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Progress in Definition, Prevention and Treatment of Fungal Infections in Cystic Fibrosis

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Abstract Cystic fibrosis (CF) is a chronic lethal multi-system condition; however, most of the morbidity and mortality is dependent on the status of the respiratory system. Progressive respiratory decline is mediated by chronic infection and inflammation, punctuated by important acute events known as pulmonary exacerbations which can lead to accelerated decline. The main bacterial species causing infections include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Achromobacter xylosoxidans.* In addition to bacteria, fungi are detected in a significant number of patients. The impact of fungal colonization of the airways is still not completely elucidated, but an increasing body of evidence suggests an important role for moulds and yeasts. Although fungal infections are rare, fungi can cause severe pneumonia requiring appropriate targeted treatment. The most common fungi in respiratory samples of patients with CF are *Aspergillus fumigatus*, *Aspergillus terreus* and *Scedosporium* species for filamentous fungi, and yeasts such as *Candida albicans* and *Candida glabrata.* Therapeutic strategies depend on the detected fungus and the underlying clinical status of the patient. The antifungal therapy can range from a simple monotherapy up to a combination of three different drugs. Treatment course may be indicated in some patients for two weeks and in others for up to six months, and in rare cases even longer. New antifungal drugs have been developed and are being tested in clinical studies offering the hope of therapeutic alternatives to existing

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drugs. Identifying relevant risk factors and diagnostic criteria for fungal colonization and infection is crucial to enabling an adequate prevention, diagnosis and treatment.

Keywords Yeasts · Filamentous fungi · Azoles · Polyenes · Echinocandins · Allylamines

Introduction

Patients with cystic fibrosis (CF) suffer from chronic infections of the lung and multiple recurrent bronchopulmonary disease exacerbations. Besides bacteria such as *Pseudomonas aeruginosa*, some filamentous fungi such as *Aspergillus* spp., *Scedosporium* spp. and *Exophiala* spp. are gaining increasing importance as cause of CF bronchopulmonary exacerbations. The prevalence of these pathogenic fungi ranges from 1.9 to 56.7% [1, 2], and their pathogenicity may differ from that of bacteria as fungi may differ in their ability to colonize the airways. Therefore, their pathogenicity may be dependent on certain immunological pathways modifying patients' susceptibility. Predisposing factors such as defective muco-ciliary clearance, prolonged antibiotic treatments, local inflammation, and the use of inhaled and systemic corticosteroids may facilitate fungal growth in the CF lungs.

The fungal biota is dominated by filamentous fungi such as *Aspergillus fumigatus*, *Aspergillus terreus*, *Scedosporium apiospermum*, and yeasts such as *Candida albicans* and *Candida glabrata* [1, 2]. However, rare fungi such as *Exophiala dermatitidis*, *Trichosporon mycotoxinivorans* and *Rasamsonia argillacea* can colonize the airways of CF patients, causing significant clinical infections. Therapy can be challenging as some of the moulds are multi-drug resistant, for example *Lomentospora prolificans*. Others like *A. fumigatus* usually tend to be easily treatable. Nevertheless, an increasing number of azole-resistant *Aspergillus* species have been described in the recent years (for a review, see Hamprecht et al. in this special issue). In this context, this review will address therapeutic strategies and prevention of fungal infections in patients with CF.

Since criteria for invasive fungal infections (pneumonia) in CF patients have not been defined yet, the following criteria for "highly probable" invasive pulmonary fungal infection were considered by the authors:

1. Increased sputum production.
2. Multiple isolation of the same fungal species from sputum or bronchoalveolar lavage (BAL) (at least two culture-positive samples in 6 months).
3. Pulmonary infiltrate(s) on chest CT scan or X-ray.
4. Treatment failure with antibiotic therapy (two and more antibiotic treatments, duration two or more weeks).
5. Unexplained lung function decline (exclusion of new CF-related diseases, e.g. diabetes mellitus).
6. Exclusion of new/other bacteria (e.g. non-tuberculous mycobacteria or *Pseudomonas aeruginosa*).
7. Exclusion of allergic bronchopulmonary aspergillosis.

Antifungal Treatment Strategies

Aspergillus spp.

Aspergillus spp. are the most frequent colonizing fungal pathogens in patients with CF. In a recent study examining 25,975 sputum samples from patients with CF, *Aspergillus* spp. were detected in 35% of samples (29% with *A. fumigatus*) [2]. The inhalation of *Aspergillus* conidia can chiefly result in two clinical scenarios, either *Aspergillus* colonization of the airways or allergic bronchopulmonary aspergillosis (ABPA), but sensitization, aspergilloma and pulmonary infections may also occur. *Aspergillus* infections are treated with antifungal drugs. In contrast, the mainstay of treatment of acute exacerbations of ABPA is corticosteroids, which may be augmented chronically with antifungal agents. The use of the anti-IgE monoclonal antibody omalizumab has been reported in small case series [3–5], often with an antifungal therapy to reduce fungal burden and prevent exacerbations. The relatively small number of antifungal agents limits treatment options currently available. One of the major concerns in patients with CF is that they do not achieve adequate therapeutic levels with the usual doses and require higher doses, up to 30–50% of recommended dose [6–9]. In addition, there is a lack of prospective intervention studies. In a recently published Cochrane review, no randomized controlled trials that evaluate the use of antifungal therapies for the treatment of ABPA in CF patients were found [10].

For *Aspergillus* infections, especially in invasive infections, voriconazole is the recommended treatment according to almost all guidelines based on a significant survival benefit, which is maintained in multiple real-life retrospective studies [11–13]. Until now, no consensus recommendations for treatment of *Aspergillus* infections specifically in the CF context have been reached. Therefore, when treating *Aspergillus* infections in CF, most clinicians will refer to the aforementioned guidelines with voriconazole as first-line therapy. In addition to voriconazole, posaconazole can also be recommended for *Aspergillus* infections and its use has been evaluated in severely ill patients. In 67 non-CF patients receiving posaconazole therapy for at least 6 months, a response was seen in 41 patients; 6 patients died, 9 had an adverse event, and 11 showed clinical and/or radiological deterioration. Therefore, at 6 months, posaconazole treatment was successful for 41 (61%) of 67 patients and failed for 26 (39%) of 67. Overall improvement at 6 months was observed in 9 patients (13%). There were 41 evaluable patients at 12 months, of whom 2 had primary posaconazole therapy. Nineteen of these patients responded to therapy, 7 died, 9 had an adverse event, and 6 showed clinical and/or radiological deterioration. Therefore, at 12 months, posaconazole therapy was successful for 19 (46%) out of the 41 patients and failed for 22 patients (54%). Overall improvement at 12 months was observed in 6 patients (15%). The 7 patients who died in the first 12 months of posaconazole therapy succumbed to a respiratory failure secondary to pneumonia. There were no instances of massive hemoptysis or non-respiratory causes of death [14].

A high number of *Aspergillus*-colonized patients and patients with ABPA or with *Aspergillus* bronchitis (discussed in another paper in this special issue) are receiving azoles with the accompanying concern of azole resistance. In a recent publication, the emerging azole resistance in *A. fumigatus* has been described and discussed [15]. The resistance phenotype is associated with key mutations in the *cyp51A* gene, including TR_{34}/L98H, TR_{53} and TR_{46}/Y121F/T289A resistance mechanisms (for a review, see also Hamprecht et al. in this special issue). Early detection of resistance is of paramount importance. Therefore, in the case of azole resistance, azole monotherapy should be avoided. Liposomal amphotericin B or a combination of voriconazole and an echinocandin is recommended for azole-resistant aspergillosis. Resistance to azoles might emerge as a new therapeutic challenge in several countries. Although de novo azole resistance occurs occasionally in patients during azole therapy, the main threat is the acquisition of resistance through the environment. In this setting, the evolution of resistance is attributed to the widespread use of azole-based fungicides [15], increasing the risk of failure of antifungal treatment in patients with CF.

In a study from Burgel et al. [16], *A. fumigatus* was isolated from the sputum of 131/249 (52.6%) adult patients with CF. In this cohort, 47/131 (35.9%) patients had received previous treatment with itraconazole. Interestingly, reduced susceptibility of *A. fumigatus* isolates to itraconazole (minimum inhibitory concentration or MIC > 2 mg/L) was confirmed in 6/131 (4.6%) subjects. A further important issue regarding the risk of aspergillosis arises following lung transplantation. As CF is one of the most common indications for lung transplantation, identifying risk factors for worse outcome after transplantation is crucial [17, 18]. Pre-transplantation *Aspergillus* colonization is a risk factor for the development of a post-transplantation infection. In a study encompassing 93 patients with CF who underwent lung transplantation, 70% (65/93) of the patients had pre-transplantation *Aspergillus* colonization. Thirty-six patients had positive intra-operative *Aspergillus* culture from the native lung BAL. Overall, 22.5% (20/93) of transplanted patients with CF developed invasive aspergillosis. Median time to aspergillosis was 42 days post-transplantation. Positive intra-operative *Aspergillus* culture and treatment for acute cellular rejection within 90 days post-transplantation were independent risk factors for aspergillosis. Antifungal prophylaxis with either inhaled amphotericin B or voriconazole (intravenous followed by oral voriconazole) was administered to 61% (57/93) of CF lung transplant recipients. One-year mortality rate was 16% (15/93). But interestingly, invasive aspergillosis was not associated with increased risk of death [19]. However, other studies have clearly identified *Aspergillus* spp. as a risk factor for increased post-transplantation mortality [20, 21].

Candida spp.

In the aforementioned German study, about 75% of patients with CF were colonized by yeasts, mainly *C.*

albicans (38%), *Candida dubliniensis* (12%), *C. glabrata* (9%), *Candida parapsilosis* (3%), *Candida lusitaniae* (2%) and *Candida krusei* (1%) [2]. These results are similar to those previously reported on fungal colonization of the respiratory tract in CF [22–24]. The pathogenicity of these organisms and their influence on disease progression in CF is less clearly understood and continues to be debated. In the late 1990s, registry data from 7010 patients with CF showed the association of *Candida* spp. and lower FEV1 [25], although whether this is due to a direct effect of *Candida* or an observation for its predilection for damaged pulmonary parenchyma is unknown. In terms of pathogenicity in CF, *Candida* spp. can cause localized and systemic infections and induce oral and genital thrush, vascular access device-related infections and post-transplantation complications [26]. The potential of *Candida* spp. to cause lung function decline implementing a significant impact was demonstrated in three different studies in patients with CF [27]. However, whether treatment against *Candida* spp. influences the course of disease or the drop of lung function remains unknown and needs further investigation. In the very rare cases of highly probable pulmonary infection due to *Candida* spp., the accurate identification of the infecting *Candida* species is crucial in determining which antifungal agent to use, because fluconazole-resistant *Candida* species exist [28]. In *C. albicans* infections, it is recommended to start with an azole, preferably fluconazole, and to modify treatment if needed according to susceptibility tests. Echinocandins (e.g. caspofungin, anidulafungin, micafungin) are effective drugs for *C. glabrata* and *C. tropicalis* infections. Amphotericin B is also useful for *Candida* infections but has the disadvantage of nephrotoxicity, hypokalemia and acute infusion-related side effects [13]. It remains, however, unusual that *Candida* spp. are identified as causing acute pulmonary infection in CF requiring treatment and more research is needed to determine their true position as pathogenic organisms in CF.

Scedosporium Species and *Lomentospora prolificans*

Fungi of the genus *Scedosporium* and *Scedosporium prolificans*, recently renamed as *Lomentospora prolificans* [29], are the second most frequent colonizing, allergenic or invasive fungal pathogens in patients with CF [30]. Prevalence rates from patients with CF in single centres in Europe and Australia range from 3.4 to 17.4% [1, 31, 32]. One large prospective and multi-centre study on the prevalence of these fungi in Germany revealed a mean prevalence of 3.1% with a range from 0.0 to 10.5% [33]. In this study, all participating centres used a selective medium for isolation of *Scedosporium* and *Lomentospora* species from 11,600 respiratory samples collected from 2346 patients with CF. The benefit of the SceSel+ agar could be demonstrated by showing a missing rate of 54% if no selective media had been used. The therapy of *Scedosporium/Lomentospora* infections can be very challenging as these fungi are known to be highly resistant to antifungal drugs [33, 34]. Regarding the antifungal therapy of these infections, the European guidelines recommend voriconazole/triazoles as first-line treatment together with surgical debridement when possible but these relate to non-CF patients [35]. Although favourable results have been observed following these recommendations, the outcome remained poor with mortality rates >65% and around 100% when infection with central nervous system involvement or dissemination occurs [36].

In non-transplanted patients with CF, the situation is not comparable to immunosuppressed patients. Patients with CF may experience a subtle increase in symptoms of infection that results in a slow decline in lung function test. In addition, the clinical picture is characterized by increased respiratory symptoms (increased sputum production, cough and dyspnoea) as well as failure to respond to conventional antibiotic treatment targeted at their colonizing bacteria (see also above). Fungal pulmonary infections in CF have in the authors' opinion no indication for surgery as the causative fungus likely infects all lobes of the lungs and the resultant resection permanently removes what may be viable pulmonary parenchyma. In rare cases, it might be discussed and indicated. In this context, systemic antifungal therapy is recommended for pulmonary infections caused by *Scedosporium/Lomentospora* species. Four cases treated with antifungal drugs due to a suspected pulmonary scedosporiosis have been reported since 2013. The first case describes an adolescent with CF and *Scedosporium apiospermum* infection who has been treated successfully with systemic application of amphotericin B and voriconazole in addition to inhaled voriconazole [37]. Also in a 35-year-old female with *S. apiospermum* infection,

treatment was successful by using systemic caspofungin and voriconazole together with inhaled amphotericin B [38]. A third case revealed a rare manifestation of an endo-bronchial acute manifestation of a scedosporiosis. Treatment with voriconazole revealed no clinical improvement. Therefore, a bronchoscopy was initiated that showed an obstruction by mucus plugs and bronchial cast which were removed during the procedure [39]. The fourth case describes a 24-year-old female with CF who developed an acute infection caused by *S. apiospermum*. Treatment with posaconazole failed, but the combination of oral voriconazole and terbinafine stabilized the patient's clinical status who ultimately underwent lung transplantation. After lung transplantation, the BALs were negative for *Scedosporium* species [40]. Therefore, we recommend as antifungal treatment for pulmonary infections due to *Scedosporium* species an oral triazole (voriconazole, posaconazole or isavuconazole), together with an intravenous echinocandin (caspofungin or micafungin) and inhaled amphotericin B. Good experience already exists over years with inhaled amphotericin B. Experience from the post-lung transplantation arena with inhaled amphotericin B to prevent or treat (add on) invasive aspergillosis has demonstrated that this mode of delivery leads to high local drug concentration [41].

In terms of in vitro activity of double combinations against *Scedosporium* spp. and *L. prolificans*, studies have been performed to support clinical decisions. Combinations of voriconazole with amphotericin B or echinocandins have shown synergistic effect against both *S. apiospermum* and *L. prolificans* [42] as well as terbinafine plus itraconazole, miconazole or voriconazole against *L. prolificans* [43–45]. But combination of voriconazole with terbinafine or liposomal amphotericin B also demonstrated variable outcome regarding the treatment of scedosporiosis [46–55]. In vitro data evaluating antifungal combinations using more than two antifungals are rare in the literature. Two triple combinations (amphotericin B plus voriconazole plus anidulafungin or micafungin) have been reported. They were tested against *L. prolificans. In vitro* results showed synergy for the triple antifungal combinations against *L. prolificans* [42]. However, when tested in a murine model of disseminated *Lomentospora* infection, the triple combination of amphotericin B plus voriconazole and micafungin did not show significant improvement compared to the double combinations of micafungin plus amphotericin B or voriconazole [56].

Interestingly, combinations of antifungals with miltefosine, antipsychotic drugs or cysteine derivatives might be promising therapeutic strategies and have been already tested for treatment of scedosporiosis [57–60].

Exophiala dermatitidis

Exophiala dermatitidis was first described to be associated with CF by Haase et al. [61] in 1990. Numerous studies have reported that this fungus may colonize the respiratory tract of CF patients with a rate of occurrence ranging from 1 to 19% [62–64]. Outside the human body, *E. dermatitidis* usually occurs in warm and humid areas and is therefore believed to originate in tropical climates [65]. It is also encountered worldwide in the man-made environment, for example in dishwashers, steam baths and sauna facilities [66, 67]. Detection of this fungus can be problematic on routine sputum testing, and prolonged culture on dedicated plates may be necessary to confirm its presence.

Kusenbach et al. [68] described a severe pneumonia in a 7-year-old girl with CF already in 1992. It seemed highly probable that *E. dermatitidis* was the causal agent for fungal pneumonia in this case. Following therapy with amphotericin B and flucytosine, the clinical course and radiological appearance improved, but definitive eradication of *E. dermatitidis* was only achieved after treatment with itraconazole.

In a retrospective study, the clinical records of 17 patients with CF who had positive sputum tests for *E. dermatitidis* were analysed [64]. Analysis showed that four patients received antifungal therapy due to suspected infection. Patient one was a 22-year-old male who received posaconazole for 3 months after failure of i.v. antibiotics and itraconazole. Respiratory symptoms subsided, and results from sputum culture were negative again. Patient two, a 34-year-old male, was treated with voriconazole with no success. Treatment led to negative sputum cultures regarding *E. dermatitidis* but without influencing respiratory symptoms. As the patient suffered from significant gastro-oesophageal reflux disease, fundoplication was performed which resulted in some improvement in respiratory symptoms. Patient three was a 34-year-old female not responding to antibiotic treatment. After

implementing an antifungal treatment with voriconazole, clinical response was difficult to interpret, as emesis was significant leading to termination of the antifungal treatment. Sputum cultures only revealed sparse growth of *E. dermatitidis* at treatment termination. Patient four was a 12-year-old boy developing multiple filled cavities in the lungs. Treatment with i.v. amphotericin B for 14 days initially, followed by posaconazole for seven months, resulted in clinical and radiological response. Recurrent fungal infection due to *E. dermatitidis* may be successfully treated also with posaconazole.

As highlighted by these cases, antifungal treatment may be difficult and hampered by limited effectiveness and adverse events; nonetheless, positive treatment outcomes can occur. Biofilm formation might be the cause of limited effectiveness. Kirchhoff et al. [69] found that *E. dermatitidis* can form biofilm and that invasive isolates exhibit significantly higher biofilm-forming ability than do isolates from patients with CF. The metabolic activity and the biomass involved in biofilm are strain specific. *Exophiala dermatitidis* biofilm is susceptible to the antifungal agents micafungin and voriconazole during the early steps of biofilm formation. The antibiotic colistin reduces as well the fungal growth rate, especially during treatment of mature biofilms. In this context, a therapeutic failure should lead to change in antifungal treatment from itraconazole to posaconazole or even to micafungin if fungal infection due to *E. dermatitidis* is highly probable.

Trichosporon mycotoxinivorans

Trichosporon spp. are basidiomycetous yeast-like anamorphic organisms (Basidiomycota, Tremellomycetes, Trichosporonales). *Trichosporon* species are uncommon pathogens in patients with CF, but in rare cases, they have the ability to cause life-threatening infections, especially in immunocompromised patients. Yeast-like *Trichosporon* spp. can be detected throughout the environment, but they grow predominantly in tropical and temperate areas. Members of this genus can colonize the gastrointestinal tract, respiratory tract, skin and vagina. Superficial infections are more common in immunocompetent hosts, but *Trichosporon* spp. can cause deep-seated mucosa-associated or superficial infections. Very rare is invasive trichosporonosis, mostly in patients with malignancies [70]. The first but severe human case was described in a patient with CF in 2009 [71]. This 20-year-old male with CF initially presented with a pneumothorax and was afterwards treated with antibiotics due to pyrexias up to 40 °C. Gram staining of sputum collected at the time of admission revealed no bacteria but 30 budding yeasts and 30 polymorphonuclear leucocytes per field. On day six of hospital stay, the yeast was identified as *Trichosporon* species. The initially commenced liposomal amphotericin B therapy was stopped, and voriconazole was started due to concerns of intrinsic drug resistance. The therapy could not stop the severe life-threatening infection, and the patient died on day 11 of hospital stay. Autopsy was performed which revealed diffuse haemorrhagic and suppurative consolidation of the lungs with chronic bronchiectasis. Cultures of tissue collected from each lobe post-mortem grew *Trichosporon* species, and histology demonstrated diffuse infiltration of the lung parenchyma with budding yeasts. In this case report, it remains unclear whether the treatment failure at the beginning of treatment was the reason for this fulminant clinical course or whether an undiagnosed immune deficiency was the underlying issue.

Amphotericin B and lipid formulations as well as the echinocandins have limited efficacy against *Trichosporon* species. Triazoles are considered the therapeutic class of choice on the basis of in vitro data, animal models and individual case descriptions [72–76]. Shah et al. [77] described four additional cases with CF and *Trichosporon mycotoxinivorans* infection but none of them had a clinical course as fulminant as described by Hickey et al. [71]. One patient received antifungal treatment due to failure of antibiotic treatment. Therapy was started with oral voriconazole, then combined with inhaled amphotericin B. The biggest cohort was analysed by a German research group [78]. *Trichosporon* species were found in 8 out of 360 (2.2%) patients with CF. Data suggested that age, prior systemic or inhaled steroid treatment, ABPA and possibly CF-related diabetes may predispose to colonization by *Trichosporon* species. Two of the eight patients received treatment, because of a prolonged severe cough for one of them. For this patient, inhaled amphotericin B led to significant resolution of the symptom. The second patient had a significant drop in lung function, and the severe clinical symptoms responded poorly to

antibiotic treatment. Therefore, i.v. amphotericin B was started as susceptibility testing revealed good efficacy of amphotericin B, posaconazole and voriconazole. After 8 weeks of amphotericin B treatment, the patient's condition improved considerably and oral therapy with voriconazole was initiated, but it was changed to posaconazole due to side effects (impaired colour vision). In an immunocompromised patient with no response to antifungal monotherapy, a combined antifungal therapy should be discussed. A neutropenic patient with acute myeloid leukaemia experienced a breakthrough infection of *Trichosporon asahii* during posaconazole treatment. Treatment was then changed to a combination therapy with voriconazole and liposomal amphotericin B, and the infection resolved [79]. As recommended for other fungi, it is also crucial to performing susceptibility testing in patients with CF suffering from lung infections with *Trichosporon* spp.

Other Fungal Species

In addition to the already mentioned fungi, others can be detected in CF specimens including *Alternaria*, *Cladosporium* and *Penicillium* species, as well as *Paecilomyces variotii*, *Acrophialophora fusispora* and *Rasamsonia argillacea* (e.g. *Geosmithia argillacea*) which was initially identified as *Penicillium emersonii* [1]. The clinical consequences for patients with CF are unknown, and therapeutic intentions are not defined yet.

As for all indications and therapies, an adequate monitoring of side effects is mandatory as well as the monitoring of plasma concentrations of antifungals [80].

Prevention

The high prevalence of fungi in CF and the risk of a range of fungal related diseases from allergy to severe infections raise the question of prevention.

In a German study, a high percentage (75%) of yeast colonization was found [2]. This can probably be explained by recurrent use of corticosteroids and antibiotic treatments against chronic bacterial infections and the resulting advantage for yeast growth [1, 81, 82]. As reported in other studies, *C. albicans* was the most prevalent species, followed by *C. dubliniensis* [83, 84]. Therefore, in patients with long-term or recurrent corticosteroid treatment or with inhaled, oral or even i.v. antibiotic treatment, screening should be considered for fungal colonization and fungal infection.

Jensen et al. [85] speculated that the oral cavity may be an unrecognized reservoir of resistant *Candida* species, especially *C. glabrata* following azole or echinocandin treatment. In addition, there are concerns about a changing epidemiology towards *Candida* species less susceptible to fluconazole combined with the acquisition of echinocandin resistance, in particular among *C. glabrata* isolates.

Additionally, azithromycin, a routinely used macrolide in CF care, may be implicated in *Aspergillus* colonization. Azithromycin reduces neutrophils and IL-8 [86]. Multivariate analysis has identified an independent association between low body mass index and ABPA ($p = 0.004$) and intriguingly between long-term azithromycin use and *Aspergillus* colonization ($p = 0.001$). This latter association might be due to the inhibitory effect of azithromycin on recruitment and activation of neutrophils, which are crucial in host defences against *Aspergillus* [87].

As patients with CF inhale several different drugs once, twice or even sometimes three times daily, the inhalation device is one risk factor if disinfection is not done hygienic adequately. In a study of patients with CF, a total of 170 nebulizers from 149 subjects were screened by wetting a sterile cotton swab with sterile water and swabbing each drug chamber. The swab was then plated out on Sabouraud and on SceSel+ agar and incubated at 27 °C for up to 2 weeks. Overall, 86/149 (57.7%) of subjects had positive fungal cultures from at least one of their devices, with 39/149 (26.2%) being yeasts, 47/149 (31.5%) moulds and 20/149 (13.4%) a combination of yeasts and moulds. *Aspergillus fumigatus* was the most frequent mould isolated followed by *Penicillium* spp., *P. commune* being the most common species from this genus. Several *Lecanicillium* sp. isolates were also identified. *Exophiala* species were also isolated from five devices. The most frequent yeast to contaminate devices was *Candida guilliermondii* followed by *C. parapsilosis*. Contamination with environmental basidiomycetous yeasts in the genera *Rhodotorula* and *Cryptococcus* (but not *C. neoformans*) was also common. Interestingly, the most common cause of

oral colonization and infection, *C. albicans* was isolated only on a single occasion. This study suggests that inhalation devices can play an important role as an individual risk factor as contamination with fungi can occur [88].

The prevention of infection or colonization with *Scedosporium/Lomentospora* species is difficult as it occurs only in low numbers of patients. These organisms naturally live in soil and water, and therefore, patients who have a hobby of gardening may be at increased risk. Therefore, we recommend awareness of the risk of acquiring fungal colonization when gardening. Colonization by *Scedosporium* or *Lomentospora* species is associated with younger age ($p < 0.005$) and absence of *H. influenzae* ($p < 0.001$). In addition, patients colonized by these fungi had more often ABPA ($p < 0.01$) and have been colonized more often with the mucoid phenotype of *Pseudomonas aeruginosa* ($p < 0.05$) [89]. Although difficult, clinicians should be mindful of these associations, particularly in children who have naturally closer exposure to soil and water.

A new risk factor for acquisition of fungi has been recently identified and is now recognized by patients with CF. Dishwashers can host the black yeast *E. dermatitidis* which can be found to grow on the rubber seals of the doors [67]. Therefore, to prevent colonization with *Exophiala* species, special precautions regarding dishwashers use can be recommended. Patients should be aware of this entity when opening a dishwasher and should not clean the rubber seals of the dishwasher doors themselves. Some patients may reasonably consider the use of masks, but currently there is insufficient evidence to support or oppose this.

In terms of ABPA, our research group have reported that pet ownership is a risk factor for ABPA [89]. One hundred and nine patients were included in the study. The mean age of the total group was 25.4 ± 13.2 years. Adjusted analysis revealed that ABPA ($p = 0.029$) was associated with pet ownership in patients with CF. Furthermore, ABPA in pet owners with CF was associated with an increased number of exacerbations ($p = 0.043$). A significant higher proportion of pet owners (65.5%) were sensitized to *A. fumigatus* in unadjusted analyses compared to non-pet owners (33.3%). In addition, the rate of sensitization to dust mite, dog and cats was higher in pet owners compared to non-pet owners. In particular, with regard to sensitization to house dust mite (25.5% pet owners and 7.4% non-pet owners) and dogs (23.6% pet owners versus 5.6% non-pet owners), the difference was significant. These results suggest screening for ABPA if patients are pet owners and if ABPA is recurrent, pet ownership should be excluded.

The aim should be to introduce these relevant risk factors to patients and their families to enable an adequate prevention of fungal colonization or even infections. Communication of specific risks should include gardening, dishwasher and pet ownership. Long-term corticosteroid therapy and antibiotics always have to be considered under a risk benefit calculation not only regarding fungi but also other side effects.

New Future Therapies

Currently, the treatment for fungal pulmonary infections is limited to few drugs, with relevant side effects, drug interactions and variable host response. Therefore, decision regarding when to commence treatment and with which agent is a challenge. However, there is a light on the horizon with new antifungal drugs in the pipeline and the use of antifungal therapeutic drug monitoring in daily practice.

With the development of ravuconazole and albaconazole (isavuconazole is already commercialized), two new azoles exist potentially enlarging therapeutic options in cases where additional azoles are needed. The group of echinocandins received a new addition with aminocandin [90]. A glucan synthase inhibitor, MK-3118, is a derivate of enfumafungin that has an antifungal activity profile similar to that of echinocandin and is orally available. Biafungin is also an echinocandin but is long acting and developed for the treatment of *Candida* infections, with potent activity against both *Candida* and *Aspergillus* spp., including azole- and echinocandin-resistant isolates [91].

E1210, a glycosylphosphatidylinositol (GPI) anchor biosynthesis inhibitor, inhibits fungal GPI-anchored protein biosynthesis through the inhibition of inositol acyltransferase [92]. It is a broad-spectrum investigational agent resulting in the inability to form cell walls and to bind to host cells.

Another new drug in the pipeline is T-2307, an arylamidine derivative. While it appears that T-2307 may interfere with the mitochondrial function of yeasts, its mechanism of action is not completely

understood, but T-2307 is taken up into cells via transporter-mediated systems, leading to collapse of fungal mitochondrial membrane potential [93].

Trials are commencing using monoclonal antibodies as an antifungal therapeutic strategy. Efungumab is one of these antibodies. The spectrum of activity of efungumab (Novartis Pharmaceuticals) is limited to *Candida* spp., including fluconazole-resistant organisms, when used as monotherapy or in combination with other antifungal agents (such as fluconazole, caspofungin and amphotericin B) [94].

As antifungal treatment may be life-saving not only for patients with CF but also for immunocompromised patients in general, novel therapeutic options based on completely different strategies are very encouraging. The potential of several T-cell-based therapeutic approaches in the prophylaxis and treatment of infectious diseases with a particular focus on persistent viral infections and opportunistic fungal infections is promising [95]. Antifungal immune responses could be improved by adaptive transfer of pathogen-specific T cells directed against invasive and pulmonary fungal infections, particularly infections with C*andida* spp., *Aspergillus* spp. and mucoromycetes, especially after allogeneic stem-cell transplantation. T-cell responses are MHC class I restricted (for CD8-positive T cells) or MHC class II restricted (for CD4-positive T cells), and thus, an effective T-cell response needs to match the genetic background of the patient. T-cell transfer approaches have been used to obtain these pathogen-specific T cells. Anti-pathogen-specific T cells can be expanded ex vivo under appropriate conditions (usually with the help of recombinant cytokines, synthetic peptides or cellular components representing the pathogen). Responder T cells are identified by interferon-γ production, removed via an interferon capture assay and transferred into the patient [96].

Compared to existing antifungal drugs, a new antiseptic drug belonging to chloramins and named N-chlorotaurine has also very promising properties. This new drug shows strong in vitro effects with fungicidal activity against multi-resistant fungi such as *Lomentospora prolificans* or *Scedosporium boydii* [97–103].

Better estimation of host risk of the development of allergic or invasive forms, for instance through the identification of informative genetic polymorphisms, will allow optimization of prophylactic and therapeutic strategies. The indications for the use of therapeutic drug monitoring to improve therapeutic efficacy and control toxicity are also an unresolved issue, as is the role of combination antifungal therapy, given the potential for synergism and antagonism. New immunomodulatory strategies, including vaccine development and taking advantage of the immunomodulatory effects of antifungal agents, may be clinically relevant and therapeutically exploitable. Future research will decide if these new approaches are able to lower morbidity in addition to the new antifungal drugs.

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Compliance with Ethical Standards

Conflict of interest None of the authors has any potential financial or non-financial conflicts of interests related to this manuscript.

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References

1. Pihet M, Carrère J, Cimon B, et al. Occurrence and relevance of filamentous fungi in respiratory secretions of patients with cystic fibrosis-a review. Med Mycol. 2009;47:387–97.
2. Ziesing S, Suerbaum S, Sedlacek L. Fungal epidemiology and diversity in cystic fibrosis patients over a 5-year period in a national reference center. Med Mycol. 2016;54:781–6.
3. Wong R, Wong M, Robinson PD, Fitzgerald DA. Omalizumab in the management of steroid dependent allergic bronchopulmonary aspergillosis (ABPA) complicating cystic fibrosis. Paediatr Respir Rev. 2013;14:22–4.
4. Tanou K, Zintzaras E, Kaditis AG. Omalizumab therapy for allergic bronchopulmonary aspergillosis in children with cystic fibrosis: a synthesis of published evidence. Pediatr Pulmonol. 2014;49:503–7.
5. Nové-Josserand R, Grard S, Auzou L, et al. Case series of omalizumab for allergic bronchopulmonary aspergillosis in cystic fibrosis patients. Pediatr Pulmonol. 2017;52:190–7.
6. Berge M, Guillemain R, Boussaud V, et al. Voriconazole pharmacokinetic variability in cystic fibrosis lung transplant patients. Transplant Infect Dis. 2009;11:211–9.
7. Billaud EM, Guillemain R, Berge M, et al. Pharmacological considerations for azole antifungal drug management in cystic fibrosis lung transplant patients. Med Mycol. 2010;48(Suppl 1):S52–9.
8. Shields RK, Clancy CJ, Vadnerkar A, et al. Posaconazole serum concentrations among cardiothoracic transplant

recipients: factors impacting trough levels and correlation with clinical response to therapy. Antimicrob Agents Chemother. 2011;55:1308–11.
9. Brett J, Chong O, Graham GG, et al. Antifungal use and therapeutic monitoring of plasma concentrations of itraconazole in heart and lung transplantation patients. Ther Drug Monitor. 2013;35:133–6.
10. Elphick HE, Southern KW. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database Syst Rev. 2016;11(4):CD002204.
11. Walsh TJ, Anaissie EJ, Denning DW. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327–60.
12. Singh N, Husain S, AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):228–41.
13. Mousset S, Buchheidt D, Heinz W, et al. Treatment of invasive fungal infections in cancer patients-updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol. 2014;93:13–32.
14. Felton TW, Baxter C, Moore CB, et al. Efficacy and safety of posaconazole for chronic pulmonary aspergillosis. Clin Infect Dis. 2010;51:1383–91.
15. Meis JF, Chowdhary A, Rhodes JL, Fisher MC, Verweij PE. Clinical implications of globally emerging azole resistance in *Aspergillus fumigatus*. Philos Trans R Soc Lond B, Biol Sci. 2016;371(1709). pii: 20150460.
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. Kotloff RM, Thabut G. Lung transplantation. Am J Respir Crit Care Med. 2012;184:159–71.
18. Hirche TO, Knoop C, Hebestreit H, et al. Practical guidelines: lung transplantation in patients with cystic fibrosis. Pulm Med. 2014;2014:621342.
19. Luong ML, Chaparro C, Stephenson A, et al. Pretransplant *Aspergillus* colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis. Transplantation. 2014;97:351–7.
20. Solé A, Morant P, Salavert M, Pemán J, Morales P. Valencia Lung Transplant Group. *Aspergillus* infections in lung transplant recipients: risk factors and outcome. Clin Microbiol Infect. 2005;11:359–65.
21. Iversen M, Burton CM, Vand S, et al. *Aspergillus* infection in lung transplant patients: incidence and prognosis. Eur J Clin Microbiol Infect Dis. 2007;26:879–86.
22. Valenza G, Tappe D, Turnwald D, et al. Prevalence and antimicrobial susceptibility of microorganisms isolated from sputa of patients with cystic fibrosis. J Cyst Fibros. 2008;7:123–7.
23. Muthig M, Hebestreit A, Ziegler U, Seidler M, Müller FMC. Persistence of *Candida* species in the respiratory tract of cystic fibrosis patients. Med Mycol. 2010;48:56–63.
24. Gileles-Hillel A, Shoseyov D, Polacheck I, et al. Association of chronic *Candida albicans* respiratory infection with a more severe lung disease in patients with cystic fibrosis. Pediatr Pulmonol. 2015;50:1082–9.
25. Navarro J, Rainisio M, Harms HK, et al. Factors associated with poor pulmonary function: cross-sectional analysis of data from the ERCF. European epidemiologic registry of cystic fibrosis. Eur Respir J. 2001;18:298–305.
26. Chotirmall SH, Greene CM, McElvaney NG. *Candida* species in cystic fibrosis: a road less travelled. Med Mycol. 2010;48(Suppl 1):S114–24.
27. Hector A, Kirn T, Ralhan A, et al. Microbial colonization and lung function in adolescents with cystic fibrosis. J Cystic Fibros. 2016;15:340–9.
28. Ullmann AJ, Akova M, Herbrecht R, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect. 2012;18(Suppl 7):53–67.
29. Lackner M, de Hoog GS, Yang L, et al. Proposed nomenclature for *Pseudallescheria*, *Scedosporium* and related genera. Fungal Divers. 2014;67:1–10.
30. Symoens F, Knoop C, Schrooyen M, et al. Disseminated *Scedosporium apiospermum* infection in a cystic fibrosis patient after double-lung transplantation. J Heart Lung Transplant. 2006;25:603–7.
31. Blyth CC, Middleton PG, Harun A, et al. 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.
32. Paugam A, Baixench MT, Demazes-Dufeu N, et al. Characteristics and consequences of airway colonization by filamentous fungi in 201 adult patients with cystic fibrosis in France. Med Mycol. 2010;48(Suppl 1):S32–6.
33. 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. J Cyst Fibros. 2015;14:237–41.
34. 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.
35. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *fusarium* spp., *Scedosporium* spp. and others. Clin Microbiol Infect. 2014;20(Suppl 3):27–46.
36. Troke P, Aguirrebengoa K, Arteaga C, et al. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob Agents Chemother. 2008;52:1743–50.
37. Holle J, Leichsenring M, Meissner PE. Nebulized voriconazole in infections with *Scedosporium apiospermum*—case report and review of the literature. J Cyst Fibros. 2014;13:400–2.
38. Schwarz C, Thronicke A, Staab D, Tintelnot K. *Scedosporium apiospermum*: a fungal pathogen causing pneumonia in a patient with cystic fibrosis. JMM Case Rep. 2015;2(3).
39. Padoan R, Poli P, Colombrita D, et al. Acute *Scedosporium apiospermum* endobronchial infection in cystic fibrosis. Pediatr Infect Dis J. 2016;35:701–2.

40. Rolfe NE, Haddad TJ, Wills TS. Management of *Scedosporium apiospermum* in a pre- and post-lung transplant patient with cystic fibrosis. Med Mycol Case Rep. 2013;2:37–9.
41. Solé A. Invasive fungal infections in lung transplantation: role of aerosolised amphotericin B. Int J Antimicrob Agents. 2008;32(Suppl 2):S161–5.
42. Martin-Vicente A, Guarro J, Capilla J. Does a triple combination have better activity than double combinations against multiresistant fungi? Experimental in vitro evaluation. Int J Antimicrob Agents. 2017;49:422–6.
43. Meletiadis J, Mouton JW, Meis JF, Verweij PE. Combination chemotherapy for the treatment of invasive infections by *Scedosporium prolificans*. Clin Microbiol Infect. 2000;6:336–7.
44. Meletiadis J, Mouton JW, Meis JF, Verweij PE. In vitro drug interaction modeling of combinations of azoles with terbinafine against clinical *Scedosporium prolificans* isolates. Antimicrob Agents Chemother. 2003;47:106–17.
45. Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by *Scedosporium* spp. Clin Microbiol Rev. 2008;21:157–97.
46. Gosbell IB, Toumasatos V, Yong J, et al. Cure of orthopaedic infection with *Scedosporium prolificans*, using voriconazole plus terbinafine, without the need for radical surgery. Mycoses. 2003;46:233–6.
47. Howden BP, Slavin MA, Schwarer AP, Mijch AM. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. Eur J Clin Microbiol Infect Dis. 2003;22:111–3.
48. Studahl M, Backteman T, Stålhammar F, Chryssanthou E, Petrini B. Bone and joint infection after traumatic implantation of *Scedosporium prolificans* treated with voriconazole and surgery. Acta Paediatr. 2003;92:980–2.
49. Tong SY, Peleg AY, Yoong J, et al. Breakthrough *Scedosporium prolificans* infection while receiving voriconazole prophylaxis in an allogeneic stem cell transplant recipient. Transpl Infect Dis. 2007;9:241–3.
50. Bhat SV, Paterson DL, Rinaldi MG, Veldkamp PJ. *Scedosporium prolificans* brain abscess in a patient with chronic granulomatous disease: successful combination therapy with voriconazole and terbinafine. Scand J Infect Dis. 2007;39:87–90.
51. Li JY, Yong TY, Grove DI, Coates PT. Successful control of *Scedosporium prolificans* septic arthritis and probable osteomyelitis without radical surgery in a long-term renal transplant recipient. Transpl Infect Dis. 2008;10:63–5.
52. Ananda-Rajah MR, Grigg A, Slavin MA. Breakthrough disseminated *Scedosporium prolificans* infection in a patient with relapsed leukaemia on prolonged voriconazole followed by posaconazole prophylaxis. Mycopathologia. 2008;166:83–6.
53. Uno K, Kasahara K, Kutsuna S, et al. Infective endocarditis and meningitis due to *Scedosporium prolificans* in a renal transplant recipient. J Infect Chemother. 2014;20:131–3.
54. Nishimori M, Takahashi T, Suzuki E, et al. Fatal fungemia with *Scedosporium prolificans* in a patient with acute myeloid leukemia. Med Mycol J. 2014;55:E63–70.
55. Ochi Y, Hiramoto N, Takegawa H, et al. Infective endocarditis caused by *Scedosporium prolificans* infection in a patient with acute myeloid leukemia undergoing induction chemotherapy. Int J Hematol. 2015;101:620–5.
56. Rodríguez MM, Calvo E, Serena C, et al. Effects of double and triple combinations of antifungal drugs in a murine model of disseminated infection by *Scedosporium prolificans*. Antimicrob Agents Chemother. 2009;53:2153–5.
57. Biswas C, Sorrell TC, Djordjevic JT, et al. In vitro activity of miltefosine as a single agent and in combination with voriconazole or posaconazole against uncommon filamentous fungal pathogens. J Antimicrob Chemother. 2013;68:2842–6.
58. Compain F, Botterel F, Sitterlé E, et al. In vitro activity of miltefosine in combination with voriconazole or amphotericin B against clinical isolates of *Scedosporium* spp. J Med Microbiol. 2015;64:309–11.
59. Homa M, Galgóczy L, Tóth E, et al. In vitro antifungal activity of antipsychotic drugs and their combinations with conventional antifungals against *Scedosporium* and *Pseudallescheria* isolates. Med Mycol. 2015;53:890–5.
60. Homa M, Galgóczy L, Tóth E, et al. In vitro susceptibility of *Scedosporium* isolates to *N*-acetyl-L-cysteine alone and in combination with conventional antifungal agents. Med Mycol. 2016;54:776–9.
61. Haase G, Skopnik H, Kusenbach G. *Exophiala dermatitidis* infection in cystic fibrosis. Lancet. 1990;336(8708):188–9.
62. Bakare N, Rickerts V, Bargon J, Just-Nübling G. Prevalence of *Aspergillus fumigatus* and other fungal species in the sputum of adult patients with cystic fibrosis. Mycoses. 2003;46:19–23.
63. Lebecque P, Leonard A, Huang D, et al. *Exophiala* (*Wangiella*) *dermatitidis* and cystic fibrosis—prevalence and risk factors. Med Mycol. 2010;48(Suppl 1):S4–9.
64. Kondori N, Lindblad A, Welinder-Olsson C, Wenneras C, Gilljam M. Development of IgG antibodies to *Exophiala dermatitidis* is associated with inflammatory responses in patients with cystic fibrosis. J Cyst Fibros. 2014;13:391–9.
65. Sudhadham M, Prakitsin S, Sivichai S, et al. The neurotropic black yeast *Exophiala dermatitidis* has a possible origin in the tropical rain forest. Stud Mycol. 2008;61:145–55.
66. Matos T, de Hoog GS, de Boer AG, de Crom I, Haase G. High prevalence of the neurotrope *Exophiala dermatitidis* and related oligotrophic black yeasts in sauna facilities. Mycoses. 2002;45:373–7.
67. Zalar P, Novak M, de Hoog GS, Gunde-Cimerman N. Dishwashers—a man-made ecological niche accommodating human opportunistic fungal pathogens. Fungal Biol. 2011;115:997–1007.
68. Kusenbach G, Skopnik H, Haase G, Friedrichs F, Dohmen H. *Exophiala dermatitidis* pneumonia in cystic fibrosis. Eur J Pediatr. 1992;151:344–6.
69. Kirchhoff L, Olsowski M, Zilmans K, et al. Biofilm formation of the black yeast-like fungus *Exophiala dermatitidis* and its susceptibility to antiinfective agents. Sci Rep. 2017;7:42886.
70. Colombo AL, Padovan ACB, Chaves GM. Current knowledge of *Trichosporon* spp. and Trichosporonosis. Clin Microbiol Rev. 2011;24:682–700.
71. Hickey PW, Sutton DA, Fothergill AW, et al. *Trichosporon mycotoxinivorans*, a novel respiratory pathogen in patients with cystic fibrosis. J Clin Microbiol. 2009;47:3091–7.

72. Walsh T. *Trichosporon beigelii*, an emerging pathogen resistant to amphotericin B. J Clin Microbiol. 1990;28:1616–22.
73. Anaissie E, Gokaslan A, Hachem R, et al. Azole therapy for trichosporonosis: clinical evaluation of eight patients, experimental therapy for murine infection, and review. Clin Infect Dis. 1992;15:781–7.
74. Erer B, Galimberti M, Lucarelli G, et al. *Trichosporon beigelii*: a life-threatening pathogen in immunocompromised hosts. Bone Marrow Transplant. 2000;25:745–9.
75. Antachopoulos C, Papakonstantinou E, Dotis J, et al. Fungemia due to *Trichosporon asahii* in a neutropenic child refractory to amphotericin B. J Pediatr Hematol Oncol. 2005;27:283–5.
76. Girmenia C, Pagano L, Martino B, et al. Invasive infections caused by *Trichosporon* species and *Geotrichum capitatum* in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature. J Clin Microbiol. 2005;43:1818–28.
77. Shah AV, McColley SA, Weil D, Zheng X. *Trichosporon mycotoxinivorans* infection in patients with cystic fibrosis. J Clin Microbiol. 2014;52:2242–4.
78. Kröner C, Kappler M, Grimmelt AC, et al. The basidiomycetous yeast *Trichosporon* may cause severe lung exacerbation in cystic fibrosis patients—clinical analysis of *Trichosporon* positive patients in a Munich cohort. BMC Pulm Med. 2013;13:61.
79. Rieger C, Geiger S, Herold T, Nickenig C, Ostermann H. Breakthrough infection of *Trichosporon asahii* during posaconazole treatment in a patient with acute myeloid leukaemia. Eur J Clin Microbiol Infect Dis. 2007;26:843–5.
80. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009;53:24–34.
81. Leclair LW, Hogan DA. Mixed bacterial-fungal infections in the CF respiratory tract. Med Mycol. 2010;48(Suppl 1):S125–32.
82. Montagna M, Barbuti G, Paglionico F, et al. Retrospective analysis of microorganisms isolated from cystic fibrosis patients in Southern Italy, 2002–2010. J Prev Med Hyg. 2011;52:209–14.
83. Nagano Y, Elborn JS, Millar BC, et al. Comparison of techniques to examine the diversity of fungi in adult patients with cystic fibrosis. Med Mycol. 2010;48(166–76):e1.
84. Masoud-Landgraf L, Badura A, Eber E, et al. Modified culture method detects a high diversity of fungal species in cystic fibrosis patients. Med Mycol. 2013;52:1–8.
85. Jensen RH. Resistance in human pathogenic yeasts and filamentous fungi: prevalence, underlying molecular mechanisms and link to the use of antifungals in humans and the environment. Dan Med J. 2016;63(10). pii: B5288.
86. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2006;174:566–70.
87. Jubin V, Ranque S, Stremler Le bel N, Sarles J, Dubus JC. Risk factors for *Aspergillus* colonization and allergic bronchopulmonary aspergillosis in children with cystic fibrosis. Pediatr Pulmonol. 2010;45:764–71.
88. Peckham D, Williams K, Wynne S, et al. Fungal contamination of nebuliser devices used by people with cystic fibrosis. J Cyst Fibros. 2016;15:74–7.
89. Schwarz C, Brandt C, Antweiler E, et al. Prospective multicenter German study on pulmonary colonization with *Scedosporium/Lomentospora* species in cystic fibrosis: epidemiology and new association factors. PLoS ONE. 2017;12(2):e0171485.
90. Drew RH, Townsend ML, Pound MW, Johnson SW, Perfect JR. Recent advances in the treatment of life-threatening, invasive fungal infections. Expert Opin Pharmacother. 2013;14:2361–74.
91. Wiederhold NP, Patterson TF. What's new in antifungals: an update on the in vitro activity and in vivo efficacy of new and investigational antifungal agents. Curr Opin Infect Dis. 2015;28:539–45.
92. Miyazaki M, Horii T, Hata K, et al. In vitro activity of E1210, a novel antifungal, against clinically important yeasts and molds. Antimicrob Agents Chemother. 2011;55:4652–8.
93. Shibata T, Takahashi T, Yamada E, et al. T-2307 causes collapse of mitochondrial membrane potential in yeast. Antimicrob Agents Chemother. 2012;56:5892–7.
94. Karwa R, Wargo KA. Efungumab: a novel agent in the treatment of invasive candidiasis. Ann Pharmacother. 2009;43:1818–23.
95. Mancini N, Marrone L, Clementi N, et al. Adoptive T-cell therapy in the treatment of viral and opportunistic fungal infections. Future Microbiol. 2015;10:665–82.
96. Zumla A, Memish ZA, Maeurer M, et al. Emerging novel and antimicrobial-resistant respiratory tract infections: new drug development and therapeutic options. Lancet Infect Dis. 2014;14:1136–49.
97. Gottardi W, Debabov D, Nagl M. N-chloramines, a promising class of well-tolerated topical anti-infectives. Antimicrob Agents Chemother. 2013;57:1107–14.
98. Ammann CG, Fille M, Hausdorfer J, et al. Influence of poly-N-acetylglucosamine in the extracellular matrix on N-chlorotaurine mediated killing of *Staphylococcus epidermidis*. New Microbiol. 2014;37:383–6.
99. Coraça-Huber DC, Ammann CG, Fille M, et al. Bactericidal activity of N-chlorotaurine against biofilm-forming bacteria grown on metal disks. Antimicrob Agents Chemother. 2014;58:2235–9.
100. Gottardi W, Klotz S, Nagl M. Superior bactericidal activity of N-bromine compounds compared to their N-chlorine analogues can be reversed under protein load. J Appl Microbiol. 2014;116:1427–37.
101. Arnitz R, Nagl M, Gottardi W. Comparison of the microbicidal activity of monochloramine and iodine. Lett Appl Microbiol. 2015;61:518–22.
102. Lackner M, Binder U, Reindl M, et al. N-Chlorotaurine exhibits fungicidal activity against therapy-refractory *Scedosporium* species and *Lomentospora prolificans*. Antimicrob Agents Chemother. 2015;59:6454–62.
103. Gruber M, Moser I, Nagl M, Lackner M. Bactericidal and fungicidal activity of N-chlorotaurine is enhanced in cystic fibrosis sputum medium. Antimicrob Agents Chemother. 2017;61. pii: e02527–16.