent allergen with a rate of 17.6%. In another cohort study from Turkey [65], *Aspergillus* sensitization was reported in 3.6% of patients with CF.

## Respiratory Colonization

Fungal colonization is commonly caused by *Candida* and *Aspergillus* species, and has shown some association with clinical presentation in patients with CF [11]. In some

studies, from ME countries the correlation between colonization with fungi and respiratory function was considered [56, 60, 66, 68]. Three reports noted that fungal colonization in CF patients leads to a decrease in forced expiratory volume in the first second (FEV1), Forced vital capacity (FVC), and forced mid-expiratory flow (FEF) by 25–75% [15]. They also emphasized that *Aspergillus* colonization may contribute to lung failure and should be followed up in patients with CF. In addition, the association between fungal colonization and pulmonary exacerbations, asthma, and pancreatic insufficiency has been mentioned [11]. In two studies, persistent fungal colonization especially with *Candida dubliniensis* and *A. fumigatus* was significantly associated with body mass index (BMI) [11, 69].

In Imrak et al. [70] study from Turkey, three different groups of CF patients (fungal disease group, colonization group, and non-isolated group) were studied. History of pulmonary worsening symptoms, number of admissions to emergency unit, ABPA, and higher isolation rate of bacterial species from sputum were significantly higher in the fungal disease group. Parenteral administration of antibiotics in the fungal disease group was higher than in other groups whereas lung functions were similar. Potential risk factors for fungal isolation were the use of dietary supplements and intravenous antibacterial therapy. They have also shown that the association of increased fungal colonization with age may be due to frequent severe bacterial infections and long-term use of antibiotics, which lead to damage to the lung structure.

Although, there is no evidence of the significant relationship between fungal colonization and mutations in *CFTR* in ME, in a study from Qatar [11], the isolation of *Aspergillus* and *Candida* species in CF patients with *CFTR* I1234V mutation was reported. Interestingly, 62% of CF patients who had HLA-DRB1 alleles from Iran showed *C. albicans* colonization and 6% had ABPA [71].

## Spectrum of Isolated Fungi From Respiratory Tract of CF Patients in ME

*Candida albicans*, *Aspergillus fumigatus*, *Scedosporium/Lomentospora* spp. and *Exophiala dermatitidis* were reported as the most frequently detected fungal species in respiratory tract of CF patients worldwide [15, 57, 68, 70, 71].

According to a recent review by Magee et al. [72], the prevalence rate of colonization and/or infection with *Aspergillus fumigatus* or *Candida albicans* in CF patients has been reported in the range of 5–78%. Data from a retrospective study in nine European CF centers showed that of 66,616 samples from 3235 CF patients [73], *C. albicans* is the most common yeast in each center (33.8% up to 77.9%) and *A. fumigatus* (3.9% up to 42.4%) is the most prevalent

among mold fungi. *Scedosporium* spp. and *Lomentospora prolificans*, *Exophiala dermatitidis*, *Trichosporon mycotoxinivorans*, and *Pneumocystis jirovecii* have also been isolated [33].

Epidemiological studies on respiratory fungal infections or colonization in CF patients in ME countries are mostly limited to Iran, Turkey, and Qatar. In addition, it should be indicated that most of these studies were small single center studies. In a study by Hedayati et al. [67], sputum samples were collected from 90 CF patients and cultured in different culture media. Generally, *Candida* spp. (48.3%) were the most commonly isolated fungi followed by *Aspergillus* spp. (47.4%). In this study, among filamentous fungi, *Aspergillus* spp. (91.7%) was the most common followed by *Penicillium* spp., *Alternaria alternata*, *Fusarium fujikuroi*, and *Scedosporium* species. Among *Aspergillus* species, *A. flavus* (29.4%) was the most common followed by *A. tubingensis* (24.7%), *A. niger* (17.0%), and *A. fumigatus* (14.5%). Of three isolated species of *Scedosporium*, two isolates were *S. boydii*, and one *S. ellipsoideum*. *A. flavus* was also reported as the most common species causing invasive aspergillosis (IA) and allergic fungal rhinosinusitis (AFRS) from Iran [67, 74]. However, geographical variation in reported isolated species of *Aspergillus* may exist within the ME; as shown by Nasri et al. [63] in a cohort of 42 CF patients, where the most common filamentous fungi were *Aspergillus terreus* (7.14%) followed by *A. fumigatus* (4.76%), *A. oryzae* (2.38%), and *A. flavus* (2.38%). Hassanzad et al. [75] reported *Candida albicans* (9.6%) and *Aspergillus fumigatus* (8.8%) as the most common fungi in the lung sputum of 192 CF patients. In several studies from Turkey, *C. albicans* and *A. fumigatus* were the most commonly isolated fungi from CF patients [64, 65, 68, 70]. In Turkey, the reported rates of colonization with *A. fumigatus* as the most prevalent mold in the respiratory tract were 10.4% [76], 29.5% [70], and 76.3% [65].

In a study from Qatar [11], *Candida* and *Aspergillus* species were the most commonly colonizing species in CF patients with a prevalence of 81% and 45%, respectively. Among *Candida* species, 55.6% of CF patients were colonized by *Candida dubliniensis*, whereas *Aspergillus fumigatus* was the most common (50.0%) among *Aspergillus* colonized patients.

With the exception of the study conducted by Hedayati et al. [67] from Iran, there is no report on *Scedosporium* species isolation from ME countries, which may have to do with the fact that this pathogen can be identified in many settings. In fact, Hedayati et al. [67] used specific culture media targeting these rare molds, including Scedo-Select III, a semi-selective medium, which is not available in many other laboratories in ME. Table 1 shows detailed information on the obtained spectrum of fungal pathogens across different studies in CF patients in the ME countries during

1990–2022. Moreover, two case reports from Turkey [60, 61] and one from Qatar [66] reported the isolation of *A. fumigatus*, and also, *Exophiala (Wangiella) dermatitidis* and *Candida krusei* from Qatar [77] and *A. ochraceus* and *A. terreus* from Iran [56].

Geographical location, number of included patients in the study, type of clinical sample, type of collected samples, type of culture media and temperature and duration of incubation for isolation of fungi from respiratory samples and the method of identification of isolated fungi at species level may have been influenced on the distribution pattern of isolated fungi in CF patients [76]. For the proper recovery of fungi, particularly some molds, the use of selective media enriched with antimicrobial agents such as erythritol-chloramphenicol agar for *Exophiala dermatitidis* and Scedo-Select III medium for detecting *Scedosporium* in CF patient samples has been recommended [41, 63, 77].

## Mixed Colonization with Fungal and Bacterial Pathogens

In some studies, co-colonization of bacterial and fungal pathogens in the respiratory tract of patients with CF was described [63, 78]. A study in Turkey [76] has shown mixed fungal cultures, yeast along with mold, which were detected in 31 (41.3%) of the 75 culture-positive samples. Analysis of fungal-bacterial showed in the mentioned study, bacterial co-colonization with *A. fumigatus* and *C. albicans* were observed in 100% and 98.2% of the fungal culture-positive samples, respectively. *A. fumigatus* and *Pseudomonas aeruginosa* or *A. fumigatus* and *Staphylococcus aureus* were detected together in 75% of *A. fumigatus* positive samples. *Stenotrophomonas maltophilia* was co-colonized with *A. fumigatus* in 16.60% of positive samples [76]. In a similar cohort study in Iran, mixed bacterial and fungal colonization was reported in 68.9% of patients with CF [63]. In both of these reports, no relationship was found between the specific fungal and bacterial agents grown on the culture medium in samples obtained from CF patients.

## Antifungal Treatment

There are three main approaches to preventing and treating respiratory tract infections in pwCF: (a) continuous prophylaxis, (b) treatment based on respiratory symptoms only, and (c) treatment based on microbial detection of pathogens in the lung [78]. Based on new guidelines for children with CF [79], the treatment of ABPA focuses on down-regulation of the inflammatory host response to *Aspergillus* antigens. For this reason, the use of corticosteroids (prednisolone) in conjunction with an oral antifungal agent

**Table 1** Detail information on the obtained results from different studies about isolated fungi in CF patients in the ME countries during 1990–2022

Author (reference)	Year	Country	Study type/case number	Isolated fungal agent (%)
ATAY et al. [68]	2022	Turkey	Cross-sectional/51	<i>Aspergillus fumigatus</i> (17.6%)
Asef et al. [71]	2022	Iran	Cross-sectional/50	<i>Candida albicans</i> (62%), <i>Aspergillus</i> spp. (6%)
Kartal et al. [64]	2021	Turkey	Cross-sectional retrospective/40	<i>Aspergillus fumigatus</i> (30%), <i>Penicillium notatum</i> , <i>Cladosporium herbarum</i> and <i>Alternaria alternata</i> (15%)
Irmak et al. [70]	2021	Turkey	Retrospective/88	<i>Candida</i> spp. (50%), <i>C. albicans</i> (43.2%), <i>C. parapsilosis</i> (3.4%), <i>C. glabrata</i> complex (4.5%), <i>C. dubliniensis</i> (4.5%), <i>Aspergillus</i> spp. (31.8%), <i>A. fumigatus</i> (29.5%), <i>A. terreus</i> (2.3%), <i>A. flavus</i> (3.4%), <i>A. niger</i> (1.1%), <i>Penicillium</i> spp. (8%), <i>Saccharomyces cerevisiae</i> (1.1%), <i>Cryptococcus albicus</i> (1.1%)
Thomas et al. [11]	2021	Qatar	Descriptive/31	<i>Candida</i> spp. (58%), including <i>Candida albicans</i> (44.4%), <i>Candida dubliniensis</i> (55.6%), <i>Candida tropicalis</i> (11.1%), <i>Candida parapsilosis</i> (5.5%) <i>Aspergillus</i> spp. (32.2%), including <i>Aspergillus fumigatus</i> (50%), <i>Aspergillus niger</i> (20%), and other species (30%), <i>Curvularia</i> and <i>Exserohilum</i> spp. (9%)
Maleki et al. [57]	2020	Iran	Retrospective/86	<i>Aspergillus</i> species (87.3%), including <i>A. flavus</i> (33.3%), <i>A. tubingenensis</i> (27.5%), <i>A. fumigatus</i> (18.8%), <i>Penicillium</i> spp. (6.3%), <i>Scedosporium species</i> (3.8%), <i>Alternaria alternata</i> (1.3%), <i>Fusarium fujikuroi</i> (1.3%)
Emiralioglu et al. [65]	2020	Turkey	Retrospective/100	<i>A. fumigatus</i> (76.3%), <i>A. flavus</i> (9.4%), <i>A. terreus</i> (5.7%), <i>A. niger</i> (3.8%)
Hedayati et al. [67]	2019	Iran	Prospective/90	<i>Aspergillus</i> spp. (47.4%), including <i>A. flavus</i> sensu stricto (30.9%), <i>A. tubingenensis</i> (25.4%), <i>A. fumigatus</i> sensu stricto (12.7%), <i>A. niger</i> sensu stricto (15.4%), <i>A. terreus</i> sensu stricto (5.4%), <i>A. welwitschiae</i> (4.5%), <i>A. foetidus</i> (2.7%), <i>A. ochraceus</i> (1.8%), <i>A. nomius</i> (1%), <i>Candida</i> spp. (48.3%), <i>Scedosporium</i> spp. (0.4%) including <i>Scedosporium ellipsoideum</i> (100%), <i>Penicillium</i> spp. (2.1%), including <i>P. citrinum</i> (40%), <i>P. chrysogenum</i> (60%), <i>Alternaria alternata</i> (0.9%), <i>Fusarium fujikuroi</i> (0.9%)
Nasri et al. [63]	2019	Iran	Cohort/42	<i>C. albicans</i> (57.14%), <i>C. parapsilosis</i> (4.76%), <i>C. dubliniensis</i> (4.76%), <i>C. glabrata</i> (2.38%), <i>C. tropicalis</i> (2.38%), <i>Myerozomya caribbica</i> (2.38%), <i>A. terreus</i> (7.14%), <i>A. fumigatus</i> (4.76%), <i>A. oryzae</i> (2.38%), <i>A. flavus</i> (2.38%)
Salah et al. [101]	2019	Qatar	Prospective/8	<i>Aspergillus fumigatus</i> (37.5%), <i>Aspergillus terreus</i> (37.5%), <i>Aspergillus tubingenensis</i> (12.5%), <i>Aspergillus sublatus</i> (12.5%)
Güngör et al. [102]	2018	Turkey	Retrospective cross-sectional/48	<i>A. fumigatus</i> complex (12.5%)
Alyasin et al. [58]	2018	Iran	Cross-sectional/33	<i>Aspergillus</i> spp. (30.3%), <i>Penicillium</i> spp. (15.15%), <i>Alternaria</i> spp. (3.03%)
Khalilzadeh et al. [59]	2018	Iran	Cohort/62	<i>Aspergillus</i> spp. (6.45%), <i>Candida</i> spp. (3.22%)
AbdulWahab et al. [69]	2017	Qatar	Prospective observational/52	<i>Candida dubliniensis</i> (65%), <i>C. albicans</i> (27.2%), <i>C. tropicalis</i> (6.5%), <i>C. glabrata</i> (1.3%)
Hassanzad et al. [75]	2016	Iran	Surveillance/192	<i>Candida albicans</i> (9.6%), <i>Aspergillus fumigatus</i> (8.8%)
Emiralioglu et al. [62]	2016	Turkey	Retrospective/28	<i>Aspergillus</i> spp. (100%)
Karaman et al. [103]	2013	Turkey	Prospective/37	<i>Candida albicans</i> (54%)
Güngör et al. [76]	2013	Turkey	Prospective/48	<i>Candida albicans</i> (62.5%), <i>Candida parapsilosis</i> (12.5%), <i>Candida dubliniensis</i> (10.4%), <i>Candida kefyr</i> (6.25%), <i>Candida tropicalis</i> (6.25%), <i>Candida glabrata</i> (4.16%), <i>Candida guilliermondii</i> (4.16%), <i>Candida krusei</i> (4.16%), <i>Candida lusitanae</i> (2.08%), <i>Candida norvegensis</i> (2.08%), <i>Rhodotorula mucilaginosa</i> (2.08%), <i>Saccharomyces cerevisiae</i> (2.08%), <i>Aspergillus fumigatus</i> (10.41%), <i>Non-fumigatus Aspergillus</i> (8.33%), <i>Penicillium</i> spp. (2.08%)
Wahab et al. [104]	2004	Qatar	Cohort/36	<i>Candida</i> spp. (25%)
Al Arrayed et al. [105]	1996	Bahrain	Retrospective/27	<i>Candida</i> spp. (not mentioned)

posaconazole benefits treatment management. For this reason, the use of corticosteroids (prednisolone) in conjunction with an oral antifungal agent, posaconazole, benefits treatment management. Nebulised amphotericin B and IV caspofungin may be useful in difficult and refractory cases of ABPA, respectively. A newer azole anti-fungal, isavuconazole, is being used for ABPA treatment in CF adults. One month course of oral posaconazole shows promise for *Aspergillus* bronchitis treatment for children with positive growth *Aspergillus* in sputum but if *Aspergillus* is not eradicated, a 3-month course of posaconazole is needed. The incidence of invasive aspergillosis is lower but may occur in immunosuppressed, neutropenic, and post-transplant CF patients. In these cases, warrants treatment with IV caspofungin.

Posaconazole and combination posaconazole and terbinafine use for *Scedosporium apiospermum* and *Lomentospora prolificans*, highly drug-resistant and the second most common filamentous fungus recovered from CF respiratory secretions, respectively.

Dual therapy (terbinafine and an azole antifungal) is required for *Exophiala dermatitidis*. Finally, for *Candida* species, local treatment with nystatin is given; otherwise, oral fluconazole, if yeast is found in BAL, is needed.

Aaron et al. [80] conducted a randomized, double-blind, placebo-controlled trial to study the effect of itraconazole on CF patients with positive *A. fumigatus* pulmonary samples cultures. The analysis showed no obvious benefits in the frequency of exacerbation and poor lung function. By contrast, in a small study on CF patients ( $n = 13$ ) with *Aspergillus* infection who were treated with 6 weeks of itraconazole, respiratory symptoms and pulmonary exacerbations were reduced [81]. Notably, in retrospective data from Sweden, the impact of antifungal therapy in 42 patients without clinical symptoms of infection with positive *A. fumigatus* cultures (19 treated with antifungals) was examined. The treated group had a more pronounced lung function decline during follow-up compared to the untreated group, suggesting no benefit from antifungal treatment in the setting of the positive culture without symptoms [82].

There are low data on the treatment of CF patients with aspergillosis in ME countries. High minimum inhibitory concentration (MIC) of all triazoles except voriconazole against *Scedosporium* isolates from CF patients were also reported in Iran [67]. Hasanzad et al. [56] reported an Iranian 12-year-old boy with CF who suffered from recurrent ABPA. Antifungal therapy started with itraconazole and corticosteroid therapy. Two months after discontinuing therapy, the patient was re-admitted to the hospital with progressive respiratory symptoms. *Aspergillus terreus* and *A. ochraceus* were identified from sputum using  $\beta$ -tubulin gene sequencing both of which were sensitive to itraconazole and voriconazole. The treatment was changed to voriconazole and the patient's clinical symptoms improved.

## The Role of Geoclimatic Factors in Global Distribution of Fungi

Several climatic factors including high temperature, water scarcity, relative humidity, and air quality were accounted for human health risks and also microbial viability and function [83].

Geographical and human-induced climate changes may alter the environmental reservoir of pathogenic bacteria and fungi and lead to widespread changes in fungal pathogenicity [84]. Significantly, higher stable temperatures in higher latitudes expand the geographical range of dimorphic fungi such as *Coccidioides*, *Blastomyces*, *Histoplasma*, *Talaromyces marneffeii*, and *Paracoccidioides* [84]. In addition, recently due to global warming, species sensitive to climate change such as *Trichophyton mentagrophytes* have emerged in India [85]. It is also assumed that a higher stable environmental temperature in the future can lead to the emergence of less known and unknown pathogenic fungal species [84, 85]. *Aspergillus fumigatus* as the major causative agent of invasive aspergillosis is able to adapt to warmer climates compared with other *Aspergillus* spp. [86, 87]. Some studies suggest that constant temperatures lead to substitution of environmental species including *A. flavus* by *A. fumigatus* [88]. Although *A. fumigatus* is more thermotolerant, *A. flavus* is primarily involved in aspergillosis in Asia, the Middle East, and Africa [67, 74, 89, 90].

In the ME, warmer climates support fungal allergens survival in the environment. In addition, sand storms might be carrying fungal allergens and trigger allergic diseases in ME parts [83]. Interestingly, specific air pollutants may interact with *A. fumigatus* allergens and promote their allergenic potency [88, 91]. Several pollutants induce epithelial barrier damage and contribute to microbial or fungal infection [92]. In this situation, the fungal conidia have the opportunity for morphological alternation and germination and release allergenic proteins [93]. Recent studies show that higher ambient temperature, being close to the equator and also the summer season can be related to the increased prevalence of *Pseudomonas aeruginosa* in CF patients [94]. Emerging data suggest that environmental and climatic factors may influence the risk of fungal infections in people living in rural environments [94].

Climate change also impacts agricultural activities and can change microbial population [95]. For example, recent modeling-based studies show that climate change affects the ecology of *Fusarium oxysporum* [96]. Environmental factors may interact with plant pathogens and affect the effectiveness of pesticides, thereby increasing the use of fungicides [88, 97]. Therefore, it was hypothesized that the extensive use of fungicides has increased the trends of

azole-resistant fungi [98]. Several factors such as climate change, human migration, transport of agricultural commodities, and migratory birds have increased the global extent of these isolates.

The ME is known as the most exposed region to climate change [99]. However, regarding the literature review, no data are available in the field of climate change and its role in ecology of fungi and the effect on CF patients throughout the ME.

## Conclusion

A genetic predisposition in CF patients results in thick, sticky mucous secretions in the respiratory tract, which makes them significantly different from the normal population in terms of their susceptibility to bacterial and fungal respiratory infections and colonization. Chronic colonization of the airways due to a wide variety of opportunistic fungal pathogens including *Aspergillus fumigatus*, *Candida* spp. were reported in CF patients from ME countries. Some studies have also increasingly reported colonization with non-*fumigatus* species of *Aspergillus* including *A. niger*, *A. flavus*, *A. nidulans*, *A. terreus*, and other less common fungi such as *Exophiala dermatitidis*.

Although globally, *Scedosporium* spp. is the second most common fungal pathogen after *A. fumigatus* responsible for chronic airway colonization in CF patients, *Scedosporium* spp. have rarely been reported in CF patients from ME countries which may be driven in part by limited laboratory capacities to detect these organisms. Some other important fungal species such as the *Rasamsonia argillacea* complex and *Lomentospora prolificans* have not been reported in CF patients from ME so far, which may have again been driven also by limited laboratory capacities.

Future efforts should focus on improving laboratory capacities in ME for detection of common and rare fungal pathogens, including broad distribution of selective culture media and improved access to ITS sequencing and MALDI-TOF for species identification. National CF registries could help to collect more systematic data on fungal colonization and infection in patients in the ME.

Highly effective modulating therapy (HEMT) is an emerging and priority research topic for members of the CF community and clinicians [100]. The use of HEMT has profoundly influenced the care of many pwCF and could serve as considerations for ME countries regarding the future management of CF airway infections. Ongoing efforts to monitor and control infections with antifungal-resistant strains continue to be a cornerstone of care for clinicians in the care of pwCF.

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**Data Availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing Interests** The authors declare no competing interests.

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