Clinical Management of Fungal Biofilm Infections

Gordon Ramage, Bryn Short, Emily McKloud, Om Alkhir Alshanta, Mark Butcher, William McLean, and Jason L. Brown

Abstract Fungal biofilms are highly resilient to antifungal therapies, of which there are relatively few licensed options available in clinical medicine. Nonetheless, there is a vibrant research culture aimed at enhancing and expanding the arsenal of antifungals capable of inhibiting, killing, and disrupting fungal biofilms. This chapter aims to explore the wide variety of fungal biofilms affecting human health and to discuss the clinical options for existing and novel chemotherapeutics.

1 Introduction

Fungal biofilms have gained notoriety over the past two decades, with studies and reviews of *Candida* biofilms alone amassing approximately 4000 publications. Whilst relatively slower to generate general interest within the biofilm community, it is increasingly clear that they are a clinically challenging issue due to the difficulties in treating these infections (Ramage et al. 2009). Microbiologically, fungi are amongst the most important clinical infections, globally accounting for 300 million infections, and mortality rates of up to 50% in some diseases (Brown et al. 2012). Many of these fungal infections predominantly affect immunocompromised individuals and may be impacted by a diverse range of risk factors (Table 1), which can result in a wide range of fungal infections (Table 2). Management of these patient groups, or lack thereof, is exacerbated by a limited arsenal of antifungal agents capable of killing or disrupting these tenacious structures.

So, what antifungals are commonly used to manage fungal infections, and how do they fare against biofilms? Classically, azole antifungals are the mainstay of treatment for many pathogenic fungi, albeit with a few exceptions; e.g. *C. glabrata* and

G. Ramage (✉) · B. Short · E. McKloud · O. A. Alshanta · M. Butcher · W. McLean · J. L. Brown
Glasgow Biofilm Research Network, Oral Sciences Research Group, School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK
e-mail: gordon.ramage@glasgow.ac.uk

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Table 1 Predisposing factors for fungal infections

Systemic	Local
Human immunodeficiency virus (HIV)	Dentures
Broad-spectrum antibiotic treatment	Xerostomia
Cancers	Indwelling prosthetic devises
Immunosuppressive therapy or condition, e.g. organ transplant	Burns
Hyperglycemia	Trauma
Cytotoxic chemotherapy	Vaginal douching
Radiotherapy	Contraceptive pills
Nutrition, e.g. iron, folate, and vitamin C, B, A	
Infections such as tuberculosis	
Chronic renal failure	
Pregnancy	
Impaired liver function	
Genetic susceptibility	

C. krusei are intrinsically insensitive. Azoles function as fungistatic antimicrobials, targeting ergosterol biosynthesis. Specifically, they act upon the 14-lanosterol demethylase enzyme pathway, which results in depletion of ergosterol molecules in the cell membrane, and at the same time an accumulation of sterol precursors, such as 14-alpha methylase (Pristov and Ghannoum 2019). This leads to membrane instability of growing cells and a static impact on fungal growth. The triazoles are the most widely used azoles, which are heterocyclic compounds that include fluconazole, itraconazole, and voriconazole, amongst some others. These are not without their problems though, as resistance is common through alterations in the ergosterol biosynthesis pathway, upregulated efflux pumps, activation of heat shock proteins, and of course biofilm-mediated tolerance.

Polyenes, such as amphotericin B (AMB), nystatin, and their liposomal formulations, offer a fungicidal option. These antifungal drugs are thought to insert into the lipid membrane adjacent to ergosterol, which in turn destabilises the cell membrane by forming pores and enabling cellular lysis (Carolus et al. 2020). Moreover, oxidative stress induction is also thought to additionally contribute to its effectiveness as a fungicidal agent. Resistance is rare due to its membrane-based target, but in some cases alterations to sterols and anti-oxidative stress mechanisms can protect the cell. Cell wall changes in the form of enhanced 1,3-alpha- and 1,3-beta-glucans have also been shown to correlate with AMB resistance.

Echinocandins, which include caspofungin, micafungin, and anidulafungin, act by inhibiting 1,3-beta-glucan synthase, which results in cell wall destabilisation and fungicidal activity. They can be considered analogous to penicillin interfering with peptidoglycan in bacteria. They have a wide spectrum of activity, though are limited against septate fungi such as A*spergillus fumigatus*, as they require actively growing cells to be fungicidal. Notably, these compounds are effective, albeit paradoxically, against *Candida albicans* biofilms (Pristov and Ghannoum 2019). Nevertheless, as a

Table 2 Clinical manifestations of fungal infections. A non-exhaustive overview of the most associated fungal pathogens, their predominant affected sites, and alternative names for several clinically relevant fungal infections

Clinical manifestation	Alias	Affected site	Common pathogen
Seborrheic dermatitis	Dandruff	Scalp, hair follicles	*Malassezia* species (Grimshaw et al. 2019)
Dermatophytosis	Ringworm	Skin (Scalp)	*Trichophyton rubrum* (Wang et al. 2006)
Fungal Meningitis	None	CSF/Brain	*Cryptococcus neoformans* (Charalambous et al. 2018)
Mycotic keratitis	Corneal inflammation	Eye	*Candida albicans* or filamentous *Fusarium solani* and *Aspergillus* spp. (Thomas and Kaliamurthy 2013)
Endophthalmitis	Intraocular inflammation	Eye	*Candida albicans* (Regan et al. 2020)
Otomycosis	Ear infection	Ear	*Candida* species and *Aspergillus niger* (Anwar and Gohar 2014)
Fungal sinusitis	Rhinosinusitis	Mucosa/ paranasal sinuses	*Aspergillus fumigatus* (Chakrabarti et al. 2009)
Angular cheilitis	Lip disease	Exterior corners of mouth	*Candida albicans* (Lugovic-Mihic et al. 2018)
Oral candidiasis	Oral thrush	Interior mouth mucosa/ submucosa	*Candida albicans* (Singh et al. 2014)
Onychomycosis	Nail infection	Nail bed	*Trichophyton rubrum* (Ghannoum and Isham 2014)
Vulvovaginal candidiasis	Yeast infection	Vagina/Vulva	*Candida albicans* (McKloud et al. 2021)
Blastomycosis	Gilchrist's/ Chicago disease	Lungs	*Blastomyces dermatitidis* (McBride et al. 2017)
Aspergillosis	Brooder's pneumonia	Bronchioles	*Aspergillus* species (Sherif and Segal 2010)
Mycetoma	Madura foot	Skin/subcutaneous tissue	*Madurella mycetomatis* (Emmanuel et al. 2018)
Fungal septicaemia	Bloodstream infection	Systemic	*Candida albicans* (Delaloye and Calandra 2014)

second option for azole-insensitive yeasts and moulds, their rise in use has led to echinocandin resistance through alteration of the glucan synthase enzymes (Fks1-Fks2 complex), changes in chitin composition, and stimulation of stress pathways.

Other antifungals do exist, but these are used more infrequently. This emphasises why there is a need to improve our pipeline of antifungal drugs (Perfect 2017). These are taking the form of oral formulations, nanoparticles, pathway inhibitors, and augmentative strategies. This chapter outlines how conventional and novel

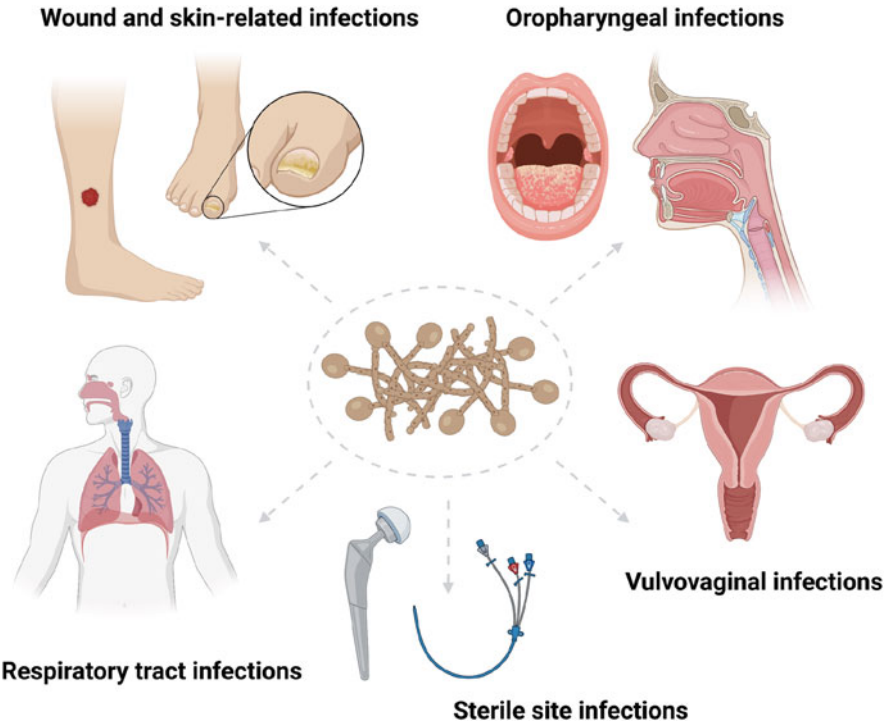

Fig. 1 Examples of sources of fungal biofilms on the human body (images produced in BioRender [biorender.com])

antifungals are being used for consideration in the management of different diseases associated with fungal biofilms, as illustrated in Fig. 1.

2 Oropharyngeal Infections

Fungal infections of the oral cavity are mainly opportunistic in nature due to host immunity impairment, which is a result of local, or more importantly, systemic factors. The frequency of these infections is increasing globally due to rise in the use of immunosuppressive drugs, broad-spectrum antibiotics, malignancies, diabetes, human immunodeficiency virus (HIV), and increased life expectancy (Richardson and Lass-Flörl 2008). Importantly, within the oral cavity these fungal species have the capacity to co-aggregate with microbial species in the form of biofilms on biological and inert substrates, or as aggregates within saliva. This has a profound effect on our ability to manage these infections with antifungal agents.

Oral fungal infections, or "oral mycoses", are broadly categorised as candidal and non-candidal fungal infections, or as superficial and deep mycoses (Santosh et al.

2021). Oral candidiasis (candidosis) is the most frequently reported oral fungal infection. This form of superficial mycoses is a result of the overgrowth of *Candida* species, mainly *Candida albicans.* Other non-*albicans* species, *Candida parapsilosis, Candida krusei, Candida stellatoidea, Candida tropicalis, Candida glabrata, Candida guilliermondii,* and *Candida dubliniensis*, have also contributed to oral candidiasis to a lesser extent. The diagnosis of oral candidiasis is usually based on the cytological/histopathological examinations and clinical presentation of the infection (Rautemaa and Ramage 2011). As *C. albicans* is a natural habitant of the oral microbiome in the majority of healthy individuals, oral samples with a positive culture for *Candida* species with absence of clinical manifestation are diagnostically inconclusive. Non-candidal oral mycoses (deep mycoses) are less common, and most infections are exotic with specific geographic distribution (Iatta et al. 2009). These infections are usually deep mycoses of other body areas other than the oral cavity, mainly pulmonary infections, which present with oral manifestations as an indication of systemic and disseminated condition. However, isolated oral lesions without systemic involvement are also reported (Scully 1913). Examples of oral non-candida infections are aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, zygomycosis, mucormycosis, geotrichosis, and rhinosporidiosis (Williams and Ramage 2015)

Dental caries and periodontal diseases are amongst the most prevalent chronic diseases in humans, and both are biofilm related (Casamassimo et al. 2009; Nazir et al. 2020). Whilst the role of bacteria in such conditions is well recognised, the role of fungi is largely unknown or unexplored due to the bias towards bacterial biofilm communities. There is growing evidence that fungi have a significant influence on oral microbiome composition and pathogenicity (Delaney et al. 2018). Clearly, interkingdom interactions play a critical role in promoting tolerance to biocides and antifungals through their extra-polymeric substrates acting like "drug sponges" (Kim et al. 2018). High levels of *Candida* species were shown to be found in children with caries (Raja et al. 2010). Though, there is limited evidence for its direct association with dental caries (Sridhar et al. 2020). Indeed, it was recently shown that *C. albicans* was not more abundant in children with caries, although those children showed less fungal abundance and diversity compared with caries-free children (Fechney et al. 2019). Likewise, higher fungal abundance was reported in patients with periodontal diseases compared with healthy individuals and shown to be associated with disease severity (Canabarro et al. 2013; Urzúa et al. 2008; Peters et al. 2017). Indeed, a recent systematic review from 21 available studies showed a positive association between periodontal disease and *Candida* species (Suresh Unniachan et al. 2020). Again, it is unclear whether this higher abundance has a direct role in disease causation, or it is simply a consequence of bacterial dysbiosis and environmental change that favours fungal growth. There is a significant growth of studies investigating synergism and antagonism amongst these interkingdom diseases to define the importance of *Candida* in the oral cavity (Delaney et al. 2018), so the increasing use of newer molecular tools begins to define a clearer idea of the role that fungi play in these seemingly bacterial centric infections. The advent of mycobiome research has helped, but also hindered our

progress of understanding. The first ever mycobiome study by Ghannoum (2010) and colleagues reported over 101 separate species from 21 individuals, though whether these fungi play defined roles remains to be ascertained (Ghannoum et al. 2010). The same authors contend that changes to the basal mycobiome can be observed in patients admitted to intensive care units (ICU) (Watkins et al. 2017).

The traditional clinical management of oral fungal infections involves the use of topical and systemic antifungals. In oropharyngeal candidiasis, identification and removal of local and systemic predisposing factors is paramount if feasible. Oral candidiasis is usually successfully managed with topical azoles and polyenes in the form of oral suspensions, lozenges, gels, creams, and ointment. Nystatin is usually effective for treatment of oral candidiasis. Amphotericin and miconazole can also be used, both of which elicit positive fungicidal effects (Farah et al. 2010). Refractory and recurrent infections usually require the use of systemic antifungals such as ketoconazole, fluconazole, and itraconazole and amphotericin in conjunction with topical agents to control the infection (Epstein and Polsky 1998). Despite treatment with antifungal, recurrence of oral candidiasis is not uncommon (Rautemaa and Ramage 2011). Recurrent infection can be due to incorrect diagnosis, inability to identify or treat underlying factors or inappropriate drug selection, or simply that the infection is biofilm-based and therefore intrinsically tolerant (Darwazeh and Darwazeh 2014). Systemic antifungals are mainly used for the treatment of deep mycoses, and drug selection depends on the severity of the infection and may require surgical debridement of necrotic tissue in some infections such mucormycosis and invasive aspergillosis. Amphotericin B, caspofungin, voriconazole, itraconazole, miconazole, ketoconazole, and fluconazole are the most commonly used systemic agents for deep fungal infections (Santosh et al. 2021).

Given that the currently available antifungal agents have many limitations, mainly drug resistance and cytotoxicity, efforts have been directed towards discovering novel antifungals. Repurposing drugs that have been previously approved for human use, plant derivatives and high-throughput screening are an appealing approach. Many anticancer, antimalarial, and antibacterial compounds have shown antifungal activity either alone or in combination with classical antifungals with less potential to develop drug resistance. However, most novel compounds are not translated into clinical trials for many reasons, mainly cost and lack of sufficient evidence. Antifungal resistance is a serious concern with classical antifungal especially with azoles. Therefore, drug combination was proposed to overcome drug resistance. With β-1,3-D-glucan of fungi being an ideal drug target, combining drugs that act on this essential cell wall component will potentially help in resolving antifungal resistance. MK-3118 (SCY-078) is a semisynthetic potent β-1,3-D-glucan synthases inhibitor. It showed a powerful *in vitro* effect on wild-type and resistant strains of *Aspergillus* species (Pfaller et al. 2013). It was also effective against *C. albicans*, C. *parapsilosis,* and *C. tropicalis* (Scorneaux et al. 2017). MK-3118 was also tested in a murine model of invasive candidiasis, and its effect was similar to that of intravenous echinocandin (Lepak et al. 2015).

3 Respiratory Tract Infections

Typically, fungi in the respiratory tract are often thought of as an innocent by-stander, but there are increasing amounts of evidence suggesting they play a major role in respiratory biofilm-associated diseases such as cystic fibrosis (CF), bronchiectasis, and chronic obstructive pulmonary disease (COPD) (Pendleton et al. 2017; Garczewska et al. 2016). However, as for fungal biofilms, our understanding of their role in COPD and bronchiectasis is in its infancy.

CF is an autosomal recessive condition, and although it is a multi-organ disease, mortality is most often determined by excess mucus production plugging the airways, chronic inflammation, and infection (Mall and Hartl 2014). Bacteria remain the most common causative agent of CF infections, but the isolation of fungi is becoming more common (Delfino et al. 2019). Lower respiratory tract infections of the CF lung are often associated with biofilms due to a decrease in volumes of periciliary fluid and diminished mucus detachment (Singh et al. 2000; Høiby et al. 2010). Indeed, there are reliable studies reporting the importance of fungal cells as a critical component of these biofilm aggregates (Mowat et al. 2007; Muller et al. 2011).

The loss of this innate clearance mechanism in the airways provides prime conditions for long-term colonisation. Spores formed by *Aspergillus,* one of the most abundant fungal species found throughout the environment (Paulussen et al. 2017), are readily inhaled, with *Aspergillus fumigatus* being the most common species identified in sputum cultures (Sabino et al. 2015). We were the first to demonstrate the biofilm forming capacity of this organism (Mowat et al. 2007), which has been followed up and expanded upon by us and others (Boisvert et al. 2016; Ramage et al. 2011). However, many CF airway infections are polymicrobial where microbe–microbe interactions can influence patient outcome. *Pseudomonas aeruginosa* is the most frequently isolated bacterial pathogen from CF sputum (Williams and Davies 2012). In vitro, *A. fumigatus* and *P. aeruginosa* exhibit a mutually antagonistic relationship (Reece et al. 2018; Shirazi et al. 2016). However, *in vivo* co-isolation of these organisms is associated with poorer patient outcomes, which may be explained by an increase in *P. aeruginosa* elastase production in the presence of *A. fumigatus* (Reece et al. 2017; Smith et al. 2015).

In cases where *A. fumigatus* colonises CF patients, the most commonly prescribed antifungals are triazoles such as voriconazole and itraconazole (Boyle et al. 2019). The consensus regarding the efficacy of azoles in CF is obscured with several smaller, non-controlled, open-label studies reporting a beneficial role for azole treatments (Hilliard et al. 2005; Shoseyov et al. 2006; Coughlan et al. 2012), whereas the only published randomised control trial (RCT) study investigating the efficacy of azoles in CF therapy reported no significant benefit in patients who were chronically colonised by *A. fumigatus* (Aaron et al. 2012). The chronic colonisation and ineffectiveness of azole interventions in this RCT points towards the presence of fungal biofilms which display high levels of azole resistance (Rajendran et al. 2011).

Aspergillus is not the only fungal species identified from the lungs of CF patients. *Candida albicans* is the most commonly isolated yeast and can be isolated from up to 75% of patients (Williams et al. 2016). As with *A. fumigatus,* co-isolation of *C. albicans* and *P. aeruginosa* from the same patient is associated with worse clinical outcomes (Dhamgaye et al. 2016). *P. aeruginosa* within these dual-species biofilms has displayed increased tolerance to meropenem when compared to a mono-species biofilm (Alam et al. 2020). This has been attributed to fungal mannans and glucans within the extracellular matrix of the biofilm. This trend of *C. albicans* protecting bacteria within a biofilm has been observed with other bacteria such as *Staphylococcus aureus,* another commonly found bacteria in CF, through production of ECM components such as glucans and extracellular DNA (Kean et al. 2017; Harriott and Noverr 2009; Kong et al. 2016).

Unlike *A. fumigatus,* there is some controversy surrounding the treatment of *C. albicans* in the airways due to clouded lines distinguishing colonisation and active infection (Pendleton et al. 2017). However, several studies have identified an association between *Candida* colonisation and worsening FEV1 in CF patients (Gileles-Hillel et al. 2015; Dhamgaye et al. 2016; Williams et al. 2016). Although *C. albicans* may not be actively causing infection, its interactions with certain bacteria indicate an indirect role in disease through protecting pathogenic bacteria and increasing their virulence (Dhamgaye et al. 2016; Kean et al. 2017; Todd et al. 2019). This raises the question: should *Candida* colonisation be addressed in order to improve patient outcomes? Although there is not a generally accepted treatment option for *C. albicans* in CF, azoles will likely prove to be ineffective due to high levels of azole tolerance in *C. albicans* biofilms, and the ease in which the organism develops resistance (El-Azizi et al. 2015; Kean et al. 2017; Rajendran et al. 2016b). Therefore, the use of echinocandins or polyenes may yield more promising clinical outcomes, particularly if nebulised to enhance delivery (Liao and Lam 2021).

Although things may appear bleak concerning our current ability to treat fungal and interkingdom biofilms in CF, there are novel drugs that show promising results. For example, a recent study by Miesel and colleagues reported on the efficacy of rezafungin, an echinocandin for use in respiratory therapy (Miesel et al. 2021). Their findings showed that prophylactic rezafungin of 10 and 20mg/kg resulted in 100% survival of mice who were subsequently challenged with *A. fumigatus.* Rezafungin has also shown promising effects against *Candida* and *Pneumocystis* (Miesel et al. 2021). Other studies have aimed to identify novel therapeutics or repurpose old ones that can be recruited in the fight against fungal biofilms. One 2016 study aimed to identify compounds with anti-*Candida* activities (Vila and Lopez-Ribot 2017), which identified several compounds that were capable of inhibiting *C. albicans* biofilm formation by more than 50%. However, only one was effective against pre-formed biofilms (MMV688768).

Currently, there are a few other potential agents with antifungal activities in preclinical stages, one of which is aureobasidin A. Although it was discovered in 1989, more recently it has shown promise as an agent to inhibit inositol phosphorylceramide synthase, an enzyme involved in sphingolipid synthesis, with activity against both planktonic and biofilm *Candida* species (Tan and Tay 2013). An

alternative compound whose exact mechanism of action remains unknown but causes mitochondrial membrane collapse is T-2307. T-2307 is a novel arylamidine that has been tested against a panel of relevant fungi such as *Aspergillus, Candida*, and *Cryptococcus* species and was more effective than fluconazole, micafungin, and amphotericin B (Yamashita et al. 2019; Mitsuyama et al. 2008). At the time of writing, T-2307 is in phase 1 clinical trials and no clinical efficacy data are available.

4 Vulvovaginal Infections

It is estimated that up to three-quarters of women will suffer from at least one episode of vulvovaginal candidiasis (VVC) during their child-bearing years (Sobel 1992). Up to 8% of these women are expected to develop recurrent VVC (RVVC) (Sobel et al. 1998), defined as three or more episodes within one year (Sobel 2016). Although not associated with mortality, the symptoms of RVVC are debilitating, impact quality of life, and can result in psychological implications (Yano et al. 2019). *C. albicans* is reported as the causative organism in up to 90% of VVC episodes (Sobel et al. 1998). Uncomplicated (sporadic) VVC is associated with mild symptoms caused by *C. albicans* and can be treated with a single dose of oral or topical fluconazole in 80% of cases (Dovnik et al. 2015; Pappas et al. 2009). Fluconazole has remained the frontline treatment for VVC owing to its high cure rates and availability at clinics as well as over the counter. It is unclear whether any azole is more effective and whether oral or topical agents can impact clinical outcome (Dharmik et al. 2013; Whaley et al. 2016).

Treatment for complicated VVC (RVVC) requires prolonged maintenance azole therapies which are often unsuccessful. Fluconazole treatments are ineffective against *C. albicans* biofilms, suggesting their formation could contribute to failed clinical treatment. Treatment for RVVC caused by azole-resistant *C. glabrata* involves daily treatment with boric acid or nystatin pessaries for 14 days (Sobel et al. 2003; Fan et al. 2015). Alternative treatments include topical 17% flucytosine administered alone or in combination with 3% amphotericin B, daily for 14 days (Phillips 2005). Failed treatment of RVVC is suppressed with 10–14-day maintenance therapy using topical or oral fluconazole followed by a weekly dose of fluconazole for the next 6 months (Donders et al. 2008). Although suppressive therapies are often sufficient to relieve symptoms and recurrence during treatment, RVVC remains uncured and subsequently patients are prescribed these treatments for years (Sobel et al. 2004). Long-term use of azoles can drive antifungal resistance in *Candida*; however, if treatment options remain limited for women with persistent RVVC, this is inevitable.

The presence of *Candida* biofilms on vaginal mucosa during VVC is an area of controversy. Some authors dispute the presence of these biofilms, suggesting VVC is a result of polymicrobial invasion of vaginal tissues (Swidsinski et al. 2019; Sobel 2015). Conversely, *C. albicans* biofilm formation on vaginal mucosa in a murine model of VVC has been visualised using confocal and electron microscopy (Harriott

et al. 2010). At present, there are no large-scale studies which aim to visualise *Candida* biofilm formation on mucosa from vaginal biopsies from women with VVC/RVVC, such as those carried out to investigate biofilm formation of *Gardnerella vaginalis* in bacterial vaginosis (Machado et al. 2015). Further, there are no characterised biofilm models representative of the vaginal environment during VVC to study potential *Candida* biofilm formation. Studies such as these would provide important knowledge of pathogenesis and resistance of RVVC which could improve future diagnosis and improve clinical treatment.

A novel potential avenue for the treatment of RVVC in the presence or absence of biofilms is the novel drug, ibrexafungerp (Ghannoum et al. 2019). It is the first of a new class of triterpenoid glucan synthase inhibitor antifungals. Orally administered ibrexafungerp has been shown to destabilise the fungal cell wall through the reduction of (1,3)-β-D-glucan polymers. This novel drug has shown efficacy against a range of *Candida* species, including azole and echinocandin-resistant isolates (Jimenez-Ortigosa et al. 2017). Importantly, it has been shown to inhibit *C. albicans* and *C. glabrata* biofilms *in vitro*, displaying lower MICs than fluconazole (Marcos-Zambrano et al. 2017). The recent FDA approval of ibrexafungerp and its broad range of activity against *Candida* species mean it could be used for the treatment of RVVC soon. Additionally, it displayed tolerability and low toxicity in phase 1 and 2 clinical trials (Akizawa et al. 2018). Although the presence of biofilms may not be universally accepted or currently diagnosed in RVVC, this drug could provide an exciting alternative treatment for women with azole-resistant, potential biofilm-associated VVC/RVVC. Moreover, topical echinocandin CD101 has also displayed significant promise against azole-resistant fungal species in the context of RVVC (Boikov et al. 2017). There is now even scope for consideration of probiotics for the management of RVVC (Pendharkar et al. 2015; Vladareanu et al. 2018).

5 Wound and Skin-Related Infections

There has been a growing recognition that complex biofilm communities of the mucosa and skin contain cross-kingdom biofilm communities of fungi and bacteria (Dowd et al. 2011; Kalan and Grice 2018; Kalan et al. 2016). Intriguingly, these relationships elicit reciprocal antimicrobial tolerance (Kong et al. 2016), meaning that we need to carefully consider and target fungi within complex infections until we more fully understand the consequences of broad-spectrum antimicrobial therapies. Regarding the local fungal microbiota, a publication by Oh et al. (2014) investigated the biogeography of the human skin, suggesting that the mycobiome consists of $<10\%$ of the total microbial population (Oh et al. 2014). The authors demonstrated that such multi-kingdom diversity is strongly shaped by the local skin microenvironment, with levels of fungal organisms varying from site to site. *Malassezia* species have been identified as the most prevalent fungal species at the skin barrier (Findley et al. 2013; Oh et al. 2014), comprising of up to 80% of the total skin population (Gao et al. 2010). Such organisms are also well represented within

chronic wounds, alongside several opportunistic fungal pathogens such as *Trichosporon*, *Rhodotorula*, *Candida,* and *Cladosporidium* species (Chellan et al. 2010; Dowd et al. 2011; Kalan and Grice 2018). Alongside the common knowledge that bacterial accumulation in the infected wound can interfere with sufficient healing and repair, it is clear from the above studies that polymicrobial biofilm formation in the wound bed needs careful consideration during clinical management of chronic wounds such as diabetic foot ulcers (DFUs).

For most infected wounds, physical debridement of the tissue is recommended which largely results in removal of the biofilm and appropriate dressing of the infected area. Empirical antibiotic therapy is then often utilised as the first-line treatment for patients, to primarily target a wide range of Gram-positive cocci, including *Staphylococcus* species such as *S. aureus* which is often the most common pathogen in infected wounds (Lipsky et al. 2016b). However, as outlined by guidance published by the International Working Group on the Diabetic Foot (IWGDF), initial treatment is often administered based on "likely or proven causative pathogens", which can obviously be problematic to determine in polymicrobial infections (Lipsky et al. 2016a). Nevertheless, depending on severity, in antibiotic naïve patients, early therapy for mild infections often consists of flucloxacillin treatment and used in combination with metronidazole for more moderate to severe infections, whilst ciprofloxacin use is recommended in severe cases particularly when DFUs are accompanied by osteomyelitis (Barwell et al. 2017). Follow-up definitive therapies may be required based on culture and susceptibility results, and the patients' response to the empirical therapy (Lipsky et al. 2016b). At this juncture, it is important to note that antifungal therapeutics are not commonly recommended for DFU and other related chronic wound therapy.

With other skin infections, antifungal treatments are only utilised for nail infections such as onychomycosis, tinea pedis (athlete's foot), and tinea corporis (ringworm), whereby the sole causative agent is fungi. For example, in onychomycosis, dermatophytes such as *Trichophyton* species can account for almost 90% of all cases (Thomas et al. 2010). Typical onychomycosis or tinea-related antifungal therapy includes oral administration of terbinafine, with azoles such as itraconazole as the first line of treatment, with fluconazole used in some cases as an alternative therapy (Thomas et al. 2010; Hay 2018). For such infections, early management involves application of topical ointments, which can contain a range of antifungals, including azoles (Kawa et al. 2019). Common disinfectants and antiseptics such as chlorhexidine and povidone iodine have also been used to treat cases of onychomycosis (Capriotti and Capriotti 2015; Silva-Neves et al. 2021), whilst such treatments are also commonplace in wound care to prevent regrowth of the microbial population (Atiyeh et al. 2009). However, careful consideration for use of such antiseptics is required given concerns over their cytotoxic effects to the host, affecting wound healing and skin regeneration.

As discussed above, although antifungal therapies are uncommon for infected wounds, they have been shown to be effective in a small number of clinical studies and *in vitro* model systems. For example, a study by Heald et al. (2001) demonstrated that antifungal treatment (a mixture of flucytosine, fluconazole, itraconazole,

and terbinafine) resulted in an improvement in wound healing in 17 DFU patients who were non-responsive to antibacterial therapy (Heald et al. 2001). Similar results were demonstrated elsewhere, where diabetic foot wounds in 38 patients given standard care alongside oral administration of fluconazole healed faster than those that received standard care alone (Chellan et al. 2012). Moving forward, research into biomaterials for "local delivery" of antibiotics has peaked in the last few years, providing a potential alternative for drug administration to infected wounds (Saghazadeh et al. 2018). Indeed, recent publications have highlighted that antifungals can be incorporated into materials such as calcium sulphate beads or polymer microparticles that can be used to effectively control fungal growth, both *in vitro* using a wide range of fungal isolates (Butcher et al. 2021) and *in vivo* in a murine model of cutaneous aspergillosis (Tatara et al. 2019). Nanotechnology is also beginning to be considered as prospective therapeutic avenue to revolutionise wound treatment using nano-drug delivery systems, although at the time of writing such research is still well in its infancy (Wang et al. 2019).

6 Medical Device-Related Infections

Nosocomial infection is a wide-scale health concern across the world, with approximately 60–70% of all hospital-based infections being accounted for by direct contact with implanted medical devices (Bryers 2008). Infection management can be successfully maintained through the removal, sterilisation, and replacement of implanted biomaterials (Khatoon et al. 2018), though biofilms remain an issue. Indeed, there is a vast range of indwelling biomaterials that have been associated with fungal biofilm infection, which have been reviewed extensively elsewhere (Ramage et al. 2006; Williams and Ramage 2015).

Prosthetic joint infection (PJI) is a significant complication to an otherwise ordinarily successful procedure. Despite strict surgical hygiene protocols, as well as carefully administered antimicrobial regimens before and after the procedure, PJI is still a prevalent outcome of joint replacement (van de Belt et al. 2001). This is not surprising given that prostheses can provide an optimal substrate and surrounding environment for the growth and development of polymicrobial biofilms (Tande and Patel 2014). PJI presents a unique issue for post-clinical management, which presents very significant and fundamental therapeutic challenges, including sepsis, amputation, and even death,

Colonisation of PJI implants is predominantly driven by biofilm adhesion and growth, which have the propensity to haematologically spread and impact distal sites (Ramage et al. 2006; Kaplan 2010). Typically there is a panel of usual suspects associated with PJIs, with the prime candidate being *Staphylococcus* species (Hall and Mah 2017; Perry and Hanssen 2017). Notably though, pathogenic fungi have been shown to exist in these biofilm-centric infections. The ability for interkingdom relationships within the biofilm can present extreme difficulty for establishing a therapeutic regimen. For example, fungal organisms account for only approximately

1% of PJI cases (Brown et al. 2018), but this small percentage can result in drastic oversight and clinical repercussions if not addressed with rapidity.

In recent years, research surrounding the management of PJI has highlighted the need for void-filling and moisture stability within the surgical site (Jones et al. 2016). This has, in turn, presented potential for novel therapeutics and the release of antimicrobial agents in a localised manner to areas of compromised vasculature using conventional filler material such as drug-loaded calcium sulphate (Butcher et al. 2021). This allows exposure to much higher effective doses of antimicrobials than would normally only be possible through a systemic route. While evidence has shown these methods to be effective, there remains the threat of infectious organisms developing antimicrobial resistance. Indeed, prevention of biofilm formation at the point of contact through alteration of the biomaterial surface proposes an interesting alternative to conventional therapy. Through alteration of variables which may significantly impact microbial adhesion, such as surface roughness and electrostatic charge (Gallo et al. 2014), the possibility for colonisation may also significantly diminish (Rzhepishevska et al. 2013; Yoda et al. 2014). Indeed, work conducted by Mayahara et al. in 2014 highlighted that adhesion of *Candida* yeast cells was up to two times greater on rougher surfaces when comparing roughness across the same substrate (Mayahara et al. 2014). Additional work has also taken place in investigating the efficacy of antimicrobial peptides against fungal pathogens (Delattin et al. 2017). More recently, it was shown that nanotopographical alterations to surface structure could significantly decrease yeast adhesion, paving out a promising strategy for implanted biomaterials (Alalwan et al. 2018).

Indwelling medical devices, such as intravascular catheters, voice prostheses, and ventricular-assisted devices (VADs), are commonly colonised with *Candida spp*. (Aslam et al. 2010; Elving et al. 2002). These infections are highly problematic due to the difficulty in effectively diagnosing them due to similar clinical symptoms to bacterial biofilm infections. Moreover, *Candida*, as in colonisation of the vocal prosthesis, is often discovered in a polymicrobial community, further exacerbating clinical identification (Leonhard and Schneider-Stickler 2015). Clinically, unless swiftly diagnosed the failure to treat a *Candida* infection in the ICU in the first 24 h can lead to a 30-fold increased likelihood of mortality (Kollef et al. 2012). Therefore, diagnosis, speed, and the choice of antifungal are all critically important in managing *Candida* spp. biofilms.

Within critical care there are a plethora of indwelling lines where adherent biofilm communities can thrive, from which cells can detach and cause a fungemia by spreading throughout the human body. These detached cells have been shown to be pathogenically primed and are associated with higher mortality rates in a murine model (Uppuluri et al. 2010). Literature has reported that biofilm formation correlates with clinical outcome, with those biofilms forming the greatest levels of bioburden being independent predictors of mortality (Rajendran et al. 2016a, b; Tumbarello et al. 2007). Moreover, it is clear from these studies that the choice of antifungal agent used is an important driver of clinical outcome, where the use of azoles is negatively correlated with clinical outcomes, whereas the use of

echinocandins and liposomal formulations of amphotericin B leads to positive patient outcomes (Tumbarello et al. 2007).

Innovations in biofilm prevention, as well as novel methods of drug delivery, indicate a hopeful outlook for future therapy. A range of studies, such as those conducted by Free et al., in 2001, and Rodrigues et al., in 2004, have indicated the production of biosurfactants produced by probiotic bacteria as having significant potential for treatment of *Candida*-driven infection of prostheses (Free et al. 2001; Rodrigues et al. 2004). Additionally, there has been a series of studies that positively highlight the use of antifungals, such as liposomal amphotericin B, as antifungal line locks in the prevention and management of fungal line infections (McGhee et al. 2016; Paul DiMondi et al. 2014). Though, the wide acceptance of such approaches is still limited due to clinical apprehensiveness of fungal line infection management, apart from line removal. Caspofungin remains an important antifungal in the management of fungal line infection and has even been shown in formulations to be useful against *Candida auris* (Sumiyoshi et al. 2020).

7 *Candida auris*: The New Superfungus on the Block

Since its discovery in 2009 (Satoh et al. 2009), the nosocomial pathogen *Candida auris* has received global attention in the world of medical mycology. This is largely due to the organisms' ability to persist within the environment (Welsh et al. 2017), exhibit unique biofilm forming capabilities (Borman et al. 2016; Sherry et al. 2017), and demonstrate an unusually high resistance to three common classes of antifungals (Kean and Ramage 2019). The simultaneous emergence of four independent geographical clades (Lockhart et al. 2017), which have been linked with the rising temperature around the globe (Casadevall et al. 2019), has added further complexity to this enigmatic panfungal pathogen. In addition, a certain biofilm heterogeneity exists within this species, which is determined by an aggregative and non-aggregative morphology: whereby some isolates can form relatively large clusters of cells vs. some that remain as single-celled entities (Borman et al. 2016; Sherry et al. 2017; Brown et al. 2020). The geographical clade and these unique morphological phenotypes can influence antifungal susceptibility. It is widely accepted that most isolates are resistant to fluconazole, likely a result of a mutation in *ERG11* gene (which encodes for lanosterol 14-alpha-demethylase) and/or overexpression in drug efflux pumps. Varying rates in susceptibility to echinocandin and polyenes have been reported in the literature too, resistance to the former likely owing to genetic mutation in the *FKS1* gene, responsible for synthesis of β-glucan, a key component of the fungal cell wall (reviewed in Chaabane et al. 2019; Kean and Ramage 2019). Due to these multidrug resistance mechanisms, the search is now on for innovative therapeutics to combat *C. auris* pathogenicity. To date, several *in vitro* biofilm studies, *in vivo* model systems, and clinical trials are in the process of investigating the novel antifungal agents. Of note, fosmanogepix (Berkow et al. 2017; Larkin et al. 2017; Ghannoum et al. 2020; Arendrup et al. 2020) and

ibrexafungerp (Hager et al. 2018; Zhao et al. 2018; Wiederhold et al. 2019), which target β-glucan synthase pathways, have been reported as effective alternatives in controlling *C. auris* biofilm formation *in vitro* and/or associated candidiasis in animal models. At the time of writing, both drugs are in phase 2 and phase 3 of clinical trials, respectively. This yeast is certainly one that will continue to be a global threat, and its propensity to form biofilms in healthcare environments, coupled with panfungal resistance, is a significant issue in this COVID era.

8 Concluding Comments

Fungal biofilms are an important clinical entity, and increasingly they are recognised as interkingdom structures alongside a myriad of bacterial species throughout the body. These difficult-to-treat infections are poorly responsive to antifungal agents routinely used in the clincial environment. However, this book chapter has demonstrated that above and beyond azoles, polyenes, and echinocandins, there are options that are in clinical trials and many other in preclinical development. The future is promising for management of fungal biofilms, but only if the wider clinical and scientific community recognise their importance.

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