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Breakthrough invasive fungal infections: Who is at risk?

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Abstract

The epidemiology of invasive fungal infections (IFIs) in immunocompromised individuals has changed over the last few decades, partially due to the increased use of antifungal agents to prevent IFIs. Although this strategy has resulted in an overall reduction in IFIs, a subset of patients develop breakthrough IFIs with substantial morbidity and mortality in this population. Here, we review the most significant risk factors for breakthrough IFIs in haematology patients, solid organ transplant recipients, and patients in the intensive care unit, focusing particularly on host factors, and highlight areas that require future investigation.

KEYWORDS

breakthrough fungal infections, fungal infections, risk factors

1 | INTRODUCTION

Despite recent advances in the diagnosis and treatment of invasive fungal infections (IFIs), morbidity and mortality from these infections remain very high, particularly in the absence of early diagnosis and prompt antifungal treatment initiation, two factors that are the most important predictors of survival from these infections.[1] IFIs caused by *Aspergillus* spp. and *Candida* spp., account for about 95% of cases of IFI.[2,3] To prevent IFIs in those most at risk, including patients with underlying haematologic malignancies, haematopoietic stem cell transplant (HSCT) recipients, solid organ transplant (SOT) recipients and critically ill patients in the intensive care unit (ICU), antifungal prophylaxis is often used during the period of greatest risk. Historically, fluconazole was often used in patients with haematologic malignancy,[4] which led to a significant decrease in the incidence of invasive candidiasis (IC); however, fluconazole offers variable protection against non-*albicans Candida* species and no protection against *Aspergillus* spp. and other moulds.

Given the gaps in fluconazole coverage, major guideline groups moved to recommend the use of newer triazoles with anti-mould activity to prevent IFIs. The European Conference on Infections in Leukemia (ECIL), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Confederation of Medical Mycology (ECMM), the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO), and the Infectious Diseases Society of America

(IDSA) all give the strongest recommendation for antifungal prophylaxis with posaconazole in patients with haematologic malignancies undergoing induction chemotherapy or suffering from graft-versus-host disease (GvHD).[5-8] Other triazoles such as voriconazole and itraconazole, as well as the echinocandins, are recommended with varying degrees of strength by these groups,[9] particularly in situations where the risk for IFI is lower.

Although primary antifungal prophylaxis has led to a decrease in IFI, a subset of patients develop breakthrough IFI (bIFI). Recently, the Mycoses Study Group Education and Research Consortium (MSGERC) and the ECMM proposed broadly applicable definitions, defining bIFI as an infection occurring during exposure to an antifungal drug, including fungi outside the spectrum of activity of the antifungal.[10] In addition, it is well-established that the performance of conventional biomarkers such as galactomannan (GM) is negatively influenced in patients receiving mould-active prophylaxis or treatment.[11-15] Thus, the diagnosis of bIFI can be challenging.

Here, we review the available literature and build on reviews previously done,[4,16,17] focusing on the most common risk factors for bIFI in haematologic malignancy patients including HSCT recipients, as well as SOT recipients and ICU patients. We also summarise fungal pathogen-related factors and antifungal drug-related factors that increase the risk for bIFI, including iatrogenic factors,[10] environmental risk factors[18] and immunomodulators,[5] which are discussed in extensive detail elsewhere. Lastly, we highlight areas that require further investigation.

2 | FACTORS ASSOCIATED WITH BREAKTHROUGH INVASIVE FUNGAL INFECTIONS

2.1 | Host factors

While numerous pharmacokinetic/pharmacodynamic factors and fungal organism specific features contribute to bIFI, host immunosuppression has been postulated to be the major predisposing condition for bIFI.[16] Several recent retrospective studies have illustrated the dominant role host immunosuppression plays in the development of candidaemia despite antifungal prophylaxis. In these reports, the absence of an appropriate and well-coordinated immune response was the principal prognostic factor, while the majority of breakthrough *Candida* isolates were susceptible to the prophylactic antifungal agent prior to the observed bIFI.[19-22] These studies determined the presence and duration of neutropenia, receipt of corticosteroid therapy and ICU stay were predisposing conditions leading to development of breakthrough candidaemia (bIC) compared to patients who received prophylaxis but did not develop breakthrough infection.[19,21,22] Others studies have found similar risk factors and additionally identified antibiotic exposure (≥2 antibiotics for at least 14 days) as a predisposing element, suggesting changes in the endogenous microbiota (eg skin and gastrointestinal) play a major role in the development of bIC.[20] These factors are reviewed in detail below for patients with haematologic malignancies, SOT recipients and patients in the ICU.

Breakthrough infection may also occur as a failure of source control. Undrained abscesses, a failure to adequately assess for possible dissemination resulting in less aggressive treatment practices, structural abnormalities leading to sustained seeding (eg postsurgical or trauma) and 'sanctuary' sites allowing for suboptimal antifungal pharmacokinetics all predispose to recurrent infection despite appropriate therapy.[23-25]

Specific host factors for breakthrough mould infections are less well defined. Neutropenia, immunosuppressive medications and receipt of antibiotics are commonplace in those at risk for mould infections, and a more nuanced evaluation of individual host immunologic parameters is thus required to define risk. Single-nucleotide polymorphisms (SNPs) within genes encoding for proteins involved in innate and adaptive immune responses (dectin-1 and DC-SIGN, TLR4 and others) convey an increased risk for mould infections despite prophylaxis.[26-30] Although comorbidities such as diabetes mellitus, chronic pulmonary disease, chronic kidney disease, chronic liver disease and hemodialysis are risk factors for invasive fungal infections, there is little evidence that these comorbidities[21,31-34] or comorbidity risk scores such as the Charlson score[21,35] increase the risk for bIFI compared to non-breakthrough IFIs.

2.2 | Fungal factors

Predisposing factors for bIFI include the interrelated elements of fungal virulence traits, antifungal drug resistance or tolerance and biofilm formation which is discussed under iatrogenic factors. Virulence factors facilitate target adherence, host defence evasion, tissue damage, thermotolerance and adaptation to unfavourable microenvironments including hypoxia and iron-poor conditions.[36,37] These traits also enable escape of exposure to antifungal drugs. Exposure to echinocandins can induce surface chitin and expression of drug resistance genes in vitro in *A fumigatus* and *C albicans* with resultant paradoxical effect.[38,39] Voriconazole[40,41] and isavuconazole[42] exposure may enhance virulence in the Mucorales.

Antifungal resistance, which typically follows antifungal exposure, can select out a breakthrough pathogen resistant to the agent prescribed.[43] bIC was first noted decades ago when the use of antifungal prophylaxis with fluconazole became more common and infections due to *Candida* spp. not susceptible to fluconazole were noted.[44-47] Breakthrough infections to echinocandins[48,49] have been noted. Drug tolerance of *Candida* spp. towards echinocandins results from enhancement of cell wall salvage mechanisms or induction of *FKS* gene mutations after drug exposure.[39] Hetero-resistance, defined as non-susceptible sub-populations within a predominantly susceptible population, occurs in *Candida* spp. and other fungi[50,51] and may explain the propensity for *C glabrata* to acquire resistance to azoles.

Although broad-spectrum antifungal agents have decreased the rates of bIC, breakthrough infection with moulds still

occurs despite a variety of antifungal agents.[52-55] *A fumigatus* and multi-resistant yeasts have caused bIFI in patients receiving caspofungin,[48,49,56,57] and *A fumigatus* resistant to azoles has started to emerge in some countries as a product of long-term therapy, or from environmental azole use.[58] Mucormycosis and infections caused by other rare moulds such as *Fusarium* spp. or *Lomentospora prolificans* are seen in patients receiving voriconazole or an echinocandin.[52-54]

2.3 | Iatrogenic factors

Iatrogenic and treatment-related factors might be the most prevalent reasons for bIFIs, including three major groups of factors: (a) inappropriate antifungal therapy including inappropriate selection of antifungals and dosing,[59,60] (b) insufficient plasma and tissue drug levels despite correct dosing because of unpredictable pharmacokinetics with high inter- and intrapatient variability[61,62] or incorrect prescription adherence,[63,64] and (c) fungal biofilm infections of vascular devices or foreign bodies with or without biofilm active antifungal treatment, which are a mixture of both fungal pathogen-related and iatrogenic factors as previously discussed.[65,66]

Pharmacokinetics of antifungals differ significantly, and intra- and interpatient variability of plasma levels as well as variability in intracellular concentrations is an important issue, particularly pertaining to broad-spectrum azoles. Therapeutic drug monitoring (TDM) may be required to achieve efficacy and also to avoid toxicity, particularly for voriconazole and the oral suspension formulation of posaconazole.[67] Antifungal drug pharmacokinetics and the risk of breakthrough infections in those with low trough levels of voriconazole and posaconazole are discussed in detail elsewhere.[9,10,68,69]

Fungal biofilms are complex, three-dimensional communities which often incorporate bacterial pathogens and are key to fungal persistence, particularly in mixed infections and in the presence of medical devices.[70] Well-documented microbial interactions include *P aeruginosa* phages inhibiting biofilms of *A fumigatus* and *C albicans*[71,72] and enhanced fungal virulence in *Galleria mellonella* models of *S aurantiacum* infection.[73] Fungal biofilms often form on indwelling medical devices, other implanted foreign bodies or mucosal surfaces, causing a spectrum of clinical entities ranging from catheter-related fungaemia to endocarditis and vaginal infections.[74] Biofilms formed by *C albicans* and *Aspergillus* spp. are an increasingly recognised clinical problem and most antifungal agents show limited penetration into and thus activity against biofilms.[65,75,76] The main exception is the echinocandin class, which shows superior activity against biofilms compared to other antifungals.[65] The most important measure for successful treatment of biofilm infections remains, however, removal or exchange of the vascular device or foreign body containing the biofilm.[77,78] In cases of suboptimal antifungal selection or insufficient treatment duration, fungal pathogens can persist within the biofilm and cause breakthrough or relapsed IFI.[77]

3 | BREAKTHROUGH INVASIVE FUNGAL INFECTIONS IN PATIENTS WITH HAEMATOLOGIC MALIGNANCY

Reports of bIC in HSCT and neutropenic patients receiving fluconazole caused by fluconazole-resistant *Candida* spp. such as *Candida krusei*,[44] *C glabrata*,[45] *C tropicalis*,[46] *C parapsilosis* and *C lusitaniae*[47] were first noted over three decades ago. Initial reports described breakthrough infection from *Candida* spp. susceptible to fluconazole, largely related to the increasing use of central venous catheters (CVCs).[79] About 20 years ago, reports of bIFIs from *Candida* and non-*Candida* yeasts[80] and moulds[81] during prophylaxis/treatment with the then newer triazoles itraconazole and ketoconazole, as well as to amphotericin B, were reported. More recently, bIFIs have been noted with voriconazole,[19,31] posaconazole[31,82,83] and isavuconazole.[82,84,85] Overall, rates are generally low with voriconazole and posaconazole (range 3.1%-6.5%) but may be higher with isavucanazole with rates of bIFI 13% in one study[86] and 8.3% in another.[87]

Several studies have described antifungal resistance as a driver of bIFI in patients with haematologic malignancies. A 5-year retrospective study at two centres in Brazil found that non-*C albicans* isolates, including *C glabrata*, *C parapsilosis* and *C tropicalis* resistant to triazoles and echinocandins, were more often recovered in patients with bIC compared with de novo IC.[35] In a single-centre study of 139 allogeneic HSCT recipients who received an azole drug for prophylaxis followed by voriconazole for the treatment of proven or probable IA, 13 patients (9%) developed a breakthrough IFI from Mucorales (6/13, 46%), *C glabrata* (4/13, 31%) and multiple fungal pathogens (2/13, 15%). All isolates available for testing had MICs ≥ 1 μg/mL (range 1-32 μg/mL) to voriconazole.[88] In another retrospective, single-centre study of 125 newly diagnosed patients with AML who were on either voriconazole, posaconazole, fluconazole or an echinocandin for prophylaxis against IFI, risk factors for breakthrough IFI vs no IFI included echinocandin prophylaxis (17/21 cases of breakthrough IFI occurred on an echinocandin).[89] A more recent study found a shift in breakthrough infections to those caused by azole resistant moulds, suggesting the epidemiology may vary significantly between countries and/or hospitals. In this study, there were 24 episodes of bIFI in patients with haematological malignancies or SOT recipients over a 4-year period, with a predominance of non-*Aspergillus* mould infections in those with a bIFI compared to those with a non-breakthrough IFIs during the same time period. In particular, the proportion of rare moulds such as the Mucorales, *Fusarium* spp., *S apiospermum* and *Scopulariopsis* spp. were higher in those with bIFI compared to non-breakthrough IFI.[90]

Notable predisposing host factors for these infections included acute leukaemia, neutropenia, mucositis, the use of CVCs and broad-spectrum antibiotics—illustrating the interplay of multiple

host factors that all play a role in breakthrough infections.[80,91-94] In addition, polymicrobial breakthrough bacteraemic and fungaemic episodes were found to be associated with CVCs and neutropenia and were associated with less favourable outcomes compared to monomicrobial infections.[92,95] We discuss these individual risk factors and others further. Lastly, low plasma levels of posaconazole[96] and voriconazole[97,98] are known risk factors for bIFI, but discussed in detail elsewhere.[9,10,68,69]

3.1 | Host and iatrogenic factors associated with breakthrough IFI in haematologic malignancies

3.1.1 | Acute leukaemia

Acute leukaemia alone is a significant risk factor for bIFI, largely due to the increased proliferation of leukaemic cells that leads to decreased production of normal neutrophils and impaired host defences.[18] The ability of leukaemic cells to protect from infection is difficult to definitively establish given the large number of genomic mutations responsible for leukaemia and the overlapping risk factors commonly seen in this population (eg neutropenia, mucositis and corticosteroid therapy). Mechanisms how host factors may predispose for bIFI are summarised in Table 1.

Multiple studies have shown that acute leukaemia is an important host factor associated with breakthrough infections.[22,33,80,99,100] Results are summarised in Table 2.

3.1.2 | Neutropenia

Profound neutropenia is a well-established risk for bIFI caused by moulds and yeast, largely due to the decreased production of neutrophils and impaired host defences (Table 1).[18] Neutropenia has been described as risk factor for bIFI caused by yeasts and moulds.[19,20,22,35,91,99-102] Results are summarised in Table 2.

3.1.3 | Systemic corticosteroids

Systemic corticosteroid use and subsequent immunosuppression are an independent risk factor for bIFI caused by moulds and yeast[18,20,22,88,101,103,104] as shown in Table 2.

3.1.4 | Mucositis/Fungal translocation

Mucositis is a risk factor for bIFI, primarily due to *Candida* spp. which are predominant in the gastrointestinal tract mycobiota. Impairment of the mucosal lining along the gastrointestinal tract may result in translocation of pathogens into the bloodstream.[105] Although *Candida* spp. including *C albicans* and *C tropicalis*, predominate in the healthy human gastrointestinal tract, other pathogenic fungi such as *Aspergillus*, *Fusarium* and *Penicillum* species are found there as well.[106]

As bIC in patients on antifungal prophylaxis became a more recognised phenomenon, there was increased interest as to what was occurring in the gastrointestinal tracts of these individuals. In a small case series from Japan of 10 episodes of breakthrough fluconazole-resistant candidaemia caused by *C albicans*, six of 10 neutropenic patients had *C albicans* on surveillance cultures from the oropharynx and stool prior to the development of candidaemia.[107] In a recent nested case-control study of eight patients with candidaemia and seven patients without candidaemia in New York, United States, all who underwent allogeneic HSCT, evaluation of *Candida* spp. burden in faecal samples before and after transplantation was undertaken. All patients were started on micafungin prophylaxis 7 days prior to transplantation. In both groups, no fungal colony-forming units (CFU) were detected in faecal samples prior to transplantation, but in seven of eight patients who developed candidaemia, rapid expansion of CFU occurred following transplantation, mostly due to *Candida* spp. In contrast, viable CFU were only recovered from one of seven patients who did not develop candidaemia and the faecal mycobiota composition was similar to that found in a

TABLE 1 Mechanism of risk increase of major predisposing host factors for breakthrough invasive fungal infections

Risk factor	Mechanism increasing risk of IFI
Acute leukaemia[18,22,34,81,101,102]	Increased proliferation of leukaemic cells leads to decreased production of normal neutrophils[18]
Neutropenia[19,20,22,34,36,92,101,102]	Decreased production of normal neutrophils[18]
Immunosuppression including glucocorticoids[20,22,89,102]	Impaired innate and/or adaptive immune response[105]; Glucocorticoid-associated dysregulation of immunity[106]
Mucositis[35,36,81,102] fungal translocation[109,110,146]	Impaired mucosal barrier with translocation of pathogens, primarily *Candida*, to the blood[107,109,110,146]
Central venous catheters[34,81,102]	Port of entry and nidus of infection for fungal pathogens, primarily *Candida*[122]
Broad-spectrum antibiotic use[20,22,35,81,101]	Alters gut flora and increases colonisation from *Candida* spp., increasing risk for IC; selective pressures and increase in *Candida* spp. resistance; alterations in host immune response to *Candida* spp.[123]
Genetic factors[27-29,126,127]	Impaired adaptive and/or innate immune function[27-29,126,127]

TABLE 2 Host and iatrogenic risk factor for breakthrough invasive fungal infection (bIFI) in patients with haematologic malignancies

Host and nosocomial factors/studies (yeast to mould)	Acute leukaemia	Neutropenia	Systemic corticosteroids	Mucositis	Central venous catheters	Broad-spectrum antibiotics
Krcmery et al JAC 1998[81] (41 yeast bIFI; 38 controls)	39% of bIFI vs 5% of control ($P < .001$)	Absent in 34% of bIFI vs 61% of control ($P < .02$)	NS	34% in bIFI vs 13% in controls ($P < .05$)	100% in bIFI vs 87% in controls ($P < .02$)	Quinolone prophylaxis; 59% bIFI vs 16% controls ($P < .001$)
Ozun et al CID 2001[22] (49 bIC vs 430 other IC)	AML 69% with bIC vs 29% others ($P < .001$)	88% bIC vs 41% others ($P < .001$)	67% biC vs 35% others ($P = .003$)	NA	NS	98% bIC vs 82% other ($P = .006$)
Puig-Asensio et al CMI 2015[102] (35 bIC vs 202 other IC)	Leukaemia 43% for biC vs 5% others ($P < .001$)	37% bIC vs 5% others ($P < .001$)	NS	27% bIC vs 6% other IC ($P < .001$)	94% bIC vs 79% others ($P = .03$)	NS
Kim et al Med Mycol. 2018[34] (21 yeast bIFI vs 28 other yeast IFI)	62% biFI vs 25% others ($P = .005$)	86% bIFI vs 43% ($P < .01$)	NS	NA	100% bIFI vs 82% others ($P = .06$; NS)	NS
Nucci et al Eur J Clin Micr Inf Dis 2002[20] (29 bIC vs 241 other IC)	NA	OR 9.14; 95% CI 3.30-25.27 ($P < .001$)	OR 3.17; 95% CI 1.31-7.70 ($P < .001$)	NA	NA	OR 2.93; 95% CI 1.13-7.61 ($P = .03$)
Pasqualotto et al J Infect 2006[35] (20 break through candidemia vs 171 with other candidaemia)	NA	NS	NS	15% bIC vs 2% other IC ($P = .027$)	NS	NA
Breda et al Med Mycol 2018[36] (27 bIC vs 121 other IC)	HSCT 59% bIC vs 2% other IC ($P < .001$)	74% bIC vs 6% other IC ($P < .001$)	56% biC vs 30% other IC ($P = .011$)	63% bIC vs 2% other IC ($P < .001$)	NS	NS
Hoenigl et al JAC 2012[103] (44 mould bIFI; 14 yeast bIFI; 116 controls)	NS	>10 d 60% vs 25% ($P < .001$)	>14 d 31% vs 8% ($P < .001$)	NA	NA	NA
Cornely et al JAC 2008[101] (26 bIFI including 18 caused by *Aspergillus*, 1 *Candida* and 8 probable with unknown pathogen; 217 without/possible bIFI)	85% newly diagnosed AML vs 60% ($P = .016$)	OR 1.043 for bIFI per additional day ($P < .001$)	NS	23% vs 11% ($P = .08$; NS)	NS	Higher number of antibiotics administered in those with bIFI ($P = .019$)

Abbreviations: bIFI, breakthrough invasive fungal infection; CI, confidence interval; IC, invasive candidiasis; NA, not applicable; NS, non-significant; OR, odds ratio.

healthy adult population. Furthermore, temporal expansion of mycobiota in the gastrointestinal tract occurred up to 7 days prior to the development of candidaemia, and the *Candida* spp. isolated in the gastrointestinal tract were genomically the same isolates that caused candidaemia. These findings suggest that the rapid expansion of *Candida* spp. in the gastrointestinal tract can lead to translocation into the bloodstream in the right host, even in patients on antifungal prophylaxis.[108]

Multiple studies have shown that mucositis is particularly a risk factor for bIC,[34,35,80,99,100] and results are summarised in Table 2.

Besides disruption of the mucosal barrier (eg caused by persistent inflammation, hypoperfusion or oxidative stress), major risk factors for fungal translocation also include alteration of the normal GI microflora and impaired host defence.[109] Multiple different underlying diseases that are associated with one of these conditions may contribute to fungal translocation, including sepsis,[110,111] kidney disease, liver cirrhosis[112] and HIV infection.[113-117] The effects of chemotherapy on fungal organisms themselves have been theorised to also play a role in translocation. Some chemotherapeutic compounds have been found to cause morphologic switching in *C albicans*, an increase in cellular adherence and proteinase production and the induction of antifungal resistance.[118,119]

3.1.5 | Central venous catheters

Due to breaching the skin barrier and serving as a port of entry and a nidus for infection for pathogens, central venous catheters (CVCs) are a risk factor for bIFI, primarily from *Candida* spp.[120] The ability of *Candida* spp. to form biofilms within a catheter additionally supports colonisation within these 'protected' sites, which may later lead to dissemination and infection. Table 2 summarised results of studies evaluating CVCs as risk factor for bIC.[33,80,100]

3.1.6 | Broad-spectrum antibiotic use

Through alterations of the gut flora resulting in increased colonisation from *Candida* spp., selective pressures and increase in drug resistance among *Candida* spp., and potential alteration in the host immune response to *Candida* spp., antibiotics increase the risk for bIFI.[121] Table 2 summarises results from studies outlining broad-spectrum antibiotic treatment as risk factor for bIFI, in particular, bIC.[20,22,80,99]

3.1.7 | Genetic risk factors

Certain genetic risk factors are known to increase the risk of IFI, particularly from IA. About a decade ago, polymorphism within IL-10 production were shown to constitute a major risk for developing IA, with the ACC haplotype resulting in increased IL-10 production translated to a 9-fold lower risk of developing IA in HSCT recipients vs the ACC/ATA and ATA/ATA haplotypes.[122,123] Toll-like receptors (TLR) are transmembrane proteins on the surface of immune cells that are crucial in the production of inflammatory cytokines and the activation of adaptive immunity. Single-nucleotide polymorphisms (SNPs) in several studies have been shown to increase the susceptibility to IA, including TLR-4[27] and TLR1 and TLR6[124] following allogeneic HSCT. Polymorphisms in tumour necrosis factor alpha (TNF-alpha), another important mediator of the inflammatory response to IFI, has been shown to increase susceptibility to IA.[125] In a cohort of patients who underwent allogeneic HSCT, genetic polymorphisms in plasminogen alleles was shown to be associated with increased risk for IA.[28] Lastly, deficiency of the long pentraxin 3 (PTX3) gene, which is a soluble pattern-recognition receptor produced by phagocytes and is involved in the activation of innate immune cells and the adaptive immune response, is associated with risk of IA in HSCT recipients.[29]

4 | BREAKTHROUGH INVASIVE FUNGAL INFECTIONS IN SOLID ORGAN TRANSPLANT PATIENTS

In the TRANSNET study, the epidemiology of IC in solid organ transplant recipients at 15 US centres was prospectively analysed from 2001 to 2006. Forty per cent of patients who developed IC developed a breakthrough infection on antifungal prophylaxis with either a triazole (75%), amphotericin B (15%) or an echinocandin (10%).[126,127] Another retrospective multi-centre study analysed risk factors for bIC at six tertiary medical centres (three in Spain, two in Argentina, and one in Brazil). Over a 7-year period from 2005 to 2012, independent risk factors for bIC included SOT recipient status.[21] In a recent single-centre study at a tertiary medical centre in North Carolina, United States, over an almost 8-year period there were 156 episodes of bIFI in lung transplant recipients, all who were on aerosolised amphotericin antifungal prophylaxis. Of 815 lung transplant recipients 156 (19%) developed an IFI, with risk factors for developing an IFI including primary graft failure/re-transplantation, the presence of diabetes mellitus, functional impairment/Karnofsky Performance Status Score ≤30%, a more complicated post-transplant course including ECMO within 7 days after surgery, ventilator support longer than 48 hours and dialysis prior to hospital discharge.[128] In a retrospective four-and-a-half-year study of consecutive liver transplantations at a tertiary medical centre in Pennsylvania, United States, risk factors for deep skin and soft tissue infections, including from *Candida* spp., included a number of transplant characteristics including living donor transplantation, prolonged operative time, increased packed red blood cell transfusions during transplantation, and a number of postoperative factors including any biliary complication or bile leak and abdominal reoperation within 90 days of transplant.[23] Several genetic polymorphisms, including interleukin 1β (*IL1β*) and β-defensin 1 (*DEFβ1*), which are both essential in the host defence against IA, are associated with increased risk of IMI in solid organ transplant recipients.[30]

5 | BREAKTHROUGH INVASIVE FUNGAL INFECTIONS IN INTENSIVE CARE UNIT PATIENTS

In a retrospective single-centre study in Texas, United States, of candidaemia in patients with cancer, risk factors for breakthrough candidaemia included intensive care unit (ICU) stay.[22] In another single-centre retrospective study of candidaemia in non-cancer patients on prophylactic fluconazole, independent risk factors for breakthrough candidaemia included the presence of a central venous catheter, artificial ventilation and total parenteral nutrition. The majority of these patients (14/33, 42%) were neonates, all had central venous catheters, 22/33 (67%) had ventilator support, and 24/33 (73%) were on total parenteral nutrition.[129] In a single-centre 8-year study, out of Brazil detailing breakthrough candidaemia of patients with a variety of risk factors including solid tumours (25%), haematologic malignancies (15%) and diabetes mellitus (15%), risk factors for breakthrough candidaemia vs de novo candidaemia included extended stay in the intensive care unit, extended periods of TPN, extended mechanical ventilation and duration of urinary catheter use.[34]

6 | MIMICKERS OF BREAKTHROUGH INVASIVE FUNGAL INFECTIONS

Non-infectious etiologies and endemic mycoses can masquerade as bIFI and vice versa. Pulmonary or extra-pulmonary infections from endemic fungi such as blastomycosis and coccidioidomycosis, as well as *Aspergillus* nodules, can mimic malignancy.[7,130] Although *Aspergillus* nodules are typically rounded, they can appear speculated which is a common appearance of carcinoma.[131] *Aspergillus* nodules can also mimic rheumatoid arthritis and bacterial infections such as *Mycobacterium tuberculosis* and non-tuberculous mycobacterial infections, and *Nocardia*[132] and actinomycosis.[7] Sarcoidosis of the liver and spleen may mimic fungal hepatosplenic microabscesses.[133] Thus, non-fungal etiologies as well as infections from endemic mycoses may present as bIFI, and vice versa, making diagnosis of bIFI challenging.

7 | FUTURE DIRECTIONS

Despite advances made in antifungal prophylactic agents with broader coverage and improvements in the detection of IFI, bIFI continue and will likely persist into the future due to the risk factors highlighted above. The majority of these risk factors are inherent to the treatment of the patients most at risk of these infections, such as the profound immunosuppression prior to and following HSCT or SOT. Other risk factors such as mucositis are secondary effects of immunosuppression, and CVC are often necessary to provide fluids, medications, and at times nutrition to these patients when they are critically ill. Prophylactic antimicrobials, of course, are given to prevent potentially devastating bacterial and fungal infections during the period of profound immunosuppression, but can increase the risk for fungal translocation and breakthrough infections.

Given that major risk factors for IFI are largely not modifiable and bIFI will likely continue to occur in the future, strategies to prevent the morbidity and mortality associated with these infections are needed. One strategy may be to diagnoses bIFIs at the very early stages before the infection has had time to progress. Given that the sensitivity of GM is decreased in patients receiving mould-active prophylaxis or treatment,[11-15] other immunologic markers may aid in the diagnosis of bIFI. We and others have shown that multiple immunologic markers, particularly IL-6 and IL-8, are accurate in discriminating between invasive pulmonary aspergillosis (IPA) and no IPA.[134-136] Both markers can also be trended during treatment to monitor treatment response,[137] and can help predict clinical outcomes in IPA and other IFIs.[138] Other immunologic markers—particularly IL-17 and IL-23—have also shown promise for discriminating between IC and other non-fungal infection,[139,140] although these will need to be validated in additional patient populations. Still, further research is needed to evaluate the impact of antifungal agents on the production of these immunologic markers. In an in vitro model of IA, cytokine levels increased substantially in blood with the addition of hyphal suspension, as expected. The addition of conventional amphotericin B further increased IL-6 and IL-8 levels but the liposomal formulation did not. In addition, conventional amphotericin B substantially increased IL-6 and IL-8 levels in blood without the presence of fungus, while fluconazole decreased IL-6, IL-8 and TNF-α levels compared to levels stimulated with hyphae without an antifungal agent.[141] Thus, the presence of antifungal agents may impact the monitoring of inflammatory markers and this needs to be further evaluated and better understood prior to using inflammatory markers levels for monitoring treatment.

8 | CONCLUSIONS

The epidemiology of IFIs in immunocompromised individuals has changed over the last few decades, partially due to the increased use of prophylactic antifungal agents to prevent IFIs, although the risk factors for these infections has largely remained unchanged. The most significant risk factors for bIFI, including acute leukaemia, prolonged neutropenia, immunosuppression and mucositis, are either inherent to the underlying disease state or result from targeted immunosuppression or transplant. Other risk factors such as CVC use or antibiotics are often necessary to provide medications, fluids, or nutrition peri-transplant or in the intensive care unit and to prevent bacterial infections, in the case of antibiotics. bIFI are likely to continue and newer strategies to diagnoses them in the very early stages may be one strategy to reduce the morbidity and mortality associated with them.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTION

Jeffrey D Jenks: Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Oliver A. Cornely:** Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Sharon Chen:** Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **George Richard Thompson:** Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Martin Hoenigl:** Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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