Diagnosis and treatment of invasive fungal disease in children with hematological malignancies after chemotherapy: Challenges and strategies (Review)

MINGXIN HE[1*], FENG CHEN[2*], XIAOMIN XIAN[3*] and ZHI GUO[1]

[1]Department of Hematology, Affiliated Nanshan Hospital of Shenzhen University, Shenzhen, Guangdong 518052, P.R. China; [2]Oncology Center, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430014, P.R. China; [3]National Cancer Center/National Clinical Research Center for Cancer, Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, Guangdong 518116, P.R. China

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Abstract. Invasive fungal disease (IFD) has a high incidence rate in pediatric patients with hematological malignancies and hematopoietic stem cell transplantation, markedly elevating mortality rates. Major pathogens include *Aspergillus*, *Candida* and emerging non-*Aspergillus* molds. Clinical manifestations such as persistent fever and dyspnea are frequently non-specific, complicating early diagnosis. Invasive candidiasis typically manifests as candidemia or hepatosplenic infection, whereas invasive aspergillosis predominantly involves the lower respiratory tract. Prophylactic antifungal therapy reduces IFD risk but may lead to breakthrough IFD, particularly during prolonged neutropenia (>14 days). Treatment strategies require individualized selection between monotherapy and combination regimens, incorporating patient status, local epidemiology, prior antifungal exposure, drug metabolism and socioeconomic factors; however, treatment strategies can be hindered by diagnostic challenges including age-specific biomarker thresholds. Emerging techniques such as metagenomic next-generation sequencing show promise for rapid pathogen identification. Central nervous system involvement occurs in a certain proportion of pediatric cases and requires multimodal intervention. Early diagnosis through optimized imaging and timely initiation of targeted therapy are key to overcome clinical challenges and improving prognosis in this vulnerable population. The present review aimed to systematically review the epidemiological characteristics, diagnostic challenges and therapeutic strategies of IFD in pediatric hematological malignancies post-chemotherapy. By collating current clinical evidence, the present review provides an evidence-based framework for optimizing management in this high-risk population.

Contents

1. Introduction

Invasive fungal disease (IFD) is a fungal infection in which fungi invade the body, grow and multiply in tissues, organs or the bloodstream, triggering both inflammatory cascades and direct tissue damage (1,2). IFD complications markedly elevate mortality in patients with hematological malignancies (3). A Chinese multicenter study (n=4,192) analyzing post-chemotherapy IFD epidemiology revealed three key findings: i) Pediatric cases accounted for 16.9% of the cohort, with acute myeloid leukemia (AML; 28.5%), non-Hodgkin's lymphoma (26.3%) and acute lymphoblastic leukemia (ALL; 20.2%) being predominant; ii) severe neutropenia occurred in 33.4% of chemotherapy sessions; and iii) while overall chemotherapy-related mortality was 1.5%, this escalated to 11.7% when IFD was present (4). IFD also has a high prevalence in patients with hematological malignancies and hematopoietic stem cell transplantation (HSCT) (5). *Aspergillus*, *Candida* and *Trichosporon* are the major pathogens of IFD: Infections caused by these fungi usually manifest as non-specific symptoms such as fever and dyspnea, making early diagnosis challenging, particularly in children. Invasive *Candida*

Correspondence to: Professor Zhi Guo, Department of Hematology, Affiliated Nanshan Hospital of Shenzhen University, 89 Taoyuan Road, Nanshan, Shenzhen, Guangdong 518052, P.R. China
E-mail: guozhi77@126.com

*Contributed equally

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infections tend to be candidemia and hepatic and splenic infections; in patients with liver and spleen infections, these infections also present with right upper abdominal tenderness and abdominal pain, making early diagnosis challenging (6,7). In conclusion, IFD not only increases mortality associated with post-chemotherapy pediatric hematological malignancies but also presents multiple diagnostic and therapeutic challenges. Previous studies highlight that pediatric IFD diagnosis faces unique challenges due to non-specific clinical manifestations and limited validated biomarkers for children (8,9).

The diagnostic challenges specific to pediatric IFD are multifaceted: Clinical manifestations such as persistent fever and dyspnea lack specificity, overlapping with bacterial or viral infections, which delays early recognition (10). Invasive candidiasis often presents as candidemia or hepatosplenic lesions, yet abdominal pain and right upper quadrant tenderness may be subtle in children, leading to underdiagnosis (11). Diagnostic biomarkers face validation gaps in pediatric populations, while (1→3)-β-D-glucan (BDG) demonstrates age-dependent diagnostic thresholds (80 pg/ml in children vs. 120 pg/ml in adults), its cross-reactivity with gut commensals limits specificity (12). Similarly, galactomannan (GM) assays require pediatric-specific cutoffs [0.7 optimal density index (ODI) for serum in children <12 years vs. 0.5 ODI in adults] (13). Emerging non-culture techniques, such as metagenomic next-generation sequencing (mNGS), show promise but lack standardized validation in children (14-18). A 2024 study demonstrated that plasma mNGS achieved 89% sensitivity and 94% specificity for diagnosing IFD in immunocompromised pediatric patients, although sample contamination risks necessitate clinical correlation (19). Furthermore, the absence of age-adjusted diagnostic criteria for IFD in children contributes to delayed treatment initiation, exacerbating mortality risks in this vulnerable population (20,21).

2. Epidemiological characteristics

General characteristics. Pediatric IFD exhibits distinct epidemiological patterns across regions. A French multicenter study involving 2,721 patients and spanning 2015 to 2018 reported a 5.3% IFD incidence rate, but the generalizability may be limited by the predominantly Caucasian population (82% of participants were of European descent) and exclusion of transplant recipients with graft-vs. -host disease (22,23). While the French cohort provides valuable multicenter data, its sample size lacks power for subgroup analyses of rare fungi such as *Fusarium*. Comparatively, Chinese cohort data (with 4,192 patients) showed higher mold predominance (73 vs. 42% in the French cohort), highlighting regional ecological variations in fungal epidemiology (4). Pediatric IFD exhibits distinct epidemiological patterns, with patients with AML and allogeneic HSCT (allo-HSCT) showing the highest susceptibility (12.9 and 4.3% incidence, respectively). Breakthrough infections under prophylaxis remain a concern, particularly with prolonged neutropenia lasting >14 days (24). The prevalence of IFD in patients with pediatric hematological malignancies is generally high, and granulocyte deficiency persisting for >10 days after chemotherapy is an independent risk factor associated with combined IFD in pediatric hematological malignancies, while granulocyte deficiency persisting for >14 days and not receiving antifungal prophylaxis (AP) is an independent risk factor associated with combined IFD in pediatric hematological malignancies after allo-HSCT. A retrospective analysis of the incidence of IFD in hematological neoplasms in children showed that IFD was diagnosed in 75 (7.2%) of 1,047 children, with 15 cases of candidemia (60% of these being non-*Albicans*) and 60 cases of mold infections (55% of these being non-*Aspergillus spp*.), and the mortality rate of IFD was 21.7%. Among hematological malignancies, AML and ALL showed the highest incidence of IFD: In pediatric patients with these malignancies who developed IFD, 89% had severe neutropenia and 73% received high-intensity therapy (25). A previous study analyzing the epidemiology of IFD occurring in children with hematological malignancies showed that among 471 at-risk patients (median age, 9.8 years) with hematological malignancies, 27 children experienced 28 IFD episodes. These included 5 cases of candidemia and 23 cases of bronchopulmonary mycosis; additionally, 20 patients developed breakthrough infections, 8 required intensive care and six succumbed to the disease (26). Rosen *et al* (14) analyzed the incidence, site of infection and mortality of IFD in pediatric patients with hematological malignancies, and retrospectively analyzed the treatment of 1,052 children with hematological malignancies from 1991 to 2001. In the pediatric hematological malignancies cohort study, the incidence of IFD was 4.9%, with the IFD incidence increasing from 2.9 to 7.8% from 1996 to 2001. Acute leukemia (AL) cases in children accounted for 36% of cases, but the incidence of IFD infection was as high as 67%. *Candida spp*. were the main pathogens of IFD, with a decrease in infections caused by *Candida* and an increase in *Aspergillus* infections over time. A total of 62% of all patients who developed infections did so during the neutropenic phase of post-chemotherapy, which was 2.6-fold higher in patients with IFD. IFD is a common complication during chemotherapy for AL in children, and relevant studies are shown in Table I (20,24,27-30).

The adoption of pharmacological prophylaxis against IFD pathogens is an effective means of addressing the risk of IFD infection. AP is preferentially recommended for pediatric patients with hematological malignancies with a risk of developing IFD >10% such as patients with AML, relapsed leukemia or undergoing allo-HSCT. However, with the widespread use of AP in pediatric patients with hematological malignancies, there is also a need to address the issue of breakthrough IFD (bIFD), which is defined as invasive fungal infection occurring during antifungal exposure, as per the European Confederation of Medical Mycology guidelines (2020) (31). bIFD has become an issue in patients receiving systemic antifungal medications, with time to bIFD defined as the first attributable clinical sign or symptom, mycological evidence finding or imaging feature. The duration of bIFD is dependent on pharmacokinetic properties and lasts at least until one dosing interval after discontinuation (32). Despite intensified AP after chemotherapy or allo-HSCT, bIFD remains a common complication and cause of mortality after hematological malignancy treatment (33). Risk factors for bIFD include severe neutropenia, use of corticosteroids and prolonged use of broad-spectrum antibiotics. The immunosuppressive state of the body in children with hematological

Table I. Analysis of IFD in AL in children.

First author, year	Research period	Type of study	Number of patients included	Number of cases of IFD	Clinical manifestation	Research results	(Refs.)
Ávila Montie *et al*, 2023	2007 to 2017	Retrospective study	129	15	A total of two children succumbed to IFD-related complications. The most common IFD type was aspergillosis (7 cases), followed by candidemia (4 cases).	Mortality due to IFD could be prevented by effective pharmacological therapy, and appropriate AP strategies still need to be developed through larger prospective studies.	(20)
Lin *et al*, 2018	2005 to 2014	Retrospective study	78	22	The prevalence of IFD was 20.5% (16/78), with *Candida spp*. accounting for 59.1% of the cases, and the overall mortality ≥10 years was 53% (8/15) for IFD and 80% for pulmonary aspergillosis.	IFD showed a notable morbidity and mortality in pediatric patients with AML, and identifying factors associated with IFD may help in early recognition of IFD and timely initiation of antifungal therapy.	(27)
Evim Sezgin *et al*, 2022	2010 to 2015	Retrospective study	307	121	Invasive aspergillosis (81.9%) was the most common infection, followed by invasive candidiasis (13.4%) and rare fungal diseases (4.8%). The majority of IFD in ALL and AML occurred during the induction phase. The overall mortality rate was 24%, while the IFD-related mortality rate was 18%.	IFD incidence increased with advancing pediatric age, particularly among adolescents with hematological malignancies, and was markedly elevated in AML and relapsed AL cohorts.	(28)
Tüfekçi *et al*, 2015	2001 to 2013	Retrospective study	174	25	A total of 14% of cases had combined IFD. The majority of children were in the consolidation phase of chemotherapy and had severe neutropenia, including 24 patients with pulmonary	Rapid and effective antifungal therapy, as well as rational treatment may reduce mortality.	(29)

Table I. Continued.

First author, year	Research period	Type of study	Number of patients included	Number of cases of IFD	Clinical manifestation	Research results	(Refs.)
					IFD. All patients received treatment with voriconazole, amphotericin B, caspofungin or posaconazole (as monotherapy or combination therapy). No IFD-related mortalities occurred.		
Yeoh *et al*, 2021	2003 to 2014	Retrospective study	63	66	The prevalence of IFD occurring with initial induction therapy for AML was 20.7%, whereas 74.4% of the pathogens were mycobacteria, 37.9% of which were non-*Aspergillus spp*. The all-cause mortality rate at 6 months after the diagnosis of IFD was 16.7%, while the IFD-related mortality rate was 7.6%.	IFD is a common and serious complication of AML treatment in children. Mold infections, including *Aspergillus spp*. predominated in this cohort, and a systematic approach is needed to identify patients at risk and develop targeted prevention strategies for IFD.	(24)
Lehrnbecher *et al*, 2023	2009	Retrospective study	6,136	224	Including 65 cases of yeast and 159 cases of mold, the mortality rates of IFD at 6 and 12 weeks were 10.7 and 11.2%, respectively. In multivariate analyses, risk ratios for event-free and overall survival were markedly increased for patients with demonstrated or probable IFD, age ≥12 years and inadequate response to treatment.	Older children with ALL and children at high risk of IFD with inadequate treatment response were independent risk factors for IFD development and overall survival and these patients may benefit from targeted AP.	(30)

IFD, invasive fungal disease; AL, acute leukemia; AML, acute myeloid leukemia; AP, antifungal prophylaxis; ALL, acute lymphoblastic leukemia.

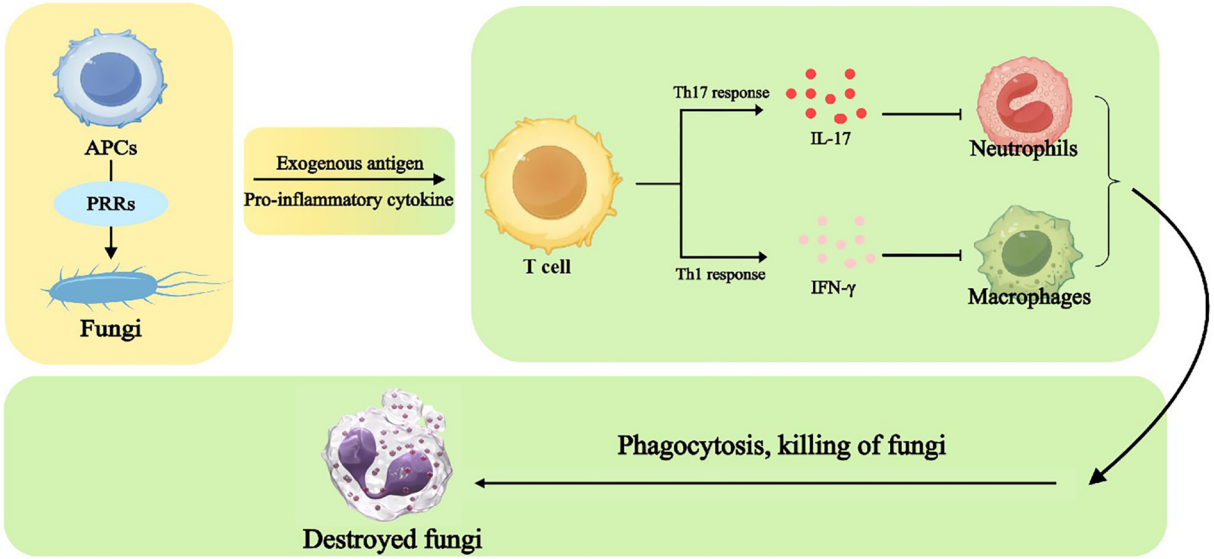

Figure 1. Activation of innate and adaptive immunity against fungal pathogens.. Fungal infections (such as *Aspergillus* and *Candida*) activate the innate immune system through PRRs that recognize pathogen-associated molecular patterns. PRRs are primarily expressed on APCs such as dendritic cells and macrophages. Fungal infections activate neutrophils, monocytes, macrophages and dendritic cells in the intrinsic immune system, which in turn stimulate the adaptive immune system. PRRs, pattern recognition receptors; APCs, antigen-presenting cells; Th, T helper cell.

neoplasms undergoing chemotherapy or post-transplantation directly contributes to the likelihood of an increased risk of developing bIFD. The occurrence of a bIFD can be fatal and early intervention may improve the outcome of IFD (Fig. 1). Persistent IFD is defined as IFD that remains unchanged and continues to require antifungal therapy since the initiation of treatment, and is distinct from refractory IFD, which is defined as disease progression. Recurrent IFD occurs after treatment and is caused by the same pathogen at the same site, but transmission may also occur (34). Fungemia is predominantly caused by *Candida*, whereas pulmonary IFD is primarily due to filamentous fungi, notably *Aspergillus*, and the widespread use of AP has increased the proportion of non-*Aspergillus* filamentous fungi (35,36).

Characteristics of IFD infection after allo-HSCT. IFD is a common and serious complication after allo-HSCT for hematological malignancies in children. The incidence of IFD is gradually increasing and has become one of the causes of mortality after transplantation (37,38), highlighting the need for IFD to be diagnosed and treated as early as possible (39,40). The occurrence of IFD is related to factors such as neutrophil deficiency, T-cell dysfunction, prolonged application of hormones or high-dose chemotherapy pretreatment during transplantation. The lack major of specificity of clinical features makes early diagnosis of IFD difficult and once it occurs the prognosis is notably poor (23,41). A study has shown that the incidence of *Aspergillus* exceeded that of *Candida* among pathogens causing IFD in transplant patients, and that IFD occurs mainly in the early and mid-transplantation periods (42). In the early stages of transplantation, generally ≥1 month after transplantation, in patients with neutropenia, broad-spectrum application of antibiotics and impaired mucosal barrier are the main risk factors for the development of IFD, with *Aspergillus* and *Candida* being the most common pathogenic organisms. The mid-transplantation period comprises 2-3 months after transplantation, and the main risk factor for the occurrence of IFD in this period is the application of anti-graft-vs. -host disease (GVHD) therapy such as glucocorticoids (43-45). Patients in this period may have a combination of GVHD or cytomegalovirus infection, and the highest percentage of *Aspergillus* infections occurs at this time, with a notable decrease in the percentage of *Candida* infections (46).

Late B-lymphocyte function after HSCT may take months to years to fully return to normal; in this period, patients are susceptible to infections and other complications during the complex process of B-lymphocyte development, in which HTSCs differentiate into lymphoid progenitor cells in the bone marrow, further differentiate into pre-B and immature B cells and finally develop into mature B cells (47,48). Following HSCT, the recovery of myeloid lineage cells precedes the reconstitution of lymphocytes, with B-cell development exhibiting a delayed time course. B cells are characterized by their cytosolic membrane surface expression of a variety of cytokine receptors (such as IL-1, IL-2 and IL-4), which can be secreted by the cytokines of T helper cells to produce a response (49,50). Cytokines such as IL-2 and IL-4 promote B cell proliferation and their subsequent differentiation into antibody-producing plasma cells. Some of the proliferating B cells migrate to the medulla of the lymphoid tissue and continue to proliferate and differentiate to provide a defensive response to antibody production by plasma cells, whereas some of the B cells and associated T cells migrate to the nearby primary lymphoid follicle B cell region to continue to proliferate and form secondary lymphoid follicles in the germinal center (Fig. 2) (51,52). The greater the intensity of transplantation preconditioning and the more immunosuppressive agents applied, the greater the possibility of IFD infection, and if a patient has a history of IFD infection prior to transplantation, the risk of IFD infection during transplantation is markedly increased (53).

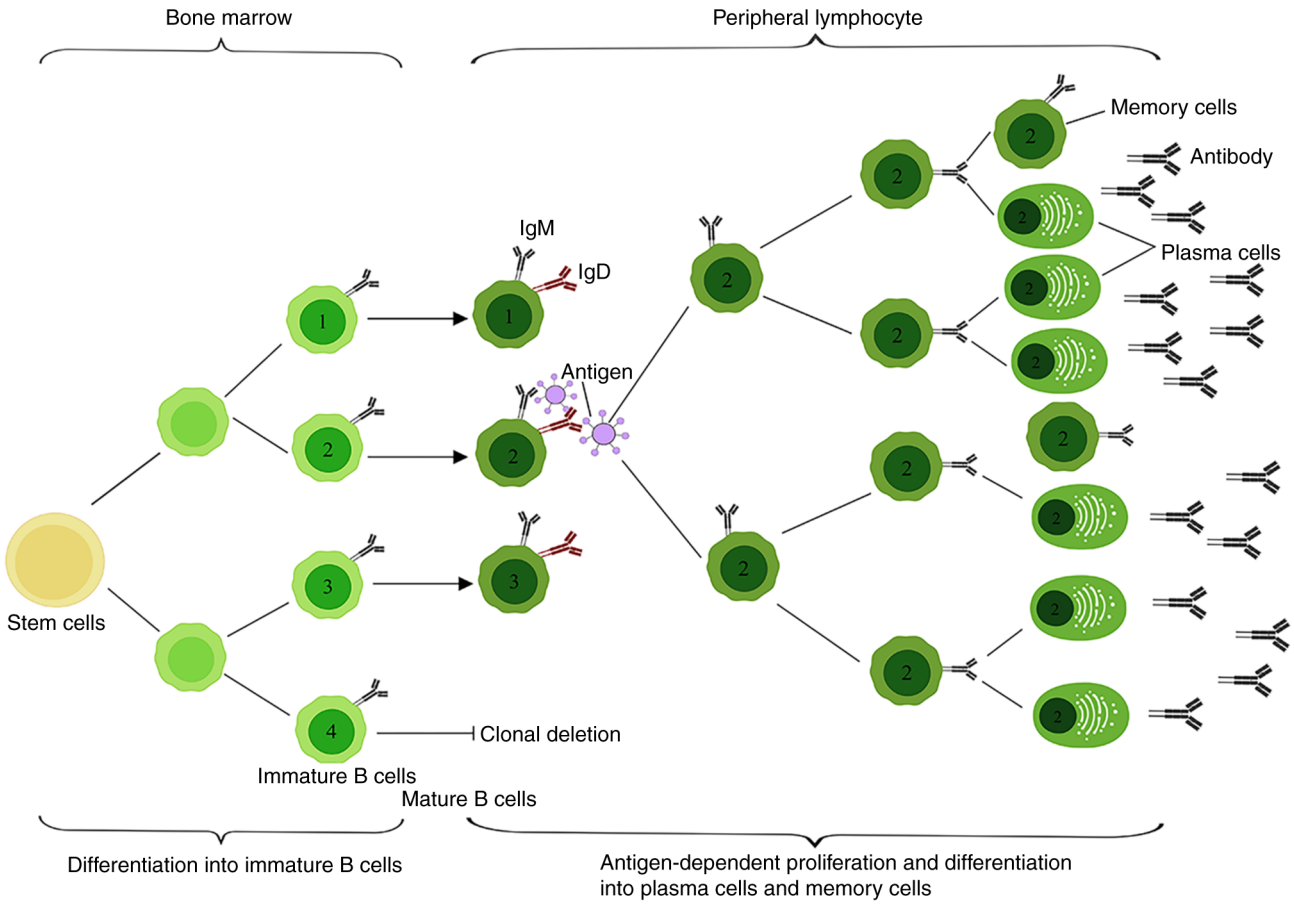

Figure 2. Schematic representation of B-cell differentiation. The process begins in the bone marrow with hematopoietic stem cells, which undergo a series of differentiation steps to become immature B cells. This antigen-independent phase involves the rearrangement and expression of immunoglobulin genes. Upon encountering a specific antigen in the periphery, mature B cells are activated, proliferate and undergo clonal expansion. These activated B cells finally differentiate into antibody-secreting plasma cells, which mediate humoral immunity, and long-lived memory B cells, which provide lasting immunological protection.

In a prospective multicenter study analyzing clinical data on combined IFD after chemotherapy or allo-HSCT for hematological malignancies in children, a total of 304 children were treated with chemotherapy or allo-HSCT, and 19 developed IFD, including 10 cases of *Aspergillus spp*. and 5 cases of *Candida spp*. that were confirmed. Among these patients, no fatalities were attributed to IFD; however, in a subgroup of 8 patients who underwent allo-HSCT and developed IFD, 3 cases resulted in mortality (54).

3. Clinical manifestations and diagnosis of IFD

Clinical manifestation. Invasive candidiasis is a common IFD in children with hematological malignancies (55). This most commonly presents as candidemia and liver and spleen infections, with the main clinical symptoms being fever and other non-specific manifestations such as fatigue and malaise or reduced appetite and weight loss. In children with hematological malignancies and suspected invasive candidiasis, if broad-spectrum antibiotics fail to improve clinical symptoms (e.g., persistent fever), laboratory examinations for fungal BDG should be performed to aid in the diagnosis (56). IFD occurring in the liver and spleen sites upon fungal infections increase the incidence and mortality after chemotherapy for hematological malignancies in children (57,58). To the best of our knowledge, there are insufficient data to support the optimal diagnosis of IFD at the liver and spleen sites in children, and clinicians should be alerted to the presence of persistent fever, back pain extending to the shoulders, widespread muscle pain and elevated serum GM levels in children with neutropenia after chemotherapy. In children with prolonged neutropenic fever, early detection and diagnosis of IFD in the liver and spleen should be recommended by abdominal ultrasound and abdominal computed tomography (CT), even in the absence of localized signs or symptoms (59). Invasive aspergillosis (IA) is the most common type of infection in children after chemotherapy for hematological malignancies, especially after allo-HSCT, and its symptomatic presentation depends on the site of infection (60,61). The most common site of infection in children with hematological malignancies is the lower respiratory tract, which can cause *Aspergillus* bronchitis and pneumonia, followed by nasal infections and central nervous system (CNS) infections. Common symptoms of respiratory *Aspergillus* infections include cough and dyspnea, brownish-black mucus plugs in some patients and coughing up blood in severe cases (62). CNS *Aspergillus* infections may present with unusual headaches, seizures and severe loss of consciousness. However, it can be difficult to recognize IA early in children, as they may present initially with only non-specific signs such as fever, which can obscure or precede

the development of more specific neurological symptoms. In CNS fungal infections, *Aspergillus spp*. are the most common pathogens, and tests such as magnetic resonance imaging are difficult to use for diagnosis: By contrast, detecting fungal antigens such as GM or BDG or early diagnosis by molecular detection of fungal nucleic acids are preferred (63). In a multicenter retrospective study, 51 children with AL combined with CNS fungal infections were analyzed, of whom six patients underwent HSCT and 17 were clinically diagnosed by combining typical imaging manifestations of fungal infections of the CNS with positive microbial results in the cerebrospinal fluid or a positive BDG or GM assay. The proposed diagnosis was made in 34 cases with only typical imaging manifestations of fungal infections of the CNS. The median time from fever to diagnosis was 5 days for all patients, and the most common fungal pathogen was *Aspergillus spp*. In total, 16 patients received monotherapy and 35 received combination antifungal therapy, whereas 23 patients underwent surgery. A total of 22 patients eventually succumbed to the disease, and 10 other patients had neurological sequelae. Early diagnosis and prompt treatment of childhood AL combined with fungal infections of the CNS, either antifungal therapy or surgery, are essential to improve clinical outcomes (64).

Imaging features. Pulmonary imaging of IFD is diverse, with *Aspergillus* infestation involving alveolar and fine bronchial walls. Imaging may present non-characteristic changes such as patchy shadows, gross glass-like changes, air bronchial sign, crescent sign and lung cavities on a chest CT. Typical halo sign imaging manifestations are generally considered for pulmonary IA, and this sign is most frequently observed in the early stage of the infection, often corresponding to the period of neutropenia before the recovery of the white blood cell count. By contrast, inversion halo and hypodensity signs are typical features of pulmonary trichothecosis, but they occur less frequently. The inversion halo sign is important in pulmonary filamentous fungal diseases, especially in trichothecene infections, and can also be used as one of the clinical diagnostic criteria for non-*Aspergillus spp*. filamentous fungal diseases (65). In addition, IFD imaging can show solid and ground-glass clouding, and pulmonary infections with *Aspergillus* tend to show more typical imaging features such as air crescent sign, intracavitary streak shadows and intracavitary air bubble shadows. In the early stage of pathogenesis, the lung CT manifestations of pediatric patients with IFD lack specificity and are mostly patchy, but some characteristic manifestations have high clinical diagnostic value:, for example, *Aspergillus* usually forms nodules or solid lesions locally in the lungs, which may be singular or multiple, and are largely located in the subpleural lungs (66).

Diagnosis. Diagnosing pediatric IFD requires overcoming three key barriers: i) Overlapping symptoms with bacterial infections; ii) lower sensitivity of GM assays in children compared with adults; and iii) invasive procedures being less feasible in young patients. Emerging non-culture techniques such as mNGS show promise but require pediatric-specific validation (67). Laboratory diagnostic methods for IFD include traditional fungal tests such as microscopic smear microscopy, culture and histopathological examination, as well as laboratory diagnostic tools such as the BDG and GM assays. The BDG assay detects cell wall components of fungi, such as the polysaccharide component of the cell wall of yeast-like fungi. The cell wall component, BDG is a component of numerous pathogenic fungi, and it is widely used as a diagnostic tool in clinical practice in assay form, including in children and neonates (68,69).

The GM assay is a serological method for detecting *Aspergillus* infections, and the main test substance is GM antigen, which is a cell wall polysaccharide component unique to *Aspergillus*; thus, the GM assay is a reliable biomarker for the early diagnosis of invasive *Aspergillus* infections (31). Patients with clear pulmonary imaging features and a positive BDG or GM assay can achieve a clinical diagnosis of IFD, with histopathological examination remaining the gold standard for the diagnosis of IFD. Diagnostic thresholds require pediatric-specific adjustments: For BDG assay, the optimal cutoff in children is 80 pg/ml (sensitivity, 82%; specificity, 74%), which is markedly decreased compared with the adult cutoff of 120 pg/ml due to developmental differences in immune responses (10,21). GM assays demonstrate age-dependent variations, with recommended cutoffs of 0.7 ODI for serum (vs. 0.5 in adults) and ≥1.0 ODI for bronchoalveolar lavage fluid (vs. ≥0.5 ODI in adults) in children <12 years, accounting for dietary GM cross-reactivity (70,71). For individuals aged ≥12 years, adult cutoffs are applied. These modifications are important given that pediatric false-positive rates exceed adult levels by 15-20% for GM assays (72).

The diagnosis of IFD can be categorized into four levels: Confirmed, clinically diagnosed, proposed and undetermined. When the condition of a patient is critical and histopathological biopsy is limited, the diagnosis of IFD consists of host factors (for example, severe immunodeficiency), clinical manifestations and microbiological basis for confirmation of the diagnosis in addition to host factors and identifying microorganisms in the histopathology (73). The basis for the proposed diagnosis requires a host factor and a major clinical manifestations, especially typical imaging basis and a laboratory basis for the diagnosis of IFD diagnostic grading to the clinical diagnosis (74). For instance, the BDG/GM assay demonstrates high sensitivity in diagnosing pulmonary IFD; a positive BDG/GM result, combined with definitive lung imaging findings, supports a clinical diagnosis of IFD. Confirmatory diagnosis requires fiberoptic bronchoscopy with lavage or tissue biopsy for pathological examination, when feasible (75).

The consensus on IFD was revised and updated by the European Organization for Research and Treatment of Cancer and the Fungal Disease Research Group Education and Research Federation in 2020 (31). This consensus suggests that there has been a marked increase in evidence for using GM to diagnose IFDs such as IA, and the detection of BDG assay should also be expanded to a wider range of patients. At present, an increasing number of fungal PCR have undergone considerable standardization, coupled with the availability of commercial analysis, external quality assessment schemes and a large quantity of performance validation data, which can be widely used for screening and diagnosing IFDs (76). Molecular diagnostics exhibit pediatric-specific characteristics: Fungal PCR achieves 92% sensitivity in children using

whole blood samples (minimum volume, 3 ml), compared with 78% with serum samples, reflecting higher fungal burdens in pediatric hematological malignancies (77). mNGS shows superior performance in pediatric pulmonary IFD, with 15% higher detection rates compared with adults, although environmental fungal DNA contamination may cause false positives in 8-12% of cases (67,78). For infections caused by *Aspergillus*, *Candida* and *Pneumocystis jirovecii*, PCR testing combined with serological assays is recommended to enhance diagnostic accuracy (77).

Diagnostic assessment. IFD often involves the lower respiratory tract and fungemia, among which, lung infection is the most common (79). Chest CT performance is complex and varied, generally manifested as nodular or a patchy shadow. Ocassionally, a typical halo or crescent sign can be observed, which is a relatively more characteristic change (80). Some patients may present non-characteristic changes in the early stage of the disease, such as bronchial dilatation sign, buds sign, hairy glass shadow, solid shadow and tiny nodular shadow (81). Ground glass shadows are notable for early diagnosis and are characteristic of *Aspergillus* airway infiltration. It is also important to note that new signs of infiltration on CT imaging should also be considered, and early use of effective antifungal medications is a key factor in good control. IFD is difficult to diagnose early due to the lack of diagnostic indicators with high specificity and sensitivity (82). In patients with hematological malignancies, the presence of characteristic imaging changes in the lungs combined with a positive specific BDG/GM assay can clinically confirm the diagnosis. Since BDG is widely present in fungal cell walls, the BDG assay is not effective in differentiating *Aspergillus* from *Candida* (21), whereas the GM assay is mostly used to carry out the diagnosis of *Aspergillus* infections (70).

Invasive trichothecenes are common in children after chemotherapy for hematological malignancies, especially after HSCT. The clinical manifestations of trichothecenes are varied and depend mainly on the site of infection, which is commonly skin, nasal and lung infections (83). A previous multicenter study was conducted to analyze the characteristics of hematological malignancies involving trichothecenes in children. In a cohort of 39 pediatric patients with combined trichothecenes, 92% of trichothecene cases occurred in patients with AL, with a notable association with high-risk ALL and advancing age, and a total of 15 patients (38%) succumbed to trichothecenes (84). Pulmonary mucormycosis may cause non-specific segmental or lobar bronchopneumonia with cavitation similar to aspergillosis and imaging may help to determine the extent of mucormycosis infection (85,86). Current serological testing for the diagnosis of trichophytosis is limited and usually relies on clinical presentation, tissue biopsy or culture results for diagnosis and PCR can assist in identifying the pathogen (87).

4. Treatment of IFD

IFD treatment using drugs can be categorized into monotherapy and combination therapy according to the presence or absence of clinical manifestations at the beginning of treatment in patients with high-risk factors, as well as the type and outcome of obtaining a diagnostic basis for IFD (88). The choice of therapeutic agents is based on a combination of factors, including condition of the patient, the local epidemiology of the fungus, previous antifungal therapy, and drug metabolism and sensitization results. IFD risk factors should be considered in clinical practice, and the increasing age of children should also be taken into account when assessing IFD risk (89). IFD treatment strategies can be categorized as preventive, empirical, diagnosis-driven or targeted. IFD needs to be treated aggressively due to its diverse clinical manifestations and high mortality rate, which notably affects the efficacy of chemotherapy (90). Common first-line antifungal agents for treating IFD include voriconazole injection, itraconazole injection, caspofungin and amphotericin B (91,92). These agents may be administered as monotherapy or in combination regimens, such as voriconazole with caspofungin, voriconazole with amphotericin B or caspofungin with amphotericin B (93,94). Previous studies on the treatment of pediatric hematological malignancies combined with IFD are shown in Table II (95-99).

Prophylactic treatment. Prophylaxis includes primary prevention and re-prophylaxis. Primary prophylaxis refers to the pre-application of antifungal medications in patients with risk factors for IFD before the patients develop symptoms of infection, with recommended medications such as posaconazole, fluconazole, itraconazole and voriconazole. Posaconazole, micafungin, fluconazole, itraconazole, voriconazole and caspofungin are recommended for patients undergoing allo-HSCT transplantation (100). Posaconazole is a triazole antifungal drug that is available as an intravenous solution, oral suspension and extended-release tablets, with the oral suspension being the preferred formulation for pediatric use (101). Micafungin is an intravenous echinocandin with activity against *Candida* and *Aspergillus* spp; it has a favorable safety profile compared with other antifungal drugs and is one of the more desirable options for IFD prophylaxis of hematological malignancies in children. Secondary prophylaxis refers to the administration of antifungal medications to prevent recurrence of IFD in patients with a prior history of confirmed or clinically diagnosed IFD who are being treated again with chemotherapy or HSCT. Re-prophylaxis recommended medications are preferred to those effective on previous antifungal therapy, at the same dosage as for primary prevention. This is due to the fact that the pathogen may have developed resistance or tolerance to previously used antifungal agents, and maintaining the same dosage ensures therapeutic efficacy while minimizing the risk of suboptimal exposure that could promote further resistance (102-104). Additionally, consistent dosing simplifies clinical management and reduces errors in high-risk populations such as allo-HSCT recipients (105). The course of prophylactic therapy is largely dependent on the improvement of the risk factors of the patient for IFD and generally covers ≥3 months post-transplantation in patients undergoing HSCT. In a prospective study comparing caspofungin with fluconazole for the prevention of IFD during post-chemotherapy neutropenia in children, adolescents and young adults with AML, there were 23 cases of comorbid IFD in 517 patients, including 6 cases of caspofungin and 17 cases of comorbid IFD after fluconazole prophylaxis and the pathogenic organisms included 14 species of molds, seven species of

Table II. Overview of studies on antifungal prophylaxis and treatment in pediatric hematological malignancies with or at risk for IFD.

First author, year	Research period	Type of study	Number of patients included	Key study characteristics and findings	Research results	(Refs.)
Tu *et al*, 2023	2017 to 2019	Retrospective analysis	275	bIFD occurred in 19 patients on voriconazole (15.8%) and 12 patients on posaconazole (7.7%), and there was no notable difference between patients on voriconazole and posaconazole in terms of IFD-free survival.	Posaconazole and voriconazole may be used in primary prophylaxis of AL in children, and posaconazole may achieve lower rates of bIFD.	(95)
Lee *et al*, 2017	2009 to 2013	Retrospective analysis	22	The overall response rate with voriconazole in combination with caspofungin was 90.9 and 86.3% of patients were completely controlled.	Voriconazole combined with caspofungin is an effective and safe treatment for AL in children.	(96)
Qiu *et al*, 2019	2008 to 2018	Retrospective analysis	95	A total of 27 patients received a combination of caspofungin and voriconazole; 28 patients received a combination of caspofungin and amphotericin B; and 40 patients received a combination of voriconazole and amphotericin B. The overall efficiency was 77.9%, and the overall survival at 100 days after allo-HSCT was 66.8%.	Multiple factors can affect IFD outcomes, and the combination of caspofungin and voriconazole is a safe and effective therapeutic option for transplant patients with comorbid IFD.	(97)
Goscicki *et al*, 2024	2011 to 2017	Retrospective analysis	129	The incidence of bIFD was 2.4% for 170 prophylactic courses of micafungin at a median dose of 3 mg/kg daily.	Micafungin prevention of allo-HSCT in children was consistent with the incidence of bIFD in adults with allo-HSCT, and micafungin was well tolerated.	(98)
Kazakou *et al*, 2020	2001 to 2016	Retrospective analysis	297	In terms of antifungal treatment, amphotericin B liposomes were the most commonly used treatment option in 21 patients, followed by voriconazole in 9 cases, caspofungin in 3 cases, posaconazole in 3 cases, micafungin in 1 case and fluconazole in 1 case. A total of 12 patients received combined antifungal treatment, with a total mortality rate of 33.3%.	Despite advances in the treatment of IFD with new antifungal drugs, mortality from these infections remains high	(99)

IFD, invasive fungal disease; bIFD, breakthrough IFD; AL, acute leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

yeasts and two species of unclassified fungi. The cumulative incidence of IFD was 0.5% in the caspofungin group and 3.1% in the fluconazole group (106).

Empirical treatment. Empirical treatment is generally defined as persistent granulocyte deficiency with fever after chemotherapy in children and ineffective treatment with broad-spectrum antibiotics for 4-7 days as the main criteria for initiating treatment (107). Risk factors for IFD after chemotherapy in children at high risk for hematological malignancies should be one of the following: i) Expected absolute neutrophil count $<0.1x10^9$/l for >7 days; ii) development of hemodynamically unstable clinical comorbidities; iii) oral or gastrointestinal mucositis and dysphagia; iv) intravascular catheter infections; v) new-onset pulmonary infiltrates or hypoxemia; and vi) hepatic insufficiency or renal insufficiency (108,109). The pathogens of IFD in pediatric hematological malignancies are predominantly *Aspergillus*; thus, broad-spectrum antibiotics covering *Aspergillus* are generally selected, and empirical treatment of IFD starting with fever after chemotherapy for pediatric hematological malignancies without any microbiological or imaging evidence is aimed at early initiation of antifungal agents to reduce the morbidity and mortality associated with IFD, this has become a standard of care in the clinic (110). Empirical treatment should be accompanied by an active search for infectious lesions, microbiological and imaging tests, such as fungal cultures, non-culture microbiological tests and chest CT, as well as tests such as bronchoscopy or biopsy when the condition of the patient permits, in order to facilitate the diagnosis of IFD and the adjustment of empirical treatment (111). For febrile neutropenia after chemotherapy for hematological malignancies in children, most centers prefer empiric treatment, and the recommended drugs for empiric treatment are itraconazole, caspofungin, micafungin, liposomal amphotericin B, amphotericin B and voriconazole. First-line treatment for candidemia includes fluconazole or liposomal amphotericin B, while voriconazole is the first-line treatment for IA (112,113).

Diagnosis-driven therapy and targeted therapy. Diagnosis-driven treatment refers to the combination of clinical imaging markers of IFD such as the presence of *Aspergillus* infection-related imaging changes on lung CT and microbiological markers such as a positive BDG/GM assay, positive fungal culture or microscopic examination of specimens obtained from non-sterile sites or non-sterile manipulations in pediatric hematological malignancies patients after chemotherapy; this is in the absence of clinical symptoms of infection, or in the presence of a persistent neutrophilic deficiency fever ineffective on treatment with a broad-spectrum antibiotics. For low-risk patients with IFD, empiric antifungal therapy, which is also diagnosis-driven therapy, is recommended in the presence of a diagnostic basis for IFD such as clinical imaging abnormalities or a positive serum BDG/GM assay (114).

Research conducted by Wu *et al* (66) indicates that empirical treatment is superior to diagnosis-driven treatment; it is recommended that high-risk patients begin empirical treatment and strive to clarify the diagnosis of the disease. The principle of drug selection for diagnosis-driven treatment can be referred to as empirical treatment, and the drugs of choice include caspofungin micafungin, voriconazole, itraconazole, amphotericin B and its liposomes (115). Targeted therapy refers to antifungal therapy for pediatric hematological malignancies meeting criteria for clinical diagnosis or confirmed IFD. As the pathogen of the infection is clearer, the choice of medication can be based on the fungal species, the antimicrobial spectrum of the drug and the specific situation of the patient (116). The initial treatment for patients with candidemia involves the use of echinocandins and removal of the central venous catheter. Echinocandins, amphotericin B and its liposomes and voriconazole are recommended for patients with disseminated candidiasis accompanied by granulomatous defects, treatment-naive or unstable clinical situations. Liposomal amphotericin B and voriconazole are recommended for CNS candidiasis. Treatment of candidemia should be continued until recovery of clinical signs and symptoms, and confirmation of bloodstream pathogenetic clearance is observed for >2 weeks. Voriconazole and liposomal amphotericin B are recommended as the first-line of treatment for invasive aspergillosis, with a recommended course of 6-12 weeks (117).

5. Discussion

Comparative analyses reveal distinct pathophysiological features between pediatric and adult IFD: Pediatric patients exhibit increased serum BDG levels (median 120 vs. 80 pg/ml in adults) and delayed GM antigenemia positivity (median 5 vs. 3 days post-symptom onset), contributing to diagnostic challenges unique to children (21,70). Notably, CNS involvement occurs in 38% of pediatric IFD cases vs. 12% in adults, with *Aspergillus* predominating in both groups but showing increased mucormycosis prevalence in pediatric AML (7.2 vs. 2.1%) (64,84). IFDs are rare in individuals with intact immune systems; however, children who have relatively low immunity are susceptible to IFD. In response to IFD innate and adaptive immune responses, several pattern recognition receptors on antigen-presenting cells (APCs) recognize the fungus. Exogenous antigens and proinflammatory cytokines presented by APCs promote T-cell activation; secretion of IL-17 by T helper (Th)17 cells promote the production of chemokines recruited by neutrophils. Interferon γ induced by Th1 cells activates macrophages, which, together with neutrophils, phagocytose and kill the fungus. The mechanisms of innate and adaptive immune responses in IFD are shown in Fig. 3. This may be one of the main reasons why children with low immune function are at risk of IFD. The heightened vulnerability of immunocompromised children stems from specific defects in both innate and adaptive immune responses. For instance, neutrophils from pediatric patients post-HSCT exhibit impaired phagocytic capacity and reduced oxidative burst activity compared with healthy controls (118).

IFD in pediatric patients with hematological malignancies undergoing chemotherapy or HSCT presents three major clinical dilemmas: The higher prevalence of IFD in specific subgroups, non-specific manifestations complicating early diagnosis and the emergence of breakthrough infections during prophylaxis or therapy. First, for the IFD prevalence profile, which is higher in children with AML and allo-HSCT combined with IFD, this group of patients requires further

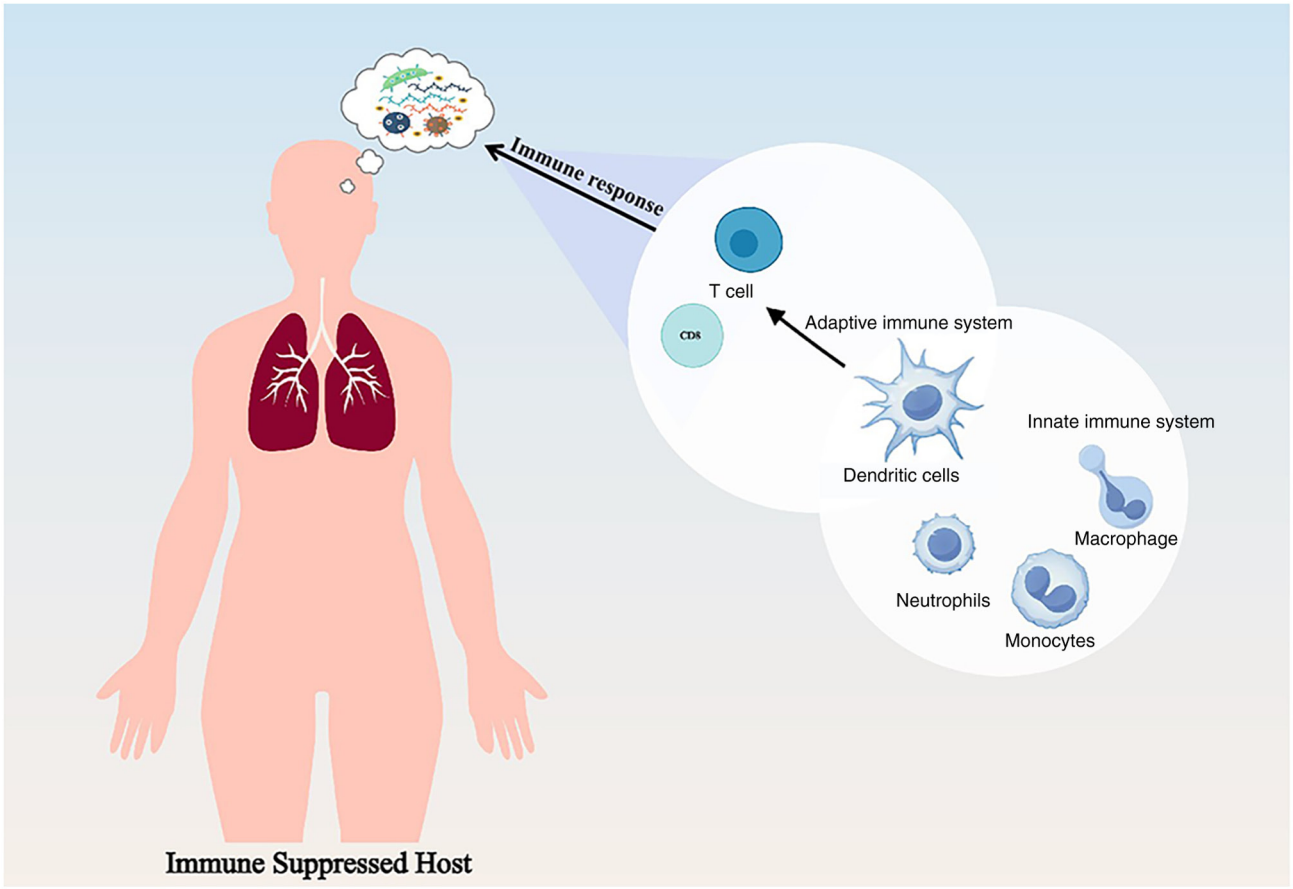

Figure 3. Mechanisms of the innate and adaptive immune response to invasive fungal disease. Antigen-presenting cells recognize the fungus via protease-associated receptors, which can release pro-inflammatory cytokines to act on T cells. A T helper 1 response occurs to promote the release of g-interferon to act on macrophages, which collectively mediate phagocytosis and fungal killing.

clinical attention and therapeutic management. Second, the clinical presentation increases the difficulty of diagnosing and treating IFD; common symptoms of IFD, including fever, cough and dyspnea, exhibit non-specific characteristics that overlap with bacterial or viral infections. Furthermore, bIFD can develop during AP or therapy as a consequence of pathogen profile shifts or resistance evolution (119). The management of bIFD in immunocompromised children presents multifaceted challenges. Diagnostic complexity is exacerbated under AP. Conventional biomarkers such as BDG may lose specificity due to cross-reactivity with gut commensals, while tissue sampling is often delayed by thrombocytopenia and bleeding risks (22).

Emerging resistance to azoles has been documented in non-fumigatus *Aspergillus* species, with 38% of breakthrough cases in a national cohort showing resistance to first-line agents (120). Limited salvage options are compounded by drug interactions in polypharmacy regimens, particularly with calcineurin inhibitors in HSCT recipients. Emerging strategies include therapeutic drug monitoring-guided dosing. A previous study on a pediatric cohort demonstrated that maintaining posaconazole trough levels >1.2 μg/ml reduced breakthrough risk by 73% compared with conventional dosing (121). Additionally, newer antifungals such as isavuconazole and rezafungin have shown promise in pediatric populations, with isavuconazole demonstrating efficacy as salvage therapy in mucormycosis cases (13). Combination therapy approaches, particularly for CNS infections, have yielded superior outcomes in children compared with adults (19). Therefore, rapid identification and confirmation of the pathogenic species of IFD is a major challenge for the effective treatment of IFD, and, despite several methods such as serological testing, tissue biopsy or PCR, can help identify the source of infection, the available diagnostic tools for certain fungal diseases such as trichothecenes are notably limited (78). Finally, in IFD treatment, the effect of medication is associated with the type of disease the patient has, and improved therapeutic outcomes can be achieved with targeted therapy compared with empirical therapy. Since different antifungal agents have their own antimicrobial spectrum and adverse effects, the safe and effective selection and use of these agents has also become another challenge in the treatment of IFD.

Therapeutic strategies diverge markedly between populations: Pediatric IFD requires 30% higher voriconazole doses compared with adult doses, to achieve therapeutic trough levels, while echinocandin clearance is 1.5-fold faster in children necessitating weight-adjusted dosing (101,116). Combination therapy shows superior outcomes in pediatric cohorts compared with adults, particularly for CNS infections where blood-brain barrier penetration differs developmentally (122). Specifically, voriconazole demonstrates non-linear pharmacokinetics in children <12 years, requiring 30-50% increased

weight-adjusted doses than adults to achieve therapeutic trough levels (2-6 mg/l) (101,123). Similarly, posaconazole exhibits 40% lower bioavailability in pediatric patients compared with adults, necessitating therapeutic drug monitoring (13,19). Implementation of first-line prophylaxis has yielded notable protective effects, and early diagnosis and prompt treatment, including antifungals and surgery, are key to improving patient survival. The use of new diagnostic techniques has helped in the rapid clinical identification of the causative fungus and the timely development of therapeutic strategies. The role of early and accurate diagnosis in the initial stages of active containment of fungal infections has become critical in preventing the development of life-threatening conditions. The growing clinical demands in medical mycology have catalyzed a diagnostic evolution from conventional microscopy and culture-based methods to advanced non-culture platforms. A total of four cutting-edge approaches, namely mNGS, novel PCR systems, next-generation biosensors and nanotechnology-enhanced tools, collectively demonstrate superior pathogen detection capabilities (124-126). These innovations address critical limitations of traditional isolation techniques, including suboptimal sensitivity and culturability constraints (67). Diagnostic advancements highlight age-specific considerations; mNGS exhibits 92% sensitivity in pediatric pulmonary IFD vs. 78% in adults, which is attributable to higher fungal burden in children (67). Conversely, the specificity of GM assay drops to 67% in children <5 years due to cross-reacting dietary GMs, compared with 89% in older populations (10). These differences underscore the need for pediatric-specific diagnostic algorithms.

In terms of antifungal regimen selection, itraconazole, voriconazole, amphotericin B and caspofungin are generally selected for patients in whom *Candida* is the primary source of infection. For *Aspergillus* infections, voriconazole continues to be used as the preferred regimen. When comparing caspofungin monotherapy and voriconazole combination therapy, voriconazole monotherapy or in combination with caspofungin resulted in a markedly lower IFD-related mortality compared with caspofungin monotherapy (122). The selection between monotherapy and combination antifungal therapy requires consideration of multiple factors, where infection characteristics carry out a key role; for example, pulmonary involvement favors voriconazole monotherapy (127). Trichophytosis is a rare but emerging life-threatening fungal disease with limited therapeutic options (128), and the novel antifungal agent esaconazole, a new triazole, has demonstrated efficacy in both initial and salvage treatment of trichophytosis in adults and children, offering more effective therapeutic options for trichophytosis and other fungal infections (129,130). There is an increasing number of novel antifungal agents that may be used in the future for pediatric hematological malignancies during chemotherapy or after allo-HSCT, such as encochleated amphotericin B deoxycholate, isavuconazole, olorofim, opelconazole, oteseconazole, fosmanogepix, ibrexafungerp and rezafungin (13,19).

Early diagnosis and effective treatment of IFD after chemotherapy and HSCT for pediatric hematological malignancies requires multiple tools to overcome clinical challenges and improve patient prognosis. Literature analysis shows that, compared with bacterial and viral infections, chemotherapy for hematological malignancies in children combined with IFD only accounts for a minority of cases, but its impact may be much more severe, especially in cases where long-term antifungal therapy or even surgical treatment is required to eradicate colonization (27,131,132). A personalized approach is recommended, as pediatric patients with hematological malignancies usually present with different comorbidities that require tailor-made treatments (133). Pediatric hematological malignancies, particularly patients with AML and relapsed patients, are prone to IFD, and the major challenges facing physicians include the diversity of pathogenic organisms, the difficulty of early identification and diagnosis, and the efficacy and safety of drug therapy.

While the present review synthesizes current evidence on IFD management in pediatric hematological malignancies, several limitations warrant acknowledgment. First, the majority of the included studies are retrospective, introducing potential selection bias and heterogeneity in diagnostic criteria across centers. Second, pediatric-specific pharmacokinetic data remain scarce for newer antifungals such as isavuconazole and rezafungin (13,19). Third, the diagnostic accuracy of biomarkers (BDG/GM assay) shows notable inter-study variability in pediatric cohorts (sensitivity range, 62-89%), reflecting unmet standardization needs (70,72). These gaps highlight the necessity for prospective multicenter studies using harmonized protocols. Further research and clinical practice are needed to advance multiple domains, including the development of novel antifungal agents, enhancement of pharmacological prophylaxis strategies, optimization of rapid pathogen detection methods and exploration of more effective infection control strategies.

6. Conclusions

The management of IFD in pediatric hematological malignancies post-chemotherapy and allo-HSCT remains a key challenge, necessitating a multifaceted approach to optimize outcomes. The present review underscores that children with AML and those undergoing allogeneic HSCT face increased susceptibility to IFD due to severe immunosuppression, with innate and adaptive immune dysregulation exacerbating fungal pathogenicity. The non-specific clinical manifestations of IFD, overlapping with bacterial or viral infections, coupled with the pathogen diversity and frequent emergence of breakthrough infections, necessitate advancements in diagnostic precision.

Emerging non-culture-based diagnostic modalities, including mNGS and nanotechnology-enhanced assays, offer high resolution in pathogen identification, enabling timely and targeted therapeutic interventions; however, challenges such as lack of standardization, high costs and complex result interpretation persist (134). For instance, mNGS may yield false positives due to sample contamination in immunocompromised hosts, necessitating integration with conventional culture and clinical context. While voriconazole retains its primacy in treating *Aspergillus* infections, combination therapies (such as voriconazole with caspofungin) demonstrate marked mortality reduction compared with monotherapy. Novel antifungals, including esaconazole and rezafungin, expand the therapeutic arsenal, particularly for refractory cases such as trichophytosis,

although their pediatric-specific safety and efficacy profiles warrant further validation (135,136).

The present review has several limitations: First, the heterogeneity in study designs (namely, high proportion of retrospective studies) may affect result consistency; second, some data derive from single-center studies with limited sample representativeness; and third, rare pathogens or special populations (such as congenital immunodeficiency) were not deeply analyzed. Therefore, future multicenter prospective studies are warranted to validate conclusions. Future efforts should prioritize the development of pediatric-optimized antifungals, enhanced pharmacovigilance frameworks and scalable rapid diagnostics to address the persistent gaps in managing this life-threatening complication. Ultimately, linking basic research, translational medicine and clinical practice is essential to redefine the diagnostic and therapeutic criteria for IFD in pediatric haemato-oncology. A key unmet need is pediatric-focused pharmacokinetic studies on antifungal agents. Current dosing regimens for novel antifungals such as isavuconazole and rezafungin are primarily extrapolated from adult data, despite documented age-dependent variations in drug metabolism. Future research should establish age-stratified dosing guidelines through prospective multicenter trials incorporating population pharmacokinetic modeling.

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Competing interests

The authors declare that they have no competing interests.

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