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Advances in the Diagnosis and Management of Invasive Fungal Disease

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Invasive fungal disease (IFD) is a major cause of morbidity and mortality in HIV-negative immunocompromised patients. The advances in management of patients with solid organ transplantation, bone marrow or stem cell transplantation, hematologic or oncologic malignancies, and chronic inflammatory diseases, as well as in non-neutropenic critically ill patients, has created a growing population at risk for IFD. Despite the life-threatening nature of IFD, prevention, diagnosis, and management strategies remain a moving target. Symptoms are frequently nonspecific, early diagnosis is often difficult to establish, and empiric therapy carries risks of both treatment-associated toxicity and development of resistant organisms.

The current article reviews recent advances and opportunities for improvement in the diagnosis and management of HIV-negative immunocompromised patients with invasive fungal infections. We discuss strategies for risk stratification and evolving methods for diagnosis. Finally, we discuss advances in the identification of new fungal-specific therapeutic targets in light of the relatively limited options currently available and resistant fungal organisms.

Seemingly esoteric and specialized to the Infectious Disease specialty, this topic is in fact relevant to the practicing Pulmonary and Critical Care physician. He or she will see invasive fungal disease as part of the ICU care of transplant and chemotherapy patients or while performing pulmonary consultations outside of the ICU. Knowing what the tools are for diagnosis and treatment is of utmost utility and importance.

Background

IFD is a life-threatening condition in HIV-negative immunocompromised and critically ill patients. Although commonly associated with neutropenic patients, IFD is related to significant morbidity and mortality in a wide range of disease states. The patient population at risk for IFD continues to grow with the advances in management of patients with solid organ transplantation, bone marrow or stem cell transplantation, hematologic and oncologic malignancies, and chronic inflammatory diseases. The most common fungal disease in hospitalized patients in developed countries is invasive candidiasis (IC), which is associated with

ABBREVIATIONS: BDG = β-D-glucan; GM = galactomannan; IC = invasive candidiasis; IFD = invasive fungal disease; IPA = invasive pulmonary aspergillosis; PCR = polymerase chain reaction

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TABLE 1] Large-scale Registries of Clinical Information for Patients With IFD

Study Title	Study Objectives
European Confederation of Medical Mycology (ECMM) Candida Registry (CandiReg) (NCT03450005)[4]	To describe the global incidence of IC and to monitor global trends over time, to define patient risk groups, to assess attributable mortality, to describe diagnostic and clinical course, to inform consensus guidelines, to set up a collection of isolates with molecular characterization and evaluation of resistance genes
Natural History of Individuals with Immune System Problems that Lead to Fungal Infections (NCT01386437)[5]	To collect medical information and samples for a long-term study of people with immune disorders that lead to fungal infections

IC = invasive candidiasis; IFD = invasive fungal disease.

mortality upward of 40%, even with treatment.[1] Invasive aspergillosis is more common in patients with hematologic malignancies and is the most common fungal infection in lung transplant recipients, with an estimated mortality up to > 80% in the ICU.[2] The impact of various fungal infections, particularly candidiasis and aspergillosis, has been widely reported, but the tools for an early diagnosis, the criteria for a convincing diagnosis, and the available therapeutic agents have not kept pace with the changing landscape of IFD. However, promising research is underway to optimize timely and appropriate diagnosis and treatment of IFD. The goal of this article was to outline approaches for ultimately improving the outcomes in patients with IC and invasive pulmonary aspergillosis (IPA) through the following means: identification of at-risk patients, early and convincing diagnosis, and advances in therapeutic management.

Identification and Management of At-risk Patients

Establishing which patients are at highest risk for development of IC and IPA can be accomplished in a multitude of ways, ranging from identification of clinical risk factors through examination of vast amounts of patient data to individual genetic testing. Here, we review the status of large-scale patient registries, clinical risk prediction scores for ICU patients, and research concerning genetic polymorphisms that confer risk for development of IFD.

A large-scale network maintaining records of epidemiologic and clinical information on patients with IFD could produce more robust data on risk factors and outcomes. Global data would be especially important for IC, given the emergence of new isolates and variations in susceptibility.[3] One example of an existing large-scale registry is the Prospective Antifungal Therapy (PATH) Alliance, which comprises a group of tertiary care centers in the United States and Canada. Current studies focused on the establishment of other repositories for information from patients with IFD are described in Table 1.[4,5] These registries can be used in the coming years to establish risk factors for IFD, study resistance mechanisms, and inform clinical guidelines.

The diagnosis of IFD may be especially challenging in ICU patients due to the presence of multiple disease states resulting in nonspecific symptoms. IC is a prevalent entity in the ICU, predominantly associated with candidemia or intraabdominal candidiasis; it carries high crude and attributable mortality rates, ranging upward of 60% when associated with septic shock.[2,6] Invasive aspergillosis, although less commonly encountered in the ICU than IC, is similarly associated with high in-ICU mortality.[2] Early institution of effective treatment is critical to reduce mortality, and differentiating between invasive disease and colonization is essential to avoiding toxicities in patients at risk for multiorgan dysfunction. To this end, multiple risk-scoring models (Table 2)[7-12] have been devised to better predict which ICU patients are more likely to have or develop IFD.

On a more individualized level, genetic propensity for vulnerability to fungal infection has been a topic of research for several years. The genetic predisposition to the development of invasive fungal infection is typically polygenic and therefore emerges phenotypically only in the presence of other predisposing factors such as an immunosuppressed state. Several associations have been identified between the development of invasive aspergillosis and genetic variants related to innate and humoral immunity in hematopoietic stem cell and solid organ transplantation recipients and patients receiving chemotherapy. These include variations in genes encoding toll-like receptors, dectin-1, CXC chemokine

TABLE 2] Clinical Prediction Scores for IPA and IC in ICU Patients

Study	Population	Parameters	Outcomes
IPA			
Blot et al, 2012[7]	115 ICU patients from 30 centers with ≥ 1 *Aspergillus*-positive endotracheal aspirate	Positive tracheal aspirate *with* • Compatible signs and symptoms • Abnormal CXR or chest CT scan • Either host risk factors (immunosuppressed state) or additional culture data	Compared with histopathologic data, • Sensitivity 92% • Specificity 61% Outperformed EORTC/MSG criteria • AUC 76% vs 57%
IC			
Playford et al, 2016[8]	6,685 non-neutropenic ICU patients admitted ≥ 72 h from 7 Australian centers	• Emergency GI/hepatobiliary surgical procedure • Noncoated central venous catheter • Total parenteral nutrition • Admitted to ICU from operating room, ED, or outside hospital • High-dose corticosteroids • Blood transfusion • Carbapenem or tigecycline • Third- or fourth-generation cephalosporin • Prior positive urine culture for *Candida* species • Prior positive throat culture for *Candida* species	With summation score thresholds ≥ 2 to ≥ 6, when compared vs culture or histopathological data: • Sensitivity 39.6%-99% • Specificity 17.7%-95.7% • PPV 1.7%-11.7% • NPV 99.1%-99.9%
Shahin et al, 2016[9]	60,778 non-neutropenic, nontransplanted patients in 96 UK ICUs	• Pancreatitis • No. of central venous catheters • No. of drains • Highest heart rate ≥ 100 beats/min • No. of samples positive for fungal colonization	Compared with histopathological or culture data, using end of day 3 model: • Sensitivity 24%-54% • Specificity 73%-94% • PPV 0.0%-1.7% • NPV > 99%
Ostrosky-Zeichner et al, 2011[10]	597 non-neutropenic, nontransplanted ICU patients admitted for at least 4 d in 6 US centers	• Mechanical ventilation for at least 48 h *and* • Antibiotic use *and* • Central venous catheter on days 1-3 of ICU admission *and* • At least one of the following: any major surgery, use of corticosteroids or other immunosuppressive agents, use of parenteral nutrition, any type of dialysis	Compared with the EORTC/MSG definitions for diagnosis of invasive fungal infection: • Sensitivity 50% • Specificity 83% • PPV 10% • NPV 97%
León et al, 2006[11]	1,699 non-neutropenic adult ICU patients admitted for at least 7 d in 70 centers in Spain	• Surgery on ICU admission • Total parenteral nutrition • Severe sepsis • Multifocal *Candida* species colonization	Compared with proven infection according to histopathological or compatible clinical data with cutoff score 2.5: • Sensitivity 81% • Specificity 74%
Ostrosky-Leichner et al, 2007[12]	2,890 adult ICU patients admitted for at least 4 d in 9 US and Brazil centers	• Any systemic antibiotic *or* presence of a central venous catheter days 1-3 *and* • At least 2 of the following: parenteral nutrition days 1-3, any dialysis days 1-3, any major surgery, pancreatitis, any use of steroids, use of other immunosuppressive agents	Compared with the EORTC/MSG definition for diagnosis of proven or probable invasive fungal infection: • Sensitivity 34% • Specificity 90% • PPV 1% • NPV 97%

AUC = area under the curve; CXR = chest radiograph; EORTC/MSG = European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group. IPA = invasive pulmonary aspergillosis; NPV = negative predictive value; PPV = positive predictive value. See Table 1 legend for expansion of other abbreviation.

TABLE 3] Laboratory Diagnosis of Candidiasis and Aspergillosis

Variable	Specimen	Sensitivity	Specificity	Speciation	Notes
Candidiasis					
Mannan/anti-mannan[22,23,25]	Serum	83%	86%-95%	No	• Result time 6-7 d
β-D-glucan[22,23,25,26]	Serum	57%-97%	56%-97%	No	• Result time 5-8 d prior to culture diagnosis • FDA-approved kit consists of one-time use trays with 96 wells; may delay sample processing
PCR[23,25]	Serum	85%-95%	38%-92%	Yes	• Result time ~6 h
CAGTA[25,26]	Blood	53%-89%	54%-100%	No	
T2MR[25]	Whole blood	91.1%	99.4%	Yes	Result time ~4.5 h
Aspergillosis					
Galactomannan[24,27]	Serum	60%-80%	80%-95%	No	
	BAL	85%-90%	90%-95%		
β-D-glucan[24,26,27]	Serum	60%-80%	80%-90%	No	
	BAL	60%-80%	64%-84%		
PCR[24,27]	Blood (serum, whole blood, plasma)	88%-91%	75%-96%	Yes	• Requires larger sample size
	BAL	70%-91%	92%-100%		
Lateral flow device[24,27,28]	Serum	40%-82%	87%-100%	No	• Result time ~15 min
	BAL	77%-91%	80%-95%		

CAGTA = *Candida albicans* germ tube antibody; FDA = US Food and Drug Administration; PCR = polymerase chain reaction; T2MR = T2 magnetic resonance.

ligand-10, mannose-binding lectin, pentraxin-related protein, and interleukin-10.[13-16] Genetic susceptibility to candidemia and other *Candida* infections has been associated with polymorphisms in genes related to innate immunity, cytokine production, and mucosal integrity, including *TLR* genes, *CD58*, *LCE4A-Clorf68*, *TAGAP*, and *IL-4*.[17] Studies focused on the genetic host factors predisposing to IFD are ongoing. The identification of at-risk patients has important implications for management, as it may be used to guide the use of prophylactic antifungal therapies in transplantation patients, patients receiving chemotherapy, or even selected ICU patients.

Another potential use for the identification of specific risk factors is the selection of patient populations appropriate for vaccination against IFD; vaccines have been investigated for both IC and IPA. Although the utility of vaccination against IFD is seemingly limited in the most relevant patient population (ie, patients with impaired immunity), vaccinations against other types of infection are commonly used in this group. Vaccines targeting *Candida* and *Aspergillus* species could be implemented in patients prior to the onset of immunosuppression (eg, those planning to undergo solid organ transplantation) or designed with adjuvants to increase immunogenicity.[18,19]

Inducing immunity against *Candida* species raises the unique issue of balancing protection against pathogenic manifestations with tolerance of fungal species widely present in the GI tract. Recombinant protein vaccines have used *Candida* species virulence factor proteins to target pathogenic forms and cell surface proteins to optimize immune recognition. These vaccines have shown promise in animal models and clinical trials (although these have been performed in patients with localized disease).[19] Vaccines targeting *Aspergillus* species have been less studied to date, but recombinant protein vaccines have similarly suggested benefit in animal models.[18]

Laboratory Diagnostic Studies for IFD

The diagnosis of IFD should ideally be both timely and clinically convincing for pathogenic effects as opposed to colonization with a fungal organism. Invasive fungal diseases have been most recently categorized for research purposes by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group into the classifications of "proven," "probable," and "possible" according to the combination of host factors, clinical signs, and mycological culture or biomarker data.[20] These classifications provide the basis for categorization of patients in the majority of trials related to the diagnosis of IFD. An alternative definition more easily applied to clinical practice is provided by the International Society for Heart and Lung Transplantation; it includes the presence of fungus in respiratory secretions (detected by culture, polymerase chain reaction [PCR], or biomarker) and the presence of symptoms and radiologic and endobronchial changes, or corresponding histologic changes. The International Society for Heart and Lung Transplantation definition of IFD carries the comparison to colonization, which involves the presence of fungus in respiratory secretions without associated symptoms or radiologic and endobronchial changes.[21]

Diagnosis via culture data is limited by poor sensitivity and by time to result, particularly in light of the prognostic importance of early diagnosis.[22-24] New diagnostic methods for the timely identification of IFD have emerged in recent years and are summarized in Table 3.[22-28] An ideal diagnostic test would be minimally invasive, have a rapid turnaround time to result, be both sensitive and specific for the diagnosis of IFD, differentiate between colonization and invasive disease, and yield speciation and susceptibility data. Clinical trials focused on new diagnostic methods or improvements of existing methods that are currently underway are described in Table 4.[29-34]

Laboratory methods for the diagnosis of candidiasis include mannan/anti-mannan testing, β-D-glucan (BDG), PCR, *Candida albicans* germ tube antibody, and T2 magnetic resonance (T2MR)/T2Candida panel (T2 Biosystems). A combined mannan/anti-mannan antibody assay performs well in *C albicans*, *Candida glabrata*, and *Candida tropicalis* infections and may be used in neutropenic patients and patients with impaired cellular immunity.[23,25] The cell wall component BDG is present in multiple fungal species and is therefore not specific for *Candida* species infection; false-positive test results may occur in bacteremic, critically ill, and lung transplantation patients.[23] The detection of *C albicans, C parapsilosis,* and *C glabrata* infections by *C albicans* germ tube antibody involves use of an indirect immunofluorescence assay against a protein expressed during tissue invasion and biofilm formation, thereby offering potentially useful information in differentiating between infection and colonization.[23,26] Although clinical studies of PCR have used a multitude of platforms and targets, it has generally performed well but is relatively high-cost and labor-intensive.[23,25] A recent development in the diagnosis of *C albicans, C tropicalis, C glabrata, Candida krusei,* and *Candida parapsilosis* infections is the T2Candida panel using T2MR technology, which enables the detection of specific molecular targets using magnetic resonance. This test has a low limit of detection and does not require the use of purification or extraction techniques, resulting in a quick turnaround time.[25,26]

Diagnostic tests for aspergillosis include the galactomannan enzyme immunoassay, BDG, PCR, and lateral flow device. Galactomannan, a cell wall component of *Aspergillus* species, is most sensitive in neutropenic patients with hematologic or oncologic disorders.[24] The role of BDG, as mentioned earlier, remains unclear, particularly in organ transplant recipients and other non-neutropenic patients. There are standardized recommendations for the use of PCR in diagnosis of aspergillosis, and diagnostic accuracy is high in both blood and BAL specimens.[24,27] Lateral flow devices are a point-of-care immunochromatographic assay for an extracellular mannoprotein specific to *Aspergillus* species, and they perform particularly well when combined with galactomannan or PCR for both serum and BAL samples. Their use has been assessed in multiple patient populations, including those with hematologic disorders, solid organ transplantation recipients, and critically ill patients. However, lateral flow devices have not yet been approved by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group committee or the US Food and Drug Administration for use in diagnosis of aspergillosis; thus, their use is not widespread.[24]

TABLE 4] Clinical Trials Evaluating Diagnostic Methods for IFD

Trial Name	Description/Objectives
Optimized Diagnostics for Improved Therapy Stratification in Invasive Fungal Infections (FUNGITECT) (NCT02492594)[29]	Evaluation of a pan-fungal PCR screening assay and other newly developed diagnostic methods compared with conventional methods in patients with oncologic or hematologic malignancies
Prospective Clinical Evaluation of Beta-D-Glucan Assay in Blood and BAL (NCT01576653)[30]	Evaluation of the clinical and diagnostic performance of the Fungitell assay in BAL fluid from patients with solid organ transplantation or hematologic malignancy
Novel Biomarker in Invasive Candidiasis/Candida Sepsis (NOBICS) (NCT02801682)[31]	Identification of biologic markers to anticipate or support the diagnosis of IC in ICU patients and to differentiate between colonization and infection
Bronchoalveolar Lavage Lateral-Flow Device Test for Invasive Pulmonary Aspergillosis: A Multicenter Study (NCT02058316)[32]	Evaluation of LFD in BAL fluid from patients at risk for IPA and evaluation of the potential of LFD in BAL fluid for prognostication
Diagnostic Accuracy of Pleural Effusion Aspergillus Biomarker Testing (EFFU-ASP) (NCT02104479)[33]	Evaluation of the diagnostic accuracy of galactomannan testing on pleural fluid for the diagnosis of aspergillosis
Clinical Evaluation of Novel Biomarkers in Patients with Septicemia (NOBIS) (NCT01359891)[34]	Evaluation of novel biomarkers sST2 and suPAR compared with other well-established biomarkers in the diagnosis of bacteremia and fungemia

LFD = lateral flow device. See Table 1 and 3 legends for expansion of other abbreviations.

Beyond providing information for the initial diagnosis of IFD, biomarkers may be used to de-escalate treatment and thereby limit potential systemic toxicities and the development of fungal resistance. The use of BDG monitoring for withdrawal of empiric systemic antifungal therapy has shown promise, and clinical trials to further evaluate its use for this purpose are ongoing.[22]

Treatment of IFD

The expansion of therapeutic targets for the treatment of IFD is another important area of research. Currently available systemic antifungal medications are limited to four classes: azoles, polyenes, a pyrimidine analogue, and echinocandins. Azoles inhibit the synthesis of ergosterol (a component of the fungal cell membrane), polyenes disrupt the fungal cell membrane causing leakage of cytoplasmic contents, flucytosine (a pyrimidine analogue) disrupts fungal nucleic acid synthesis, and echinocandins inhibit BDG synthesis.[35] The development of new antifungal agents poses a unique challenge due to the fact that, as with humans, fungi are eukaryotes. Many potential treatment targets are therefore shared with humans, increasing the risk of toxicity and side effects. However, the urgent need for new antifungal treatments has grown as resistant organisms have become increasingly prevalent. *Candida auris*, for example, has recently been widely reported in the media as an emerging resistant fungal infection. This species was identified by retrospective review in a case as far back as 1996 but has clearly become much more prevalent in recent years based on repository data. Some *C auris* isolates have exhibited high minimal inhibitory concentrations to all antifungal drug classes.[36]

Therapeutic strategies to combat resistant fungal organisms include adjunctive therapies to existing drug classes and the development of entirely new agents. Adjunctive therapies work by mitigating resistance mechanisms or augmenting antifungal drug activity. Multiple types of compounds have been shown to counteract resistance mechanisms. Efflux pump inhibitors increase the intracellular concentration of an antifungal agent. Histone deacetylase inhibitors can be used in combination with azoles to inhibit trailing growth (growth at concentrations above the minimal inhibitory concentration). Doxycycline, calcineurin inhibitors, and nonsteroidal antiinflammatory drugs have shown activity inhibiting biofilm formation.[37] Compounds that augment antifungal activity act synergistically with antifungal agents by decreasing the ability of fungi to respond to stress. These include heat shock protein 90 inhibitors, calcineurin and calmodulin inhibitors, statins, selective serotonin reuptake inhibitors, nonsteroidal antiinflammatory drugs, iron homeostasis inhibitors, and calcium homeostasis inhibitors. The use of adjunctive therapies, while not yet well supported by in vivo studies, offers a promising option to improve the efficacy of antifungal treatment.

There are several new antifungal agents currently under preclinical development. Targets of these include the fungal mitochondrial membrane, the glycosylphosphatidylinositol cell wall anchor synthesis

TABLE 5] Clinical Trials Involving Novel Antifungal Agents

Trial Name	Agent	Mechanism	Development	Description
Evaluate F901318 Treatment of Invasive Fungal Infections in Patients Lacking Treatment Options (FORMULA-OLS) (NCT03583164)[38]	F901318 (olorofim)	Disruption of de novo pyrimidine biosynthesis	Phase II	Evaluation of study drug for treatment of invasive fungal infections in patients with limited treatment options
Open-Label Study to Evaluate Efficacy and Safety of SCY-078 in Patients with Refractory or Intolerant Fungal Diseases (FURI) (NCT03059992)[39]	SCY-078 (ibrexafungerp)	Inhibition of BDG synthesis	Phase III	Multicenter noncomparator study to evaluate study drug in adult patients with documented fungal infection intolerant or refractory to standard of care
Open-Label Study to Evaluate the Efficacy and Safety of SCY-078 in Patients with Candidiasis Caused by Candida Auris (CARES) (NCT03363841)[40]			Phase III	Multicenter noncomparator study to evaluate oral SCY-078 as an emergency use treatment for patients with *Candida auris* infection
Oral SCY-078 vs Standard-of-Care Following IV Echinocandin in the Treatment of Invasive Candidiasis (NCT02244606)[41]			Phase II	Evaluation of study drug administered at differing doses compared with standard of care following IV echinocandin therapy for IC
Study to Evaluate the Safety and Efficacy of the Combination Therapy of Ibrexafungerp (SCY-078) with Voriconazole in Patients with Invasive Pulmonary Aspergillosis (SCYNERGIA) (NCT03672292)[42]			Phase II	Evaluation of combination therapy with study drug plus voriconazole compared with voriconazole monotherapy in patients with IPA
Evaluation of Rezafungin Compared to Caspofungin in Subjects with Candidemia and/or Invasive Candidiasis (ReSTORE) (NCT03667690)[43]	CD101 (Rezafungin)	Inhibition of BDG synthesis	Phase III	Multicenter, double-blind, randomized trial comparing study drug vs caspofungin in patients with candidemia/IC
CD101 Compared to Caspofungin Followed by Oral Step Down in Subjects with Candidemia and/or Invasive Candidiasis-Bridging Extension (STRIVE) (NCT02734862)[44]			Phase II	Evaluation of safety and efficacy of study drug later in disease course compared with caspofungin in patients with candidemia/IC

BDG = β-D-glucan. See Table 1 and 2 legends for expansion of other abbreviations.

pathway, carbon metabolism, and processes related to virulence factors (trehalose production and Ras function).[35] Several clinical trials evaluating novel antifungal agents are also currently underway as described in Table 5.[38-44] Even if only a few prove to be efficacious, there will likely be new and better options for treating IFD in the coming years.

Another promising therapeutic intervention for infections with *Aspergillus* and *Candida* species is phage therapy. Phage therapy involves the application of bacterial viruses to treat infection and has shown benefit in bacterial infections. There is some evidence that a bacteriophage found in *Pseudomonas aeruginosa* isolates can inhibit both *Aspergillus fumigatus* biofilms and *C albicans* growth, likely via iron sequestration. Further investigations are needed into the clinical effectiveness of phage therapy in IFD.[45]

Conclusions

IC and IPA pose risk to varied patient populations, with significant consequences. Clinical diagnosis is challenging because of the nonspecific symptoms and the unreliability of culture data, and treatment is

complicated by limited therapeutic options, the development of resistant organisms, and systemic toxicity. However, there is a good deal of momentum and promising research into optimizing the care of these patients. Within the next several years, it may be possible to better identify an individual patient's level of risk. More rapid diagnostic methods with increased accuracy will be more widely available. Finally, an expanded arsenal of antifungal medications and other therapeutic agents will be available to treat patients with IFD.

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