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Liposomal amphotericin B—the future

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Advances in medicine have led to a growing number of people with compromised or suppressed immune systems who are susceptible to invasive fungal infections. In particular, severe fungal infections are becoming increasingly common in ICUs, affecting people within and outside of traditional risk groups alike. This is exemplified by the emergence of severe viral pneumonia as a significant risk factor for invasive pulmonary aspergillosis, and the recognition of influenza-associated pulmonary aspergillosis and, more recently, COVID-19-associated pulmonary aspergillosis.

The treatment landscape for haematological malignancies has changed considerably in recent years, and some recently introduced targeted agents, such as ibrutinib, are increasing the risk of invasive fungal infections. Consideration must also be given to the risk of drug–drug interactions between mould-active azoles and small-molecule kinase inhibitors.

At the same time, infections caused by rare moulds and yeasts are increasing, and diagnosis continues to be challenging. There is growing concern about azole resistance among both moulds and yeasts, mandating continuous surveillance and personalized treatment strategies.

It is anticipated that the epidemiology of fungal infections will continue to change and that new populations will be at risk. Early diagnosis and appropriate treatment remain the most important predictors of survival, and broad-spectrum antifungal agents will become increasingly important. Liposomal amphotericin B will remain an essential therapeutic agent in the armamentarium needed to manage future challenges, given its broad antifungal spectrum, low level of acquired resistance and limited potential for drug–drug interactions.

Introduction

The end of the Cretaceous period was characterized by a fungal bloom, which favoured the selection of endothermic mammals over ectothermic reptiles because their warm body temperatures protected them from fungal diseases.[1] Of the millions of fungal species on earth, only a few dozen regularly cause human disease; however, in an era of climate change, the world is becoming a warmer place and an increasing number of fungal species are adapting to high temperatures[1] and emerging as important pathogens in humans and endothermic mammals.[2] Also, advances in medicine have led to a growing number of people with compromised or suppressed immune systems whose bodies can be overrun by a fungal invader. For example, the prevalence of invasive aspergillosis (IA) continues to increase in non-neutropenic patients with severe underlying diseases, including patients in the ICU;[3–6] this is particularly true for patients requiring intensive care for influenza[5] or severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)-associated acute respiratory distress syndrome,[7,8] solid organ transplant recipients,[9]

patients receiving systemic glucocorticoids,[10] patients with underlying respiratory conditions,[3,11,12] patients with solid cancers,[3,13] patients receiving ibrutinib or other tyrosine kinase inhibitors[14,15] and patients receiving chimeric antigen receptor (CAR) T cell therapy.[16]

On the other hand, in patients with traditional risk factors for IA, such as those with underlying haematological malignancy and prolonged neutropenia or HSCT recipients, the use of mould-active prophylaxis has been associated with a decrease in prevalence of IA.[17,18] However, if breakthrough infections occur, they are often caused by previously less common invasive moulds including Mucorales spp., *Fusarium* spp., *Lomentospora* spp. and *Scedosporium* spp., which have been described as opportunistic pathogens in patients with a variety of underlying diseases.[19–22] In addition, rare yeast infections continue to increase.[23,24] While the prevalence of these pathogens varies widely between geographical regions,[22,25–27] they are associated with resistance to many classes of antifungal treatments[28,29] and with devastating mortality rates.[27,30] Early diagnosis and appropriate treatment remain the most important predictors of survival,[31] although diagnosis remains difficult to establish[22,32] and treatment is becoming increasingly complicated due to increasing primary and secondary resistance to various classes of antifungal drugs.[22,33] Even once a fungal infection is diagnosed, mixed fungal infections remain a threat.[34,35] Finally, the emergence of antifungal resistance among the more commonly identified pathogens, such as echinocandin and azole resistance in *Candida* spp.[36] and triazole resistance in *Aspergillus* spp., caused by mutations in certain genes such as *cyp51A*,[37] complicates the selection of appropriate antifungal treatment.[33,38,39]

For these reasons, broad-spectrum antifungal agents will become even more essential for reducing morbidity and mortality in the future. Amphotericin B and in particular its liposomal formulation (liposomal amphotericin B) may be considered the epitome of a broad-spectrum antifungal agent, showing excellent activity against a wide range of moulds,[22] including most *Aspergillus* spp., Mucorales spp., *Fusarium* spp., *Schizophyllum* spp., *Scopulariopsis* spp., *Paecilomyces* spp. and pathogens causing phaeohyphomycosis, but also yeasts including *Candida* spp. and *Cryptococcus* spp.[24,40] Given that (i) rare fungal infections are likely to increase, (ii) difficulties in diagnosing these infections are likely to persist, (iii) the numbers of mixed mould and mixed yeast infections are rising[41] and (iv) rates of azole and echinocandin resistance are increasing, the importance of empirical or preemptive broad-spectrum antifungal treatment will also increase. Liposomal amphotericin B will therefore remain a gold standard for primary treatment of unspecified invasive fungal disease, as well as targeted therapy of infections caused by the multitude of pathogens in its spectrum. One of the major advantages of liposomal amphotericin B compared with modern triazoles that makes it a particularly compelling choice for ICU physicians and for primary treatment of IA is the comparatively low number of drug–drug interactions; in comparison, voriconazole, for example, is among the drugs most frequently associated with major drug–drug interactions in the ICU.[42] It is not hard to predict that the proportion of invasive fungal infections (IFIs) reported from patients being treated with multiple medications is set to increase further, for example, patients in the ICU outside of the traditional at-risk populations. The low number of drug–drug interactions sets liposomal amphotericin B apart from its competitors for primary monotherapy of mould infections in the ICU and promises to remain a valuable feature determining the drug's role in the future. It must be acknowledged that there is still a risk of nephrotoxicity associated with liposomal amphotericin B, albeit lower than with amphotericin B deoxycholate, highlighting the continued challenges of treating severe fungal infections in patients in the ICU.[43]

This review will provide an overview of the role of liposomal amphotericin B in the next 30 years. It will focus specifically on the risk of fungal disease as well as drug–drug interactions in patients receiving new biological and targeted treatments for underlying malignancies, the risk of viral–fungal coinfections in the ICU and the emergence of antifungal resistance as well as fungal infections caused by rare and multiresistant pathogens.

New biologics, targeted agents and drug–drug interactions

Major progress has been made in the past two decades in understanding the genetic basis of haematological malignancies and mechanisms of immune escape of neoplastic cells. These advances have led to the development of precision therapies with monoclonal antibodies or small-molecule kinase inhibitors (SMKIs) that target specific cytogenetic abnormalities or abnormal signalling in tumours.[44] Personalized cellular therapies such as CAR T cells and other synthetic immunity approaches can elicit powerful host immune responses against tumour cells, leading to durable remission of previously treatment-refractory lymphoid malignancies.[45] Together, these treatments have generated optimism that many haematological malignancies can be controlled chronically, if not cured, without conventional chemotherapy or HSCT.[46]

IFIs have been a major challenge in the supportive care of patients with haematological malignancies since the dawn of the modern chemotherapy era in the 1960s. However, knowledge of how these newer targeted treatments impact a patient's risk of developing an IFI is still evolving.[47] Some monoclonal antibodies and SMKIs inhibit pathways involved in protective innate and adaptive immune responses to fungi.[48,49] Some targeted therapies can induce complex iatrogenic immunodeficiencies that result in unique and sometimes unpredictable risks of infection with specific fungal pathogens.[47] Furthermore, inflammatory reactions against tumour cells by CAR T cells can result in collateral damage to host organs. Control of these immune-related adverse effects often requires powerful immunosuppressive therapy that weakens immunity against fungal pathogens.[48] Hence, IFIs will continue to be a serious complication in the treatment of haematological malignancies, even in a 'post-chemotherapy' future.

What do we know about the risk of fungal infections with precision treatments and personalized immunotherapy?

Several reviews and expert guidelines have summarized the evidence of how targeted therapies alter the risk of IFIs.[50–55] Most of these reviews have concluded that robust data on the risk of fungal infections are lacking, and interpretation of case series and clinical trials is often confounded by the chemotherapy or corticosteroids administered prior to the SMKI or monoclonal

antibody.[56] Therefore, clinical judgement remains the most important guide for identifying which patients receiving targeted therapies are at sufficiently high risk to justify routine diagnostic screening or antifungal prophylaxis.[56]

An example of how targeted therapy with SMKIs may affect IFI risk is exemplified by the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib. The BTK pathway is essential for B cell receptor and chemokine signalling in lymphocytes, which regulates cell survival, proliferation and tissue homing.[57] By inhibiting the BTK pathway, ibrutinib blocks B lymphocyte proliferation, resulting in significantly prolonged survival in patients with CLL and mantle cell lymphoma.[58,59] However, BTK signalling also plays an important role in macrophage chemotaxis, adhesion and transmigration, reactive oxygen species production, cytokine response and inflammasome activation.[15,60] After approval of ibrutinib for the treatment of B cell cancers, a number of case series were published describing unexpectedly high rates of *Pneumocystis jirovecii* pneumonia, *Cryptococcus* pneumonia and meningoencephalitis, and IA frequently involving the CNS.[14,15,61] In a retrospective analysis of over 841 treatment courses at MD Anderson Cancer Center in Houston, TX, USA, 21/841 patients (2.5%) developed proven or probable mould infections, with invasive pulmonary aspergillosis (IPA) as the most common presentation.[62] These reports suggested that 'off-target' effects of ibrutinib may predispose patients who were classically considered 'lower risk' to fungal disease reactivation or higher risk of primary infections.[15]

The ibrutinib experience also highlighted the challenges in studying the epidemiology of IFIs with SMKIs, for which the majority of therapy is administered in the outpatient setting. In a review of 378 ibrutinib-treated patients, Varughese *et al.*[61] reported IFIs in 16 patients (37.2% of 43 serious infections; 8 IA, 3 *P. jirovecii* pneumonia, 1 mixed *P. jirovecii* pneumonia plus IA, 3 pulmonary cryptococcoses, 1 invasive candidiasis). Nearly two-thirds of patients lacked 'classic' IFI risk factors and some infections were diagnosed more than 2–3 years into treatment. Future epidemiological studies are likely to be even more complex as patients receive a broadening array of novel SMKI regimens, often in combination.[63]

In contrast, personalized immunotherapies such as CAR T cell therapy do not appear to specifically increase a patient's risk of developing an IFI unless their treatment is complicated by either prolonged neutropenia or severe cytokine release syndrome/immune-effector cell-associated neurotoxicity syndrome requiring treatment with cytokine inhibitors or high-dose corticosteroids.[64] However, this risk may change as CAR T cell therapy is adapted to the treatment of patients with myeloid malignancies who have a higher baseline risk of developing IFIs.

The risk of antifungal drug interactions with targeted therapy

Nearly all SMKIs are metabolized through CYP3A4/A5, making them susceptible to pharmacokinetic drug–drug interactions with triazole antifungals.[65,66] Mould-active triazoles (i.e. isavuconazole, itraconazole, posaconazole, voriconazole) can interfere with intestinal transport and hepatic metabolism of SMKIs, potentially resulting in unpredictably high drug exposure.[65] Depending on the SMKI, elevated drug exposure may carry a greater risk for haematological, cardiovascular, pulmonary, hepatic, CNS and cutaneous toxicities.[65] The degree and timing of these toxicities can be unpredictable.[67–70] For some SMKIs, dose reduction or interruption may place the patient at an increased risk of relapse of the malignancy.[70]

Consequently, many Phase II/III trials of novel SMKIs have excluded the concomitant use of mould-active triazoles, which is reflected in prescribing information that often recommends avoiding coadministration when possible.[69,71] In the case of the B cell lymphoma protein 2 inhibitor venetoclax, empirical dose reductions were proposed several years after the drug was introduced into clinical practice.[72] Graded reductions in the daily dose of venetoclax are recommended depending on the presumed potency of CYP3A4/A5 inhibition by the respective triazole. Nevertheless, it is still uncertain if empirical dose reductions of venetoclax during triazole therapy are sufficient because prolonged cytopenias are still reported with all concomitant triazole therapy.[73]

Given the ambiguity of managing these drug–drug interactions, therapeutic drug monitoring (TDM) to guide dosing of targeted therapies would seem justified. However, therapeutic serum drug concentration ranges are not well defined for many SMKIs and testing is not currently available in most centres. It also remains to be seen whether TDM would be more effective than empirical dose reductions or careful monitoring of toxicity.[67,68] However, given the critical role of these targeted therapies for maintaining remission of haematological diseases, empirical dose reductions in the absence of toxicities should be undertaken carefully to ensure that control of the underlying malignancy is not jeopardized. The inevitable use of combination SMKI regimens in the future, some of which may have active metabolites with varying potency and off-target effects on treatment response or drug toxicity, could further complicate efforts to develop straightforward TDM recommendations.

This drug–drug interaction dilemma also highlights an urgent need for oral broad-spectrum antifungal agents that do not inhibit human CYP3A4/A5. Some promising new antifungals are in the pipeline,[74] and isavuconazole may have some advantages over other triazoles with respect to drug toxicity, drug interaction severity and QTc prolongation risk. However, the immediate challenge of using SMKIs with triazole antifungals has prompted recommendations to use IV echinocandins as prophylaxis to avoid drug interactions and QTc prolongation risk.[75] Nevertheless, this strategy may be limited by a higher rate of breakthrough infections,[74,76] including fulminant infections caused by intrinsically echinocandin-resistant yeasts.[77,78] Ultimately, some patients receiving targeted therapies will require outpatient antifungal therapy for months or years, making IV-administered antifungal agents impractical.

In summary, advances in cytogenetic analysis and drug discovery have brought new promise for the effective management and potential cure of haematological malignancies. A major challenge in the next decade will be to adapt current supportive care approaches to ensure that IFIs do not compromise a patient's opportunity to benefit from these groundbreaking therapies. In this respect, liposomal amphotericin B will undoubtably play an important role in the future of empirical treatment of fungal infections, as there will be a persistent need for broad-spectrum therapy that does not interfere with the metabolism of novel precision and personalized therapies.

Influenza and COVID-19

Viral pneumonia is a global health concern that is highlighted by the current ongoing COVID-19 pandemic. In particular, the pandemic influenza viruses and SARS-CoV-2 can infect large groups of individuals, including many healthy young people, and lead to considerable societal and economic disruption. The clinical severity of the viral infection depends on many factors, such as the immune status of the host and the presence of comorbidities, and a subset of patients with influenza or COVID-19 will develop severe mono-organ failure of the lung requiring admission to the ICU.[79–82] After the influenza H1N1 pandemic in 2009, it became clear that patients with influenza who were admitted to the ICU were at an increased risk of developing IA.[5,83] Several reports over recent years have shown that the incidence of IPA in patients with influenza in the ICU is at least 20% in Europe, but numbers from other continents such as in the USA are lacking.[5,84] The incidence of IPA is even higher for patients who also have classical risk factors for IFIs.[5] Notably, a substantial number of patients with influenza who developed IPA were relatively young and had no relevant medical history.[83] It was later discovered that influenza itself is an independent risk factor for IPA, and influenza-associated pulmonary aspergillosis (IAPA) was recognized as a new clinical entity that unfortunately is associated with considerable morbidity and mortality.[5]

IAPA and COVID-19-associated pulmonary aspergillosis (CAPA)

Understanding the pathophysiology of IAPA is crucial to develop novel management strategies and guide antifungal treatment. Influenza is a lytic infection that damages the lung epithelial barrier that protects against IPA. Importantly, the use of corticosteroids in the ICU was identified as a risk factor for IAPA, supporting the concept that a weakened antifungal host response due to immunosuppressive treatment might also play an important role in the development of IAPA.[5] When COVID-19 emerged, there was a real concern that IPA might also prove to be an important complication of SARS-CoV-2 infection, similar to influenza.[85] Initially, the use of corticosteroids was not recommended for the treatment of COVID-19 due to concerns of weakening the host response against the virus and other pathogens, including *Aspergillus* spp., that could subsequently cause secondary infections.[86] However, after several months, data from large platform trials pointed to a beneficial effect of corticosteroids, especially in the more severely ill patients with COVID-19 requiring oxygen supplementation.[87,88] This led to a change in clinical guidelines and the use of corticosteroids to treat COVID-19 in the ICU became the standard of care. Several months later it was shown that blocking the IL-6 pathway with tocilizumab or sarilumab reduced mortality when given in combination with corticosteroids.[89] Daily practice changed again and treatment with both corticosteroids and an IL-6 blocker (when available) became the standard of care in some parts of the world when a patient was admitted with COVID-19 and was hypoxic. Since corticosteroids reduce phagocytic capacity against *Aspergillus*, and IL-6 is important for induction of protective antifungal Th17 responses, it could be anticipated that an increased risk of developing CAPA would emerge.[90,91] Notably, in one of the first studies that systematically and prospectively investigated the incidence of CAPA, it was indeed observed that CAPA was present in an unexpectedly high number of patients (28% of patients admitted to the ICU with COVID-19).[92] Most patients to date with CAPA had received corticosteroids and were also treated with tocilizumab, both of which were independent risk factors for CAPA.[93,94] These data triggered a debate on how to diagnose and define CAPA and whether we would be undertreating or overtreating this new clinical entity.[8,95] Many studies that followed showed a variable incidence of CAPA in different countries, which could be explained by the lack of a uniform definition of CAPA and possibly a difference due to geographical variations in environment and clinical practice.[96,97] This is reminiscent of the variable incidence of IAPA described in different countries.[5,83,84,98] Although there are many uncertainties at this point, CAPA, like IAPA, seems to be a relevant clinical entity since it is associated with increased mortality and is difficult to diagnose and treat.[93]

Treatment

The current recommendation is to treat IAPA once it is diagnosed and the choice of treatment depends on local azole susceptibility data for *Aspergillus*.[99] When surveillance data indicate a high rate of azole resistance in *Aspergillus*, the recommended regimen for a patient with IAPA in the ICU is a combination of an azole with an echinocandin or liposomal amphotericin B.[100] It must be underscored that IAPA is a severe and acute disease and any delay in effective treatment could lead to increased risk of treatment failure.[101] When diagnostic workup identifies an *Aspergillus* sp. susceptible to an azole, combination therapy should be stopped and monotherapy with an azole continued.[99] However, if an azole-resistant isolate is identified, the use of liposomal amphotericin B is recommended, either alone or in combination with an azole pending the results of MIC testing.

Other IFIs associated with viral pneumonitis have also been noted. In particular, invasive mucormycosis has been described in both influenza and COVID-19 infections.[97,102–105] Mucormycosis is an acute and devastating fungal infection caused by fungal species belonging to the order Mucorales.[32] Pulmonary mucormycosis that is left untreated has a poor prognosis and should be promptly diagnosed and adequately managed to prevent angioinvasion and dissemination to other organs.[32] Classical risk factors for developing mucormycosis are uncontrolled diabetes mellitus and immunosuppressive conditions, such as neutropenia or the use of corticosteroid therapy.[106] Mucormycosis frequently results in an angioinvasive infection, especially when hyperglycaemia, ketoacidosis, iron overload and/or neutropenia are present.[106] The severity of the infection at this stage is characterized by endothelial damage, and local (micro) thrombosis, bleeding and necrosis can develop. Eventually, dissemination to multiple organs including the brain can occur, which has a poor prognosis. Influenza-associated mucormycosis and COVID-19-associated mucormycosis have both been described and can be added to the list of emerging infections associated with viral pneumonitis that clinicians should be aware of. Liposomal amphotericin B will be an important agent in this context because it is recommended as first-line therapy in the global guidelines for management of mucormycosis.[32]

Viral pneumonitis in the ICU is characterized by a detrimental hyperinflammatory response.[107] This had been long recognized

in influenza, but COVID-19 has made many clinicians aware of the cytokine storm that can be observed with severe infection.[108] COVID-19 has shown that in infectious diseases, host-directed therapy with corticosteroids and anti-cytokine strategies can be successful in reducing mortality. Therefore, fungal infections associated with influenza and COVID-19 will likely occur or already be present when immune modulatory therapy is initiated. Therefore, antifungal therapy will in certain conditions be combined with immunomodulatory strategies in the ICU. This was anticipated for the future but since the COVID-19 pandemic it has become a reality in daily practice.

Liposomal amphotericin B is an interesting drug in this context since both amphotericin B and liposomes have immunomodulatory properties. Fever and chills can be adverse events of amphotericin B deoxycholate and it has been shown to induce transcription of immune mediators and production of proinflammatory cytokines, such as IL-1, TNF and IFN-γ, that are crucial for optimal antifungal host defence.[109–113] Induction of cytokines by amphotericin B in macrophages is dependent on Toll-like receptor (TLR)2, CD14 and MyD88, which are important for innate pattern recognition signalling.[114] Moreover, amphotericin B can increase crucial protective antifungal pathways such as production of NADPH-dependent reactive oxygen species and boosting the Th1 response.[110,115–117] In addition to the effects of amphotericin B, liposomes can induce immune modulatory effects. It was shown that empty liposomes can skew the response of neutrophils from a predominantly TLR2- to a TLR4-induced cytokine profile, with TLR2 inducing proinflammatory cytokines (TNF) and TLR4 anti-inflammatory cytokines (IL-10). Finally, amphotericin B has also been shown to enhance protective IFN-γ-induced nitric oxide production and antifungal activity of macrophages.[118] This is especially relevant for the novel trials that are being performed in which treatment with recombinant IFN-γ is being explored to treat invasive infection in addition to standard antifungal therapy. The combination of liposomal amphotericin B with immunotherapy, such as anti-inflammatory agents (e.g. corticosteroids, cytokine blockers) and/or immune-boosting strategies (e.g. checkpoint inhibitors, recombinant IFN-γ), should be systematically investigated and trialled in the future.

Increasing azole resistance

Emergence of azole resistance

Azoles represent a major drug class for the management of IFIs and are commonly recommended as the preferred drug class for treatment of mould infections, including aspergillosis, scedosporiosis and fusariosis.[22,119] There is increasing concern about acquired resistance to azole drugs emerging in fungal pathogens. Azole resistance has emerged as a clinical problem in *Candida* spp., notably *Candida glabrata*, in *Aspergillus fumigatus*, and more recently in dermatophytes.[120–123] In addition, new drug-resistant species, such as *Candida auris*, have emerged.[123] In principle, two routes of selection for resistance are recognized: in-host resistance selection and environmental resistance selection. Although these two routes differ with regard to clinical implications, resistance mutations and pathogens involved, the dynamics of resistance evolution are similar. Emergence of resistance involves generation of spontaneous mutations by a fungus in combination with selection pressure by an azole.[124] As some of the spontaneous mutations may confer azole resistance, the resistant clone will have a survival advantage over WT clones when in an azole environment (i.e. during azole therapy) and become dominant in the population. Various factors impact the risk of resistance development, including the size of the fungal population and the concentration of the antifungal drug involved.

In general, resistance selection in *Candida* spp. takes place in the host during azole therapy, while both in-host and environmental resistance selection has been reported for *A. fumigatus*. *Candida* spp. are generally present in the human gut and may represent large populations due to previous antibacterial therapy. It is thought that antifungal therapy may enable selection of resistant *Candida* spp., which may subsequently cause resistant infections.[125] Therefore, previous azole therapy is an important factor in the development of azole-resistant invasive candidiasis. *Candida* spp. are known to develop a wide variety of complex azole resistance mechanisms, including mutations in the *ERG11* target gene and overexpression of target genes and/or drug transporters.[126] In addition, a 'mutator' phenotype has been described in *C. glabrata*, in which a mutation in the DNA mismatch repair gene was associated with a high mutational supply.[127] This mechanism would enhance the probability of escaping azole pressure and was found to be present in 55% of clinical isolates.[127] *A. fumigatus* may also develop azole resistance in the host during azole therapy. Itraconazole resistance was observed in 11% of patients with chronic pulmonary aspergillosis treated with itraconazole and in 5% of those treated with voriconazole.[128] Most of these patients have lung cavities that allow *A. fumigatus* to produce spores, which is believed to enhance the risk of resistance selection compared with hyphal growth (the predominant morphotype in patients with IA).[129] However, recently, in-host development of azole resistance was reported in patients with cystic fibrosis, in which the fungus is also confined to the hyphal state as it forms biofilms.[130] The fungus was shown to create genetic variation through parasexual recombination, which underscores the versatility of *A. fumigatus* to overcome (azole) stress. The main route of azole resistance selection in *A. fumigatus* involves resistance selection in the environment through exposure to azole fungicides. Although these fungicides are targeted at fungi pathogenic to plants, *A. fumigatus* grows in decaying plant materials and is thus exposed to azole fungicides when residues are present in the waste.[131] As the molecular structures of some azole fungicides and medical triazoles are similar, cross resistance develops. Similar to *Candida* spp., a broad range of resistance mechanisms may develop in *A. fumigatus*, including mutations in the *cyp51A* gene.[121] Unlike in-host resistance selection, azole-resistant *Aspergillus* disease may develop in patients who have not been previously treated with azoles, through inhalation of azole-resistant conidia.

Acquired resistance to polyenes has rarely been reported despite this drug class being used in medicine for several decades.[132] Amphotericin B binds to ergosterol which, unlike a protein target, is not genetically encoded, and results in a fungicidal effect. This mode of action reduces the ability of the fungus to develop resistance mechanisms and may prolong the clinical use of amphotericin B in a landscape of emerging resistance.

Treatment implications

With the limited arsenal of antifungal drug classes, azole resistance immediately impacts clinical management and subsequent treatment options. Strategies to manage drug resistance in fungi involve various approaches. An initial step would be to know the local azole resistance epidemiology in a certain hospital, region or country. However, despite an increasing number of publications on resistance in fungi, the epidemiology of azole-resistant fungi remains poorly documented.[133] Although (inter)national surveillance programmes are operational for bacterial resistance, fungal resistance has long been excluded from antimicrobial resistance initiatives. To monitor resistance trends in various fungal pathogens, such programmes are urgently needed. The recent listing of three fungi (*C. auris*, drug-resistant *Candida* and azole-resistant *A. fumigatus*) on the antibiotic resistance threats list in the USA, published by the CDC, has contributed to the realization that resistance in fungi is a growing concern for public health and should be added to the antimicrobial resistance priorities.[134] Initiatives such as the incorporation of *Candida* in the Global Antimicrobial Resistance and Use Surveillance System (GLASS) by the WHO will help us to determine resistance frequencies in various countries. Specific challenges regarding surveillance in fungi include the limited number of clinical microbiology laboratories that perform resistance testing of fungi, especially of moulds, and the difficulty in classifying fungal diseases in the expanding host groups.

Resistance surveillance data will help to guide empirical treatment choices and institutional guideline recommendations for patients who are suspected to have invasive fungal diseases. Personalized approaches will benefit from detecting resistance at diagnosis or in patients for whom antifungal therapy is failing. Species identification would be sufficient to help select an appropriate drug in the absence of resistance or for intrinsically resistant species. Acquired resistance requires demonstration of resistance markers or a resistant phenotype, which requires additional tests, time and expertise. Molecular detection of resistance mutations will allow a shorter turnaround time and detection of resistance in culture-negative cases, but an important condition is that the resistant mutation corresponds with a specific phenotype. In azole-resistant *A. fumigatus*, changing voriconazole resistance phenotype was recently observed in isolates harbouring the dominant TR_{34}/L98H resistance mutation,[135] which has the consequence that detection of the TR_{34}/L98H genotype may not predict voriconazole resistance. Furthermore, persisting azole resistance selection pressure in the environment will cause the number and diversity of resistance mechanisms to increase over time. Increasing range and complexity of resistance mechanisms will challenge our capability to diagnose azole resistance. The limitation of current PCR-based methods remains the number of resistance mutations that can be detected and the limited sensitivity of the assays.[136] Therefore, methods need to be developed that overcome these limitations, possibly involving sequence-based techniques. However, time to resistance detection must be rapid as inappropriate initial antifungal therapy was shown to be associated with increased mortality in patients with voriconazole-resistant IA.[137] In addition to diagnostic challenges, treatment response may not correspond with the resistance phenotype of the fungus (i.e. with azole-susceptible cases failing on azole therapy and azole-resistant cases responding). There are numerous factors that contribute to treatment response, including timing of antifungal therapy, drug exposure, drug penetration at the site of infection and resolution of underlying immune defects. Although pre-clinical studies, including those using animal models, generally show a good correlation between MIC and treatment response, variable correlations between MIC and outcome have been reported in clinical studies.[138]

Understanding the reasons for treatment failure is important for the design of strategies to improve treatment outcomes. Given the limited number of antifungal drug classes, a strategy involving empirical broad-spectrum therapy followed by narrow-spectrum targeted therapy, which is commonly used for bacterial infection, is not widely used in clinical mycology. A de-escalation strategy is recommended for treatment of suspected IA in regions with high azole resistance in *A. fumigatus*.[100] Such a strategy might involve initial therapy with liposomal amphotericin B or a combination of an azole with an echinocandin, followed by de-escalation to azole therapy in patients with documented azole-susceptible infection or in those who are clinically responding. Such a strategy has been recommended for regions with azole-resistance rates exceeding 10%.[100] A drawback of the de-escalation strategy is the overtreatment of most patients who still have an azole-susceptible infection. Future strategies should move away from the current generalized strategies towards personalized strategies, which can take into account factors relevant to the host, fungus and drug (Figure 1). Combining information from each of these determinants will help to provide the best treatment for the individual patient.

Emerging and rare invasive fungal infections

Pathogens expected in the future

Fungal infections can spread globally but do so at a slower pace than respiratory viral infections, for example. One reason may be that most fungal infections are not easily transmitted from person to person. However, global epidemiology is preceded by local epidemiological patterns, so it is worth identifying ecological niches harbouring future global threats. Since such threats may emerge from low- and middle-income countries, it is essential to establish reliable mycology laboratories and networks led by dedicated experts capable of identifying, analysing and publishing local and regional trends.[139]

During recent years, the global spread of *C. auris*, a pathogen that was previously regionally confined, has been observed. This pathogen was first identified in Japan in 2009 and spread within South-East Asia over the next 4 years,[140] from where the first outbreaks were reported.[139] Its spread then gained pace and it reached all inhabited continents in less than 6 years. The first hospital outbreak in Europe was reported in the UK in 2016 and was soon followed by an independent outbreak due to multi-azole-resistant isolates in Spain.[141,142] The virulence of *C. auris* has been described as similar to *Candida albicans* in a rodent model and this was supported by clinical data.[143,144] In the UK outbreak, the capability of *C. auris* to persist in the environment and to be transmitted nosocomially was documented.[145] There has been speculation about whether climate change facilitated

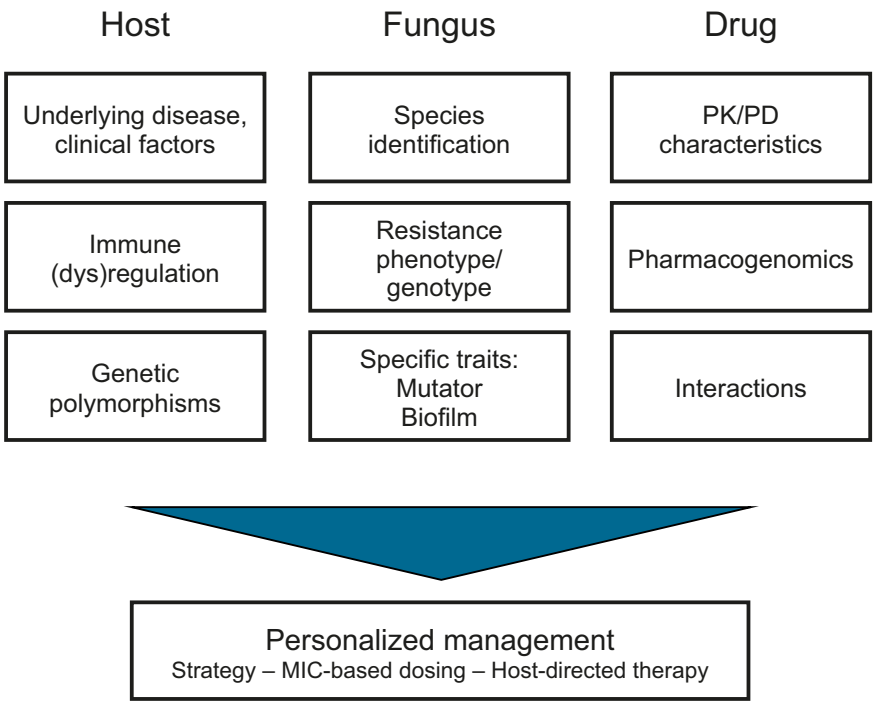

Figure 1. Determinants that may help to develop personalized treatment strategies. PD, pharmacodynamic; PK, pharmacokinetic. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

the global spread of *C. auris*, but other factors may have contributed, and the weight of individual factors has not yet been quantified. Hence, the actual impact of climate change remains unclear for now.[146] The clades of *C. auris* differ in their susceptibility patterns.[147] While they are generally resistant to fluconazole, they may be resistant to echinocandins and amphotericin B.[148,149] Pan-resistance to all three major antifungal drug groups has been described.[150] The CDC listed *C. auris* as an urgent threat in their 2019 antibiotic resistance report.[134] This was an improvement in the level of awareness, given that the listing of fluconazole-resistant *Candida* as a serious antibiotic resistance threat carried the explanatory remark 'a fungus' in 2013.[151]

Candida parapsilosis may in some settings be considered an exception to the rule that invasive candidiasis and candidaemia should be treated with an echinocandin;[152] however, the emergence of fluconazole-resistant *C. parapsilosis* has to some extent changed that paradigm.[153] Echinocandin treatment of a yeast infection is often initiated based on the first microbiological result available, namely microscopy.[154] Species identification is usually pending until the next day. If the pathogen is identified as *C. parapsilosis*, some guidelines recommend switching treatment to fluconazole, assuming that fluconazole MICs have been low for most *C. parapsilosis* strains.[152,155] Indeed, breakthrough infections in the echinocandin Phase III drug development programmes were disproportionately often caused by *C. parapsilosis*, but the overall number was too low to allow significant analyses.[156–158] Given that *C. parapsilosis* isolates are now more often fluconazole resistant and echinocandins cannot be regarded as ideal treatment, then the therapeutic choices would be narrow and treatment algorithms would need to be re-written. That is exactly what is happening currently with azole-resistant *C. parapsilosis* cases and outbreaks being reported.[153,155]

While echinocandins are generally an appropriate treatment for *C. glabrata*, triazoles are not.[155] Fluconazole is not usually a reliable treatment, and although high doses may be effective in certain isolates, current guidelines support a recommendation for triazoles with marginal strength at best.[152] In recent years, more and more reports have brought echinocandin resistance in *C. glabrata* to the attention of the scientific community.[155] Long duration of echinocandin exposure in patients who could not undergo surgical removal of abscesses appears to be a setting that promotes echinocandin resistance.[159,160] Echinocandin-resistant *C. glabrata* has already become an accepted differential diagnosis in patients with difficult-to-treat or refractory invasive candidiasis, particularly those previously exposed to echinocandins.[161]

Implications for treatment

Echinocandins and azoles, specifically fluconazole, are the antifungal agents currently listed as first-line treatment for candidaemia and invasive candidiasis. With increasing rates of infections caused by *Candida* strains resistant to these standard treatments, guidelines will need to be re-written and amphotericin B would advance back into first line in the future, whereas it was once replaced by the drugs now apparently losing efficacy. Current guideline recommendations, for example those of ESCMID, support the recommendation to use liposomal

amphotericin B in the first line with moderate strength,[152] and an 'A' recommendation may be more appropriate in the future.

Conclusions

The epidemiology of IFIs has changed dramatically over the past two decades and will continue to change. New groups of patients at risk will continue to emerge, driven by advances in medicine and new viral pandemics. Some of these populations will receive antifungal prophylaxis, and liposomal amphotericin B will remain a preferred initial therapy for breakthrough mycoses that affect 2% or more of patients receiving prophylactic treatment.[162] At the same time, climate change will result in expansion of the regions where mycoses are endemic and will potentially continue to lead to the emergence of fungal pathogens that are adapting to higher temperatures and thereby becoming a threat for humans.

The treatment landscape of IFIs will continue to change, with a number of new antifungal drugs, including three new drug classes, currently in the pipeline.[74] While these new drugs, which are all in late-stage clinical development, are unlikely to match the efficacy of liposomal amphotericin B against Mucorales,[74] some could be candidates for antifungal combination therapy with liposomal amphotericin B due to synergistic effects. In particular, the results of synergy studies with fosmanogepix and ibrexafungerp are emerging that show strong synergism in animal models.[163,164] In addition, these new drugs will target some of the (rare) pathogens that show intrinsic resistance to liposomal amphotericin B, such as *Lomentospora prolificans*.[74] Nanoparticle-based encochleated amphotericin B (MAT2203), which is currently being evaluated in Phase II studies, may provide oral availability of amphotericin B, serving a potential future role as step-down therapy after hospital discharge.[165] Also, dosing of liposomal amphotericin B may change, with less frequent but higher dose applications, as shown recently for cryptococcal meningitis in patients with advanced HIV, for which single high-dose liposomal amphotericin B combined with flucytosine and fluconazole was non-inferior to 2 weeks of amphotericin B deoxycholate, while providing a better safety profile.[40]

While resistance to most classes of antifungals, particularly azoles, has been emerging over the past decades,[36,166] the low level of acquired resistance to polyenes/amphotericin B in *Aspergillus* spp. stands out as a major strength of this drug class. However, susceptibility testing of fungal pathogens will need to improve to become a reliable measure for guiding therapy. At present, MICs frequently do not correlate with outcomes, particularly for rare moulds such as *Fusarium* spp.[22,28] Development of a 'pharmacodynamic index' analogous to an *in vivo* MIC could overcome that limitation. As well as its other major strengths, including the broad antifungal spectrum and efficacy, there is another major reason for liposomal amphotericin B to prevail, namely its comparatively low number of drug–drug interactions; this will become even more important in the future when the number of pharmaceutical treatments for patients at risk of IFIs will only increase further.[167] There are important questions that need to be answered, including those on the exact pharmacokinetics and the half-life of liposomal amphotericin B tissue concentrations, which could guide alternate dosing algorithms, for example in patients with less invasive disease and those with renal compromise.

There is an urgent need for biomarkers for treatment stratification and outcome prediction that can be broadly applied to various IFIs, in line with serum galactomannan, which currently can only be applied to the minority of patients with IA and a positive baseline serum galactomannan result.[168] Molecular imaging, such as positron emission MRI, may have an important role in the future, not only for response assessment but also for estimating the fungal burden at baseline,[169,170] which could for example be used for stratifying patients to receive combination antifungal therapy.

In patients without neutropenia in whom IPA primarily involves tissue invasion with delayed angioinvasion, inhaled treatment and particularly prophylaxis[171] will become a cornerstone of antifungal management, resulting in very high drug concentrations at the site of infection with limited or no systemic toxicity or risk of drug–drug interactions. At that point, very high inhaled dosages of antifungals may become feasible, but for now more studies and research evaluating how to best deliver liposomal amphotericin B via inhalation are needed.

Multiple studies performed *in vitro* and *in vivo* have demonstrated that amphotericin B has an effect on the host, not only in the presence of a pathogen but also when uninfected cell lines or animals are treated with the antifungal agent, inducing a proinflammatory response via various mechanisms, which has been associated with a protective effect as well as toxicity.[172] The immunomodulatory properties of liposomal amphotericin B lead to many questions about how it acts during infection, not only on the pathogen but also the immunocompromised host, which should be the subject of future research. Indeed, liposomal amphotericin B may have different effects on patients with different immunological states and therefore could have unpredicted consequences on disease outcome.[172] In addition, the use of immunomodulatory treatment strategies in fungal infections in combination with amphotericin B needs to be systematically studied.

In conclusion, we have reached the end of the mycology world as we know it, and the next 30 years will not only bring solutions but also new challenges. In this new world, liposomal amphotericin B will remain an important asset within a broad armamentarium of antifungal drugs and continue to shape the history of clinical mycology and help save the lives of patients.

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Author contributions

All authors contributed to the design of the review, undertook literature research, wrote sections of the review, reviewed the other sections and approved the final version.

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