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Combination therapy for fungal diseases: the role of immunotherapy in the present and the future

Laura Seldeslachts[a], *Simon Feys*[a,b], *Frank L. van de Veerdonk*[c] *and Joost Wauters*[a,b]

Purpose of review
Invasive fungal infections remain associated with high morbidity and mortality despite advances in antifungal therapy. Current treatments are largely pathogen-directed and fail to address the dysregulated host immune responses that drive severe disease. Together with expanding at-risk populations and environmental changes that promote fungal adaptation, spread, and emergence resistance of fungal pathogens, this underscores the need for complementary immunotherapy.

Recent findings
Disease outcome in invasive fungal infections is determined not only by fungal burden but also by host immune dysfunction. Improved understanding of antifungal immunity has led to a growing range of adjunctive immunotherapies. These include both immune-enhancing and immune-restraining approaches, such as cytokine-based therapies, pattern-recognition receptor agonists, immune checkpoint blockade, monoclonal antibodies, vaccines, cellular therapies, small-molecule immunomodulators, and corticosteroids. Accumulating evidence indicates that their efficacy depends on timing and the patient's immune status, underscoring the need for a balanced, context-specific personalized immunomodulation.

Summary
Antifungal therapy remains the cornerstone of treatment for invasive fungal diseases, but outcomes depend on drug efficacy and host immunity. Combining antifungals with tailored immunomodulation, whether immune restraining, enhancing, or both, offers a promising way to improve outcomes. Future progress will rely on personalized, immune-guided therapies that restore antifungal immunity while limiting immunopathology.

Keywords
host immunity, immunotherapy, invasive fungal infections, personalized immunotherapy

INTRODUCTION

Invasive fungal infections form some of the most lethal yet least recognized infectious diseases worldwide. Recent global estimates indicate that more than 6.55 million people are affected by potentially life-threatening fungal diseases such as candidiasis, aspergillosis and mucormycosis each year, resulting in approximately 3.75 million deaths, of which 2.55 million are directly attributable to fungal infections [1]. Delays in diagnosis contribute to these high mortality rates, yet even when timely antifungal treatment is initiated, outcomes remain poor. This highlights the shortcoming of existing antifungal therapies and indicates that we may be approaching the ceiling of their maximal achievable efficacy within a severely limited treatment arsenal.

Over the past 75 years, only five major classes of antifungal agents were developed: polyenes (amphotericin B formulations), azoles (triazoles and tetrazoles), pyrimidine analogs (flucytosine), echinocandins and other glucan synthase inhibitors, and the allylamines (terbinafine) [2]. Despite their proven antifungal capabilities, all antifungal drug classes are associated with significant shortcomings, including toxicity,

[a]Department of Microbiology, Immunology and Transplantation, Laboratory for Clinical Infectious and Inflammatory Disorders, KU Leuven, [b]Medical Intensive Care Unit, Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium and [c]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands

Correspondence to Laura Seldeslachts, KU Leuven: Katholieke Universiteit Leuven, Leuven, Belgium. E-mail: Laura.seldeslachts@kuleuven.be

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KEY POINTS

- Antifungal therapies target the fungus but do not address the underlying immune dysregulation that also determines disease outcome.
- Combining antifungal therapy with targeted immunomodulation has the potential to reduce mortality in patients with invasive fungal diseases.
- Restoration of immune balance may involve either immune-enhancing, immunosuppressive strategies or a combination of both, depending on the underlying immune landscape.
- The timing of immunotherapy is crucial and can determine the difference between benefit and harm.
- Personalized, immune profiling-based treatment strategies represent a next step in the treatment of invasive fungal infections; however, their successful implementation will require robust translational research in humans to validate and translate preclinical findings into clinical practice.

drug–drug interactions, and the emergence of antifungal resistance [3▪▪].

Several promising antifungal agents with novel mechanisms of action such as fosmanogepix, ibrexafungerp, and rezafungin are progressing through clinical development and represent important advances in the antifungal drug pipeline [2]. Nevertheless, these novel agents may not fully overcome the challenges observed with the existing therapeutic approaches. In parallel, global challenges such as climate change contribute to the emergence and geographic expansion of fungal pathogens, further complicating the therapeutic management of invasive fungal infection [4]. Strategies combining different antifungal drug classes have proven to be beneficial, for instance, in cryptococcal meningitis but may not fully solve the problem posed by invasive fungal diseases [5].

While these antifungal agents target the fungal pathogen, they do not address the dysregulated host-immune response that characterizes most life-threatening fungal infections. Indeed, the majority of life-threatening fungal infections occurs in hosts with impaired or dysregulated immunity, including patients with hematologic malignancies, advanced HIV infection, solid organ or stem cell transplantation [6], critically illness (e.g. severe influenza) [7], inborn errors of immunity [8] or specific host genetic polymorphisms (SNPs) affecting antifungal pathways [9].

These observations suggest that disease outcome is determined not only by fungal burden and antifungal susceptibility but also by the effectiveness of antifungal host immunity. Consequently, optimizing pathogen-directed antifungal therapy alone may be insufficient to achieve fungal control in hosts with profound immune dysfunction.

For this reason, there is growing interest in host-directed immunotherapies to enhance antifungal immune responses [10]. Although no immunotherapies are currently approved as primary treatment for fungal infections, this review examines the established and emerging roles of immunotherapy as adjunctive approaches to improve outcomes in invasive fungal disease.

IMMUNOTHERAPY AS ADJUNCTIVE TREATMENT

Immunotherapeutic strategies aimed at resolving the dysregulated host immune responses have transformed the treatment landscape of several malignancies and inflammatory diseases, yet their application in fungal infectious diseases remains underdeveloped [11,12]. However, recent advances in understanding the normal antifungal host immunity have provided a fundamental basis for the development of a broad array of immunotherapeutic modalities tailored to the patient immune status and evolving host–pathogen interaction. These adjunctive treatment modalities for fungal infections include cytokine-based therapies, pattern-recognition receptor agonists, immune checkpoint blockade, monoclonal antibodies, vaccines, cellular therapies, small-molecule immunomodulators, and corticosteroids. Given that the antifungal host immune response can range from insufficient activation, resulting in impaired fungal clearance, to excessive activation, leading to inflammation-driven immunopathology, these interventions can be grouped into two conceptual immunotherapeutic approaches (Fig. 1): immune-enhancing strategies and immune-restraining strategies.

IMMUNE-ENHANCING STRATEGIES

Immune-enhancing strategies aim to restore or boost the antifungal host defense in patients with impaired innate or adaptive immunity.

Cytokine-based therapies

Cytokines are key regulators of antifungal immunity and therefore have an increased potential as adjunctive immunotherapies for invasive fungal diseases. Among these, recombinant interferon-gamma (rIFN-γ) and colony-stimulating factors (GM-CSF/G-CSF) have been most extensively studied, particularly in cryptococcosis, candidiasis, and aspergillosis. IFN-γ

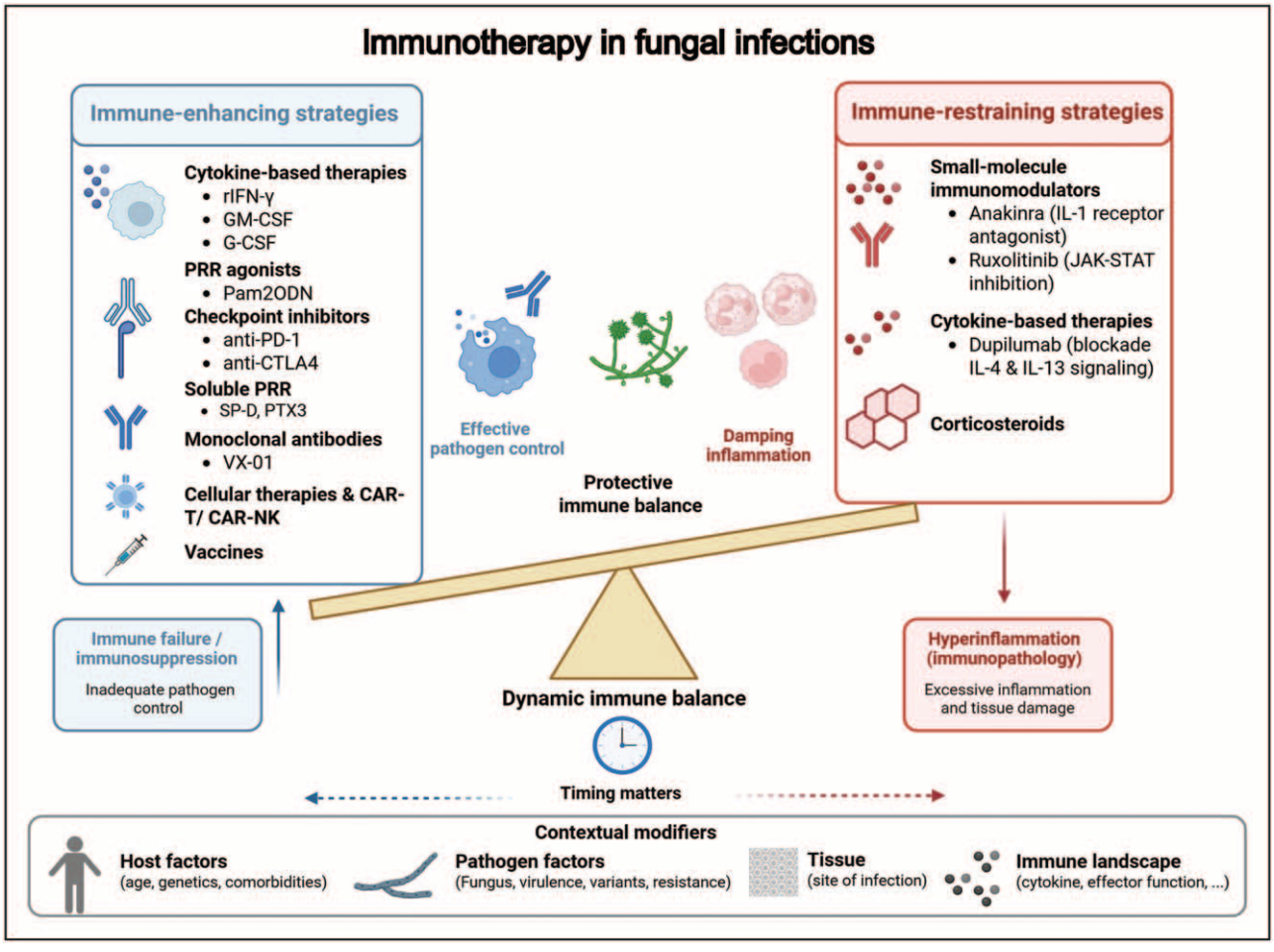

FIGURE 1. Immunotherapy to restore immune balance in invasive fungal infection. The host response to invasive fungal infections requires a dynamic balance between antifungal defense and inflammation-driven tissue damage. Immune-enhancing interventions (left), including cytokine therapies, pattern-recognition receptor (PRR) agonists, checkpoint blockade, antibodies, and cellular or vaccine-based approaches, aim to restore effective pathogen control in states of immune failure/suppression. Conversely, immune-restraining strategies (right), such as small-molecule immunomodulators, targeted cytokine blockade, and corticosteroids, mitigate excessive inflammation and immunopathology. Optimal outcomes depend on appropriately timed and context-specific modulation to maintain a balanced immune response, in which pathogen clearance is achieved without collateral tissue injury. Restoring immune balance through immunotherapy necessitates context-specific tailoring based on host factors, the pathogen, tissue environment, and the immune landscape. Figure created with BioRender.

promotes Th1 differentiation and enhances antifungal effector functions in phagocytes. In patients with a *Candida* or *Aspergillus* infection, rIFN-γ increased HLA-DR expression, thereby augmenting the capacity of the immune system to detect and combat fungal infections through antigen presentation, T-cell activation, and cytokine production [13]. In addition, rIFN-γ has shown clinical benefit as a well tolerated and effective adjunctive therapy for reducing the frequency and severity of serious fungal infection in chronic granulomatous disease (CGD) patients [14–16]. Recently, rIFN-γ was shown to exert immunomodulatory effects by rebalancing the immunopathological signature via metabolic rewiring [17▪▪]. In addition to CGD, beneficial effects of adjunctive rIFN-γ have also been reported in patients with fungal disease in the context of HIV infection, hematologic malignancies, organ transplantation [18▪▪], severe burn injuries [19], and *Aspergillus* tracheobronchitis [20▪▪]. Furthermore, a multicenter, open-label, adaptive phase II clinical trial is currently evaluating the safety and efficacy of rIFN-γ as adjunctive therapy in patient with candidemia (NCT04979052).

GM-CSF and G-CSF enhance the proliferation and antifungal activity of neutrophils, macrophages, and monocytes. In a murine model of *Rhizopus oryzae*-disseminated infection, the GM-CSF in addition to L-Amb therapy could prolong survival and reduce fungal burden compared to L-AmB treatment alone [21]. Similarly, adjunctive GM-CSF therapy enhanced

host defense against *Candida auris* infection in immunosuppressed mice [22▪]. In a clinical setting, GM-CSF was associated with lower transplant-related and invasive fungal disease-related mortality [23].

Immune checkpoint inhibitors

Prolonged fungal infection may induce immune exhaustion through sustained activation of the immune checkpoint pathways, characterized by increased expression of inhibitory receptors such as programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), impaired T-cell effector function, and reduced cytokine production [24]. Preclinical studies have shown that blockade of these pathways can enhance antifungal immunity and reduce fungal burden in murine models of paracoccidioidomycosis [25▪,26▪], mucormycosis [27], cryptococcosis [28], and aspergillosis [29], particularly when combined with conventional antifungal therapy. However, clinical evidence remains limited to isolated case reports, often involving concomitant immunomodulatory treatments such as rIFN-γ. While these observations suggest potential benefit, larger clinical studies are required to define the efficacy, safety, and optimal use of immune checkpoint inhibitors in invasive fungal infections, especially given toxicity concerns in the setting of acute infection and inflammation [30].

Combined immune checkpoint and cytokine therapy

Building on cytokine-based and immune checkpoint immunomodulatory strategies, combined cytokine and immune checkpoint therapy has emerged as a host-directed approach adjunct to antifungal treatment in invasive fungal infections, with preliminary clinical evidence suggesting benefit. Clinical data indicate that anti-PD-1 in combination with rIFN-γ may be useful in severe invasive fungal infections. In a small case series, this approach was associated with survival in six of eight patients with refractory disease, alongside elevated PD-1 expression prior to treatment. These findings provide support for the hypothesis that reversing immune paralysis may enhance pathogen clearance [31▪▪].

Pattern-recognition receptor-targeted approaches

Pattern-recognition receptor stimulation

Beyond cytokine supplementation and immune checkpoint inhibitors, immune-enhancing strategies aimed at restoring impaired innate immune sensing have gained increasing attention. In influenza-associated pulmonary aspergillosis (IAPA), desensitization of PRR signaling pathways is a pathogenic feature, leading to impaired antifungal immunity and correlating with increased mortality [32▪]. In a corticosteroid-immunosuppressed murine model of IAPA, local immunomodulation using nebulized Toll-like receptor (TLR) 2/6 and TLR9 agonists (Pam2CSK4 and CpG oligodeoxynucleotides; PAM2ODN) restored PRR signaling, induced key antifungal effector cytokine pathways, enhanced recruitment of macrophages, natural killer cells and T cells to the lung and significantly improved morbidity and mortality [32▪]. Future translational studies are needed to define the therapeutic potential of PRR stimulation in patients with fungal infections.

Soluble pattern-recognition receptor-based approaches

Alongside PRR stimulation, humoral strategies using soluble PRR mediators are emerging to enhance fungal recognition, opsonization, clearance, and inflammatory signaling [33–35]. Surfactant protein D (SP-D) shows promise: intranasal administration improved survival in a murine model of invasive pulmonary aspergillosis, while in-vitro studies demonstrated inhibition of hyphal growth, fungal surface alterations, and increased susceptibility to antifungals such as voriconazole [36,37]. Pentraxin-3 (PTX3) has likewise emerged as a potential immunotherapeutic target and biomarker in invasive aspergillosis, enhancing opsonization and modulating innate immunity [38,39]. Despite encouraging preclinical data, clinical relevance in humans remains unclear, although their use in other indications supports translational potential (e.g. inhaled recombinant SP-D in bronchopulmonary dysplasia, NCT06897839).

Monoclonal antibodies

Monoclonal antibodies represent a pathogen-directed strategy to enhance antifungal immunity by targeting fungal surface antigens or virulence factors, thereby improving opsonization, phagocytosis, complement activation, neutralization, and antibody-dependent cellular toxicity. Recently, the humanized monoclonal antibody VX-01 targeting mucormycosis was developed, interfering with angioinvasion while augmenting host immune response [40▪▪]. Similar strategies targeting cryptococcal capsular polysaccharides or conserved *Candida* and *Aspergillus* cell wall antigens have shown improved fungal clearance in experimental models [41–44]. However, clinical development has been limited, with trials in cryptococcosis (18B7) and candidiasis (Mycograb) discontinued due to lack of industrial support and safety or quality concerns in

an era where development techniques were far less advanced than current standards [43,45,46].

Cellular therapies and engineered immune cells

Effective antifungal immunity requires coordinated innate and adaptive responses. Cellular immunotherapy aims to enhance this by harnessing both arms of the immune system. Adoptive transfer of fungus-specific T cells that produce high IFN-γ and low IL-10 provides proof of concept, restoring Th1-skewed immunity and improving control of *Aspergillus* infection in immunocompromised patients and infectious mortality [47,48]. To address innate defects, alternative cellular therapies aim to overcome defects in neutropenic patients with invasive fungal infections. While transfusions of mature donor neutrophils show limited clinical benefit due to scalability and short lifespan, conditionally immortalized murine neutrophil progenitors enable generation of homogeneous granulocyte–macrophage progenitors (GMPs) and show efficacy in preclinical models of candidemia and pulmonary aspergillosis [49]. Recently, engineered immune cells have emerged. Building on cancer immunotherapy, chimeric antigen receptor (CAR)-modified cells are being adapted to target fungal cell wall components such as β-glucans and mannans, enabling pathogen-directed immune activation. CAR-T cells targeting *Aspergillus fumigatus* hyphae show potent, selective antifungal activity *in vitro* and efficacy in a murine model of invasive pulmonary aspergillosis [50]. In another study, a lentiviral approach was developed to generate CAR T cells targeting *A. fumigatus* hyphae using an antibody-derived scFv domain, resulting in potent cytotoxic responses, Th1 cytokine release, and strong antifungal activity *in vitro* and improved survival in an immunosuppressed NOD scid gamma (NSG) mouse model of invasive pulmonary aspergillosis. These AF-CAR T cells showed enhanced efficacy when combined with caspofungin to control hyphal growth [51]. In parallel, CAR-NK cells [52▪,53▪], such as SRCD5 CAR NKS cells recognizing β-glucans, demonstrate enhanced activation and cytotoxicity against multiple fungi, including *Candida albicans*, *Cryptococcus neoformans*, *A. fumigatus*, and *Fusarium solani,* reducing fungal burden and improving survival *in vivo* in fungal-infected NSG mice [52▪]. Given the central role of macrophages in antifungal immunity, CAR-modified macrophages represent a promising but still unexplored approach in human invasive fungal disease [54].

Vaccines

Currently, no fungal vaccines are licensed for human use, although several candidates targeting *Candida* spp., such as NDV-3, PEV7, and Candi5V, have progressed into clinical trials [55▪]. Despite advances with pathogen-specific vaccines, this approach is insufficient to address the wide diversity of fungal infections. Consequently, pan-fungal strategies that focus on conserved antigens shared across major fungal pathogens, including *Aspergillus* spp., *Cryptococcus* spp., and *Candida* spp., are gaining attention [55▪]. Such approaches could enable development of a single broad-spectrum vaccine that not only provides cross-protection but also serves as a flexible platform, adaptable to individual patient risk and immune status, thereby supporting personalized antifungal immunotherapies.

IMMUNE-RESTRAINING STRATEGIES

In contrast to immune enhancement, immune-restraining strategies aim to limit excessive inflammatory responses that drive host tissue damage. In certain clinical contexts, immunopathology disrupts immune homeostasis and impairs host immune cell function important to clear the fungal infection, necessitating careful immunomodulation rather than further augmentation of immunity.

Small-molecule immunomodulators

Small-molecule inhibitors provide a powerful means to rebalance dysregulated cytokine and intracellular signaling pathways and thereby restore effective antifungal immunity. One example involves dysregulated IL-1 signaling, where targeted immune-restraining may be beneficial. IL-1β is essential for early antifungal response, particularly neutrophil recruitment and Th17 differentiation, but excessive or prolonged IL-1 activity can drive tissue damage. In IAPA, IL-1-driven inflammation plays a pivotal role in the development of an immunological imbalance, leading to neutrophil dysfunction and a permissive host environment for *Aspergillus* growth [56▪▪]. Targeted immunomodulation with anakinra, an IL-1 receptor antagonist, reduced excessive inflammation, restored neutrophil effector function, and rescued mice from development of IAPA when appropriately timed [56▪▪]. These results highlight anakinra as a promising adjunctive immunotherapeutic strategy for viral–fungal superinfections and support the need for further clinical validation studies.

Beyond IL-1-mediated inflammation, dysregulated IFN-γ signaling represents another important axis of immune imbalance. In chronic mucocutaneous candidiasis (CMC), excessive IFN-γ production by mucosal T cells leads to hyperactivation of the IFN-γ/STAT pathway, resulting in epithelial barrier disruption and increased fungal susceptibility [57,58]. Both murine and human data demonstrate

that this exaggerated type-1 inflammatory response is directly pathogenic. Targeted inhibition of this pathway, either through neutralizing antibodies against IFN-γ or via JAK-STAT inhibition using ruxolitinib can lead to meaningful clinical improvement, supporting the concept that selective immune restraining with adjunctive ruxolitinib can restore mucosal antifungal defense in CMC [57–59]. Similarly, recent work in IAPA identified excessive viral-induced IFN-γ as a driver of immunopathology, impairing macrophage antifungal function and Th17 responses. Partial or complete genetic ablation of IFN-γ restored antifungal immunity and protected against IAPA [60]. Future translational studies are required to determine whether excessive IFN-γ contributes to disease pathology and whether this may represent a viable therapeutic target. These findings suggest that IFN-γ may exert either protective or detrimental effects in fungal diseases depending on the immunological context and timing of the disease.

Lung-specific cytokine delivery via adeno-associated viral vectors

Beyond systemic small-molecule inhibitors, emerging strategies aim to control local respiratory immune reactions without the use of systemic immunosuppressants. Recently, a lung-targeted delivery of anti-inflammatory cytokines using an adeno-associated viral (AAV) vector encoding IL-2, IL-1 receptor antagonist, and IL-10 has been shown to restore local immune homeostasis and reduce respiratory pathology in murine IAPA [61▪▪]. This approach improved respiratory outcomes without inducing systemic immune reactions, highlighting the potential of tissue-specific immunomodulation as a next-generation immune-restraining strategy in fungal infections.

Corticosteroids

Corticosteroids remain the most widely used immune-restraining agents in clinical practice, yet they are also among the most controversial in the context of invasive fungal infections. Indeed, corticosteroids are known to impair macrophage fungicidal activity and neutrophil recruitment, thereby increasing the risk for invasive aspergillosis [62▪]. However, in specific fungal infections where an exuberant inflammatory response is involved, corticosteroids are used as adjunctive immunotherapy, such as in patients with *Pneumocystis jirovecii* pneumonia (PCP) [63], for the treatment of coccidioidal meningitis [64] and chronic disseminated candidiasis [65].

FINDING THE RIGHT BALANCE: COMBINING IMMUNE-RESTRAINING AND IMMUNE-ENHANCING STRATEGIES

Dividing immunotherapy into purely immune-enhancing or immune-restraining approaches oversimplifies the complexity of host immune dysregulation. In some cases, achieving optimal antifungal immunity may require the combination of both strategies. An example of the need for balanced immunomodulation is the case of a previously healthy child with a life-threatening disseminated coccidioidomycosis [66]. Immunological assessment revealed enhanced interleukin-4 (IL-4) production accompanied by reduced IFN-γ responses, indicative of a skewed type 2 immune profile [66]. Adjunctive treatment with rIFN-γ alongside antifungal therapy slowed disease progression. Subsequent blockade of IL-4 and IL-13 signaling using dupilumab led to rapid clinical improvement and resolution of symptoms [66].

TOWARDS PERSONALIZED, IMMUNE-PROFILING GUIDED THERAPY

Despite the conceptual distinction between immune-enhancing and immune-restraining strategies, routine clinical practice still lacks accurate characterization of the individual immune landscape to guide treatment decisions in invasive fungal infections [67▪▪]. Consequently, immunomodulatory interventions are often applied empirically without precise insight into the dominant immune phase at a given timepoint [68▪▪]. The immune response is dynamic, ranging from hyperinflammation to immunosuppression, and patients may require either immune-enhancing or immune-restraining interventions or a combination of both depending on the disease stage. Also, the timing is critical: in a preclinical model of IAPA, early anakinra administration impaired antiviral immunity and worsened lung pathology, whereas delayed treatment restored the immune balance and prevented invasive disease [56▪▪]. These findings underscore the importance of context-dependent and timing-dependent immunomodulation.

A proof-of-concept for immune landscape-guided therapy has been provided by the recent ImmunoSep study in sepsis, in which patients were prospectively stratified based on biomarker-defined immune states and treated accordingly with either immune-restraining or immune-enhancing interventions [69▪▪]. More precisely, patients with ferritin levels greater than 4420 ng/ml were classified as having macrophage activation-like syndrome and treated with anakinra, patients with ferritin levels of 4420 ng/ml or less and less than 5000 HLA-DR molecules on CD45/CD14 monocytes were classified as sepsis-induced immunoparalysis and treated with

rIFN-γ [69▪▪,70]. This trial demonstrated the feasibility of tailoring immunotherapy to underlying immune dysfunction. However, it also highlights the current limitations of static and limited biomarker approaches.

Future progress will therefore depend on a shift towards personalized medicine, in which the immune system is comprehensively and dynamically characterized using validated biomarkers [71▪▪]. The implementation of personalized medicine based on immune-based biomarkers will require identification of patient subgroups that most likely benefit from adjunctive immunotherapy, including but not limited to patients with severe hyperinflammatory response, those with prolonged or profound immunocompromised states (e.g. hematological malignancies or neutropenia), and patients with evidence of ongoing fungal activity despite antifungal therapy, for example, reflected by persistently elevated or non-declining serum or BAL galactomannan indices [72▪,73▪,74]. In this context, integrating immune profiling with fungal biomarkers will be essential not only for initial stratification but also for longitudinal monitoring and treatment adaptation. Such immune profiling may ultimately enable timely, targeted immunomodulatory interventions in high-risk patients that are aligned with the evolving host response, aiming to restore balanced antifungal immunity while minimizing immunopathology and immune exhaustion. In parallel, international collaborative initiatives such as the recently founded International Immunotherapy Society for Fungal Diseases are expected to accelerate progress, foster collaborative research, and facilitate the clinical translation of immune-based and host-directed strategies for fungal infections [68▪▪].

CONCLUSION

Despite advances in antifungal drug development, outcomes of invasive fungal infections remain poor, due to profound and heterogenous host immune dysfunction. Adjunctive immunotherapy offers a promising avenue to complement antifungal treatment, but its success depends on appropriate patient selection, timing, and immune context. Future strategies should therefore move away from empiric immunomodulation towards personalized immune-profiling-guided approaches that dynamically balance the immune system with immune-enhancing and/or immune-restraining therapies to restore antifungal immunity. In addition, implementation of host-directed immunotherapies requires robust translational research in human cohorts, including in-vitro experiments with patient cells to validate preclinical findings and enable clinical application.

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Conflicts of interest

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