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Pulmonary Aspergillosis: clinical presentation, diagnostic tests, management and complications

Rami Sherif and **Brahm H. Segal, MD**
Departments of Medicine and Immunology, Roswell Park Cancer Institute, School of Medicine and Biomedical Sciences, University of Buffalo, Buffalo, NY

Abstract

Purpose of Review—When functioning properly, the immune system recognizes inhaled fungi and controls their growth, while avoiding injurious inflammation and allergy. "Aspergillosis" represents a spectrum of clinical diseases resulting from impaired or excessive immune responses. Invasive aspergillosis is principally disease of severely immunocompromised patients, while allergic forms of aspergillosis result from an excessive inflammatory response to hyphae colonizing the sinopulmonary tract. We will review insights gained in host defense against *Aspergillus* species and the immunopathogenesis of *Aspergillus*-related diseases as well as important advances made in fungal diagnostics and antifungal therapy.

Recent Findings—Important advances have been made in diagnosis of invasive aspergillosis and in antifungal agents. Voriconazole was superior to amphotericin B deoxycholate as primary therapy for invasive aspergillosis. There is significant interest in combination antifungal therapy for invasive aspergillosis. Fungal genomics offer a powerful opportunity to gain knowledge about fungal virulence factors that can be targets for drug development. In addition, new insights have been gained regarding host defense against *Aspergillus* species that may be exploited therapeutically.

Summary—We have gained substantial knowledge regarding how the immune system recognizes inhaled fungi and calibrates the inflammatory response. There has also been substantial progress in tools to diagnose aspergillosis and in antifungal therapeutics. Future progress will likely involve the development of more refined diagnostic tools, new classes of antifungal agents, and greater knowledge of pathogen and host factors that predispose to aspergillosis.

Keywords

Aspergillosis; Allergy; Immunity; Immunocompromised; Antifungal

Introduction

Aspergillus species are ancient lineages [1] that are ubiquitous in the environment and grow independently of an animal host. Certain pathways used by *Aspergillus* species as saprophytes in the environment (e.g., for nutrient acquisition or regulation of pH) may also enhance its virulence as a human pathogen in a susceptible host [2]. The evolution from the

Corresponding author Brahm H. Segal, MD Head, Division of Infectious Diseases Roswell Park Cancer Institute Elm & Carlton Streets Buffalo, NY 14263 716-845-5721 (voice) 716-845-5777 (fax) brahm.segal@roswellpark.org.

onset of primitive immune systems such as those in insects [3] to the complex innate and antigen-driven immune system that exist in humans and other mammals occurred in the context of continual exposure to filamentous fungi. Therefore, our immune system requires the ability to recognize inhaled mould spores and to control their growth, but also to avoid excessive inflammation [4].

Alveolar macrophages (AM) constitute the first line of phagocytic host defense against inhaled conidia [5]. Following germination, neutrophils are the dominant host defense arm against hyphae, the tissue invasive form of moulds [5]. Pathogen recognitions receptors (PRRs) recognize specific fungal cell wall motifs displayed during the conidial and hyphal stage and produce cytokines and chemokines that stimulate neutrophil recruitment and subsequent antigen-specific immunity.

There are several classes of innate PRRs that recognize fungal motifs. Examples include toll-like receptors (TLRs,) dectin-1, pentraxin-3, SP-A, SP-D, and mannose-binding lectin. Fungal cell wall beta-glucans act as a trigger for the induction of inflammatory responses in macrophages through their time-dependent exposure on the surface of germinating conidia [6–8]. Dectin-1 and TLRs permit macrophages to distinguish between *A. fumigatus* conidia and hyphae. In *A. fumigatus*, a surface hydrophobic protein, RodA, is covalently bound to the conidial cell wall and prevents innate immune and T-helper responses [9]. Stage-specific activation of innate immunity via coordinated ligation of specific PRRs likely calibrates the immune response to inhaled fungi to contain fungal growth while restraining excessive inflammation.

Activation of dectin-1 can lead to NADPH oxidase activation [10]. The neutrophil NADPH oxidase is essential in host defense against aspergillosis. Chronic granulomatous disease (CGD), an inherited disorder of the NADPH oxidase, is associated with recurrent bacterial and fungal diseases, with invasive aspergillosis being a major cause of mortality [11]. NADPH oxidase activation results in conversion of oxygen to superoxide anion that is in turn coupled to activation of preformed antimicrobial proteases sequestered in the primary granules of neutrophils [12].

Dectin-1 ligation can also lead to production of proinflammatory cytokines, such as IL-17 [13]. IL-17A influences antimicrobial host defense, but also promotes inflammatory pathology in autoimmune disease [14]. IL-17A signals through IL-17 receptor A (IL-17R), and stimulates production of G-CSF, GM-CSF, TNF-α, and chemokines that regulate myelopoiesis and neutrophil recruitment to inflammatory sites. There is debate regarding in what circumstances IL-17 may enhance versus diminish antifungal immunity [15]. In humans, mutations leading to defective dectin-1 signaling are associated with chronic mucocutaneous candidiasis [16,17].

Dectin-1-deficient mice have increased susceptibility to aspergillosis in association with impaired NADPH oxidase activity and impaired production of proinflammatory cytokines and chemokines [18]. IL-17 production in the lungs after *A. fumigatus* challenge was Dectin-1 dependent, and neutralization of IL-17 impaired *A. fumigatus* clearance. Interestingly, NADPH oxidase restrains IL-17 responses and augments regulatory T-cell activity via tryptophan catabolism in mice in experimental aspergillosis [19]. These findings in mice illustrate the complex interactions mediated by pathogen recognition receptors that sense specific *Aspergillus* motifs and control fungal growth while calibrating the immune response to avert tissue injury.

Aspergillus species cause disease only in a small proportion of persons with specific host factors – a reflection of how well the immune system functions to control fungal growth and restrain excessive inflammation. Invasive aspergillosis is typically, although not exclusively,

a disease of the highly immunocompromised. Allergic forms of aspergillosis, notably allergic bronchopulmonary aspergillosis (ABPA), result from a poorly controlled allergic response to hyphae colonizing human airways. Seen in this light, *Aspergillus*-related diseases result principally from disorders of immunity, and immune responses govern the clinical and pathological manifestations of aspergillosis.

Invasive aspergillosis: Host factors

Acute invasive aspergillosis is a devastating opportunistic infection in the severely immunocompromised (Table 1). Patients at risk for invasive aspergillosis include those with prolonged neutropenia (e.g., following cytotoxic regimens for acute leukemia), hematopoietic stem cell transplant (HSCT) recipients, solid organ transplant recipients (particularly lung transplant recipients), advanced AIDS and CGD [4,27]. Mortality from invasive aspergillosis has increased by several-fold in the 1980s and 1990s in the U.S. and Europe based on unselected autopsy reports [28,29] -- a reflection of more patients undergoing treatment for hematologic malignancies and allogeneic HSCT.

Among allogeneic HSCT recipients, three periods of risk for invasive mould disease occur: 1) the neutropenic period following the conditioning regimen; 2) acute graft-versus-host disease (GVHD); and 3) chronic GVHD (after day 100 of transplant) [30]. Invasive mould disease is more common during intensive immunosuppressive therapy for GVHD than during neutropenia [31–35]. This observation may be due to shortening of the neutropenic period following conditioning as a result of myelopoietic growth factors and use peripheral blood stem cell allografts that contain greater numbers of myeloid progenitors than bone marrow-derived allografts. T-cell depletion of allografts is also associated with a high risk of invasive aspergillosis and cytomegalovirus disease [36].

Among solid organ transplant recipients, the risk of invasive aspergillosis correlates with the intensity of immunosuppression used to prevent or treat allograft rejection. The incidence of invasive aspergillosis is highest after lung transplantation [37]. Colonization of the native lung with *Aspergillus* species, a common occurrence in end-stage lung disease, may be a source of fungal disease following single-lung transplantation [38,39]. Intensive immunosuppressive therapy used in non-transplant recipients, such as those with autoimmune diseases, can occasionally be complicated by aspergillosis [40].

There is also a growing appreciation of invasive aspergillosis in persons with less severe levels of immunocompromise. For example, chronic necrotizing pulmonary aspergillosis (CNPA) generally occurs in with patients pre-existing structural lung diseases such as prior tuberculosis or lung abscess or modest immune impairment, such as occurs with diabetes, poor nutrition, chronic obstructive pulmonary disease, or low-dose corticosteroids [25]. Fungal disease is slowly progressive over months to years, and may require life-long therapy. Mannose-binding lectin polymorphisms may be susceptibility factors for CNPA [41]. Invasive pulmonary aspergillosis has also been reported in critically ill patients without a documented systemic immune disease [42–44].

Clinical Manifestations and Diagnosis

Invasive aspergillosis principally involves the sinopulmonary tract, a reflection of inhalation being the most common route of entry of *Aspergillus* spores (rarely, other sites of entry, such as the gastrointestinal tract or skin, occur). Fever, cough, and dyspnea are frequent, although non-specific, findings of pulmonary aspergillosis, the most common site of invasive aspergillosis. Vascular invasion may manifest as pleuritic chest pain due to pulmonary infarction or hemoptysis. Central nervous system involvement is a devastating consequence of disseminated aspergillosis, and may manifest with seizures or focal

neurological signs from mass effect or stroke. Premature neonates can also develop aspergillosis, with the skin being the most common site of disease [45,46].

Diagnosis of invasive aspergillosis is difficult. Therefore in both clinical practice and research, different levels of certainty exist regarding the diagnosis of invasive aspergillosis. Demonstration of invasive hyphae histologically or a positive culture from a normally sterile environment (e.g., pleural fluid) is equated as proven invasive fungal disease. “Probable” invasive aspergillosis requires a combination of host factors that predispose to invasive aspergillosis (e.g., prolonged neutropenia, transplantation) and clinical (e.g., evidence of pneumonia) and mycological criteria [47]. These consensus criteria were designed for clinical research, but can be applied to clinical practice with the understanding that therapy for suspected invasive aspergillosis is commonly initiated prior to fulfilling these intentionally restrictive criteria.

In neutropenic patients, persistent fever may be the only sign of invasive fungal disease. A chest CT scan is more sensitive than radiographs for detection of early pulmonary aspergillosis [48], and should be considered in patients with 10 to 14 days of neutropenia (neutrophil count < 500/ul) and persistent or recurrent fever of unknown etiology unresponsive to empirical antibacterial agents [49]. The earliest radiological sign of invasive aspergillosis is a nodule[50]. A halo sign defined as a macronodule surrounded by a perimeter of ground-glass opacity corresponding to alveolar hemorrhage, is suggestive of invasive aspergillosis in patients with compatible host factors and initiation of treatment based on this sign has been associated with a better response compared to when therapy was initiated for more advanced fungal disease [51]. However other moulds and bacterial pathogens capable of angioinvasion (e.g., *Pseudomonas aeruginosa*) can produce a similar appearance. Other radiographic findings associated with invasive aspergillosis are consolidation, wedge-shaped infarcts, and cavitation. In contrast to adults, children with invasive pulmonary aspergillosis frequently do not manifest cavitation or the air crescent or halo signs [52].

Mycological criteria require either isolation of *Aspergillus* species from the sinopulmonary tract or positive antigen-based laboratory markers. Bronchoalveolar lavage fluid (BALF) cultures have at best 50% sensitivity in focal pulmonary lesions [53]. Antigen-based diagnosis relies on serum detection of either galactomannan or beta-D-glucan, two fungal cell wall constituents. The galactomannan assay is relatively specific for invasive aspergillosis, whereas the beta-D-glucan assay also detects other invasive fungal diseases, including candidiasis, other mould pathogens (excluding zygomycetes), and *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) [54,55].

The serum galactomannan assay has been principally studied in patients with leukemia and HSCT recipients, and its performance varies in different reports. In a meta-analysis, the serum galactomannan assay had a sensitivity of 71% and specificity of 89%, with significant heterogeneity in diagnostic accuracy among different patient groups [56]. Use of mould-active agents decreases the sensitivity of the galactomannan assay [57]. There are causes of false-positive results, including concomitant piperacillin/tazolbactam, other beta-lactam antibiotics, and gluconate-containing intravenous fluids. Cross-reactivity with other fungi (e.g., *Histoplasma capsulatum*) with similar cell wall galactomannan to *Aspergillus* can cause positive results [58]. Galactomannan detection in BALF appears to be more sensitive than serum detection [43,58], and can be used to support a diagnosis of probable aspergillosis [47]. As an alternative to bronchoscopy, percutaneous lung biopsy may be attempted for peripheral nodules. Thoracoscopic lung biopsy should be considered in a deteriorating patient when less invasive procedures produce negative results. Thrombocytopenia may limit the ability to perform invasive procedures.

In addition to serving as a diagnostic adjunct for invasive aspergillosis, a falling or rising serum galactomannan level may be useful as an early marker of therapeutic success or failure, respectively, in invasive aspergillosis [59–61]. More research is required to validate the use of serum galactomannan monitoring as a therapeutic marker in different patient populations with invasive aspergillosis [62].

PCR-based diagnosis of invasive fungal diseases, although promising, is currently investigational. Potential advantages include rapidity, low cost, the ability to establish a diagnosis at the species level and to detect genes that confer antifungal resistance. Limitations include lack of standardized methods, difficulty in reliably distinguishing fungal colonization from disease, and the potential for contamination with fungal DNA [63].

Therapy for invasive aspergillosis

Voriconazole has become the gold standard as primary therapy for invasive aspergillosis [64] (Table 2).

Voriconazole was more effective than amphotericin B deoxycholate (AmB-D) as initial therapy for invasive aspergillosis and was associated with significantly improved survival (71% vs. 58%, respectively) in a randomized trial [51]. The rate of successful outcomes was superior in voriconazole compared to AmB-D recipients (53% versus 32% respectively). The poorest prognosis occurred in extrapulmonary aspergillosis and in allogeneic HSCT recipients.

Voriconazole exhibits non-linear elimination in adults. It is estimated that increasing the oral dose of voriconazole from 200 mg Q12h to 300 mg Q12h leads to a 2.5-fold increase in exposure, and increasing the intravenous dose from 3 mg/kg Q12h to 4 mg/kg Q12h results in a 2.3-fold increase in exposure (package insert). In contrast, clearance of voriconazole in children is linear, necessitating higher dosing per kg of body weight in children to achieve comparable exposure as adults [74,75].

There can be considerable inter-individual variability and intra-individual variability over time in voriconazole exposure [76,77]. Small studies have noted a relationship between low plasma voriconazole levels and failure of therapy of invasive mycoses [78,79], and between high voriconazole levels and toxicity [79,80]. Therapeutic drug monitoring for voriconazole should be considered, particularly in cases of refractory fungal disease or drug toxicity. Therapeutic drug monitoring is however limited by lack of well-defined reference ranges for serum drug levels. In cases of suspected therapeutic failure, aiming for a serum voriconazole of at least 2 ug/ml is reasonable based on limited published data is reasonable [78].

Mould-active azoles and ketoconazole are potent inhibitors of cytochrome P450 3A4 (CYP3A4), which catalyzes the initial step in the clearance of several drugs. Inhibition of the CYP3A4 isoenzyme by azoles accounts for the majority of drug-drug interactions. Certain drugs metabolized by CYP3A4 require dose reduction when co-administered with voriconazole (e.g., calcineurin inhibitors).

Resistance of *Aspergillus* species to antifungal agents is a possible cause of failure of therapy. *Aspergillus terreus* is resistant to amphotericin B [81]. Mutations in the cyp51A gene of *A. fumigatus* have been linked to resistance to itraconazole; isolates harboring this mutation as also less sensitive to other mould-active azoles [82].

For patients with invasive aspergillosis refractory to voriconazole or who are intolerant of voriconazole, a lipid formulation of amphotericin B or an echinocandin can be used. Lipid formulations are generally preferred over amphotericin B deoxycholate for invasive

aspergillosis, given that prolonged use of the conventional formulation is poorly tolerated because of nephrotoxicity. Of the echinocandins, caspofungin is approved by the U.S. FDA as salvage therapy for invasive aspergillosis. Caspofungin monotherapy led to a successful outcome in 37 (45%) of 83 patients with invasive aspergillosis, 86% of whom had disease refractory to standard antifungal therapy [83].

There is substantial interest in pairing cell wall-active echinocandins with either amphotericin B formulations or mould-active azoles as therapy for invasive aspergillosis. In one provocative study, Marr et al.[84] reported a survival advantage of voriconazole plus caspofungin compared to voriconazole alone in a retrospective analysis of salvage therapy for invasive aspergillosis. However, this database involved small numbers of patients, and the two groups were non-contemporaneous; therefore, other host and infection-related factors may have influenced the outcome. A randomized trial comparing voriconazole (the gold standard) with voriconazole and anidulafungin (an echinocandin) has been initiated.

When feasible, immunosuppressive therapy (e.g., corticosteroids) should be reduced or discontinued. Adjunctive myeloid colony-stimulating factors (G-CSF or GM-CSF) should be considered in neutropenic patients with severe infections, such as aspergillosis [85]. Granulocyte transfusions in neutropenic patients can be considered in refractory or disseminated aspergillosis, realizing that their benefit versus toxicity risk has not been established [86]. Although marrow recovery is critically important for host defense against aspergillosis, myeloid recovery may lead to the liquefaction of pulmonary foci and increase the risk of pulmonary hemorrhage [87] and may increase pulmonary consolidation as part of an immune reconstitution syndrome in patients with invasive aspergillosis [88,89]. Adjunctive recombinant interferon-γ, which activates neutrophils and monocytes, can also be considered in cases of severe or refractory aspergillosis [90].

Future perspectives

We are gaining more knowledge about how the host response to *Aspergillus* species that may prove to be useful in developing novel prevention and treatment strategies. In addition to the severe forms of immune impairment that predispose to invasive aspergillosis (e.g., prolonged neutropenia, immunosuppressive regiments used in transplantation), variations in specific host defense alleles also likely affect risk offungal disease. As examples, Bochud et al. [91] showed that donor TLR4 polymorphisms affected the risk of invasive aspergillosis in allogeneic HSCT recipients. Zaas et al. [92] showed in both mouse models of aspergillosis and in human allogeneic HSCT recipients that polymorphisms in the plasminogen allele affected the risk of aspergillosis. Such studies may be useful to more precisely stratify immunocompromised patients regarding risk of aspergillosis, and potentially use more targeted approaches to antifungal prophylaxis.

We are also learning more about the biology of *Aspergillus* species that might be exploited therapeutically. Fungal genomic studies have shown that members of the *Aspergillus* genus are extremely diverse. The level of molecular divergence among certain *Aspergillus* species is similar to the divergence between humans and fish [93]. Although most cases of invasive aspergillosis are caused by *A. fumigatus*, it represents a small minority of aerosolized spores that would be in contact with human respiratory mucosa. Therefore, one of the major benefits of comparative genomics among pathogenic and non-pathogenic *Aspergillus* species will be to identify pathways (virulence factors) that enable disease to occur in susceptible hosts, and to identify novel targets for drug development. The recent discovery of a sexual cycle in *A. fumigatus* provides an invaluable tool top study the genetic basis of pathogenicity and antifungal resistance in *A. fumigatus* [94].

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Table 1

Predisposing host factors and immunopathogenesis of invasive, saprophytic, and allergic bronchopulmonary aspergillosis

Patient populations	Predisposing host factors	Clinical and histological features
Acute leukemia, myelodysplastic syndrome, aplastic anemia, other causes of marrow failure	Neutropenia	Hyphal angioinvasion with vascular thrombosis and tissue infarction; scant inflammatory response; may evolve to cavitation
Allogeneic HSCT after neutrophil recovery	Immunosuppression for GVHD (e.g., corticosteroids, T-cell-depletion; tumor necrosis factor-□ inhibition)	Inflammatory fungal pneumonia; angioinvasion with coagulative necrosis resembling aspergillosis classically associated with neutropenia may occur [20–22]
Solid organ transplantation	Immunosuppression to prevent allograft rejection	May range from an acute inflammatory pneumonia to a chronic necrotizing aspergillosis; in lung transplant recipients, *Aspergillus* tracheobronchitis may affect the anastomotic site and cause dehiscence
Advanced AIDS	CD4+ T-cell count generally < 100/ul; immunocompromising conditions (e.g., neutropenia) and other opportunistic infections often co-exist	Acute to slowly progressive necrotizing pneumonia; variable histological findings: neutrophilic infiltrates, vascular invasion, walled-off abscesses and cavitation occur; extrapulmonary dissemination observed [23]
Chronic granulomatous disease	Defective NADPH oxidase	Varies from acute pneumonia to slowly progressive disease; pyogranulomatous inflammation without hyphal vascular invasion or coagulative necrosis; “mulch pneumonitis” is an acute hypersensitivity response to a large aerosolized exposure [24]
Pre-existing structural lung disease (e.g., emphysema, prior cavitary tuberculosis)	Comorbid conditions, including diabetes, malnutrition, inhaled and low-dose systemic corticosteroids	Chronic necrotizing pulmonary aspergillosis: slowly progressive invasive fungal pneumonia with inflammatory necrosis [25]
Aspergilloma	Pre-existing structural lung diseases, e.g. bronchiectasis or prior cavitary tuberculosis	“Fungal ball” composed of hyphal elements in pre-existing cavity; erosion into adjacent vessels can cause life-threatening hemoptysis; surgical resection is the definitive treatment for hemoptysis from aspergilloma
Allergic bronchopulmonary aspergillosis (ABPA)	Allergic disease; can be an important complication of cystic fibrosis [26]	Airway plugging with hyphae, mucous, and inflammatory cells; hyphae do not invade lung parenchyma; airway and lung hypereosinophilic inflammation; goblet cell hyperplasia; central bronchiecatasis in advanced disease

Table is adapted from [4].

Table 2

Antifungal agents used to prevent and treat aspergillosis

Antifungal drug	Dosing	Comments
Voriconazole	Adults: Intravenous (IV) 6 mg/kg Q12h × 2 doses, then 4 mg/kg Q12h; Oral 200 mg or rounded to 4 mg/kg twice daily Pediatric: 7 mg/kg twice daily without a loading dose is approved by the European Medicines Agency (EMEA) in children aged 2 to 11 years; older children should be dosed as adults	■ Superior to amphotercin B as primary therapy for invasive aspergillosis ■ Toxicities: reversible visual symptoms are common, but rarely require stopping drug; liver enzyme abnormalities, encephalopathy (uncommon) ■ Drug-drug interactions similar to other mould-active azoles ■ Significant inter-individual variability in systemic exposure; therapeutic drug monitoring can be considered ■ CYP 2C19 has genetic polymorphisms, with 15–20% of Asians expected to be slow metabolizers ■ IV formulation should be used with caution in patients with significant renal impairment (e.g., creatinine clearance < 50 ml/min) because of potential for systemic accumulation of the cyclodextrin vehicle that can, in turn, cause renal toxicity.
Itraconazole	- Oral capsules: 400 mg daily, which can be administered QD or divided b.i.d.. -Oral solution: 2.5 mg/kg b.i.d. - Pediatric oral dosing for children aged > 5 years: 2.5 mg/kg b.i.d; experience in younger children is lacking - Intravenous (no longer marketed in U.S.) : 200 mg b.i.d. × 4 doses, then 200 mg daily	■ Oral solution has better bioavailability compared to the capsule ■ Therapeutic drug monitoring is advised, aiming for a trough of at least 250 ng/ml by HPLC ■ Contraindicated in patients with systolic cardiac dysfunction of a history of congestive heart failure ■ Effective in corticosteroid-dependent ABPA ■ IV formulation should be used with caution in patients with significant renal impairment because of potential for systemic accumulation of the cyclodextrin vehicle that can, in turn, cause renal toxicity.
Posaconazole	U.S. FDA-approved prophylactic dose: 200 mg T.I.D. in patients aged 13 years and over at high risk for invasive fungal disease	■ Currently, only available as an oral formulation ■ Variable serum levels ■ Must be taken with food or enteral nutrition; oral bioavailability is maximized when taken with fatty food ■ Effective as prophylaxis in patients with acute myelogenous leukemia and myelodysplastic syndrome receiving induction chemotherapy [65] and in patients with severe GVHD [66].
Amphotericin B deoxycholate	Invasive mould diseases: 1.0 to 1.5 mg/kg daily	■ Significant infusional and nephrotoxicity can limit its use ■ Saline hydration may avert nephrotoxicity ■ Lipid formulations are generally better tolerated
Liposomal amphotericin B	Adults: 3 mg/kg daily Clearance and volume of distribution influenced by body weight in pediatric oncology patients; higher mg/kg dosing may be optimal in patients weighing less than 20 kg [67]	■ 3 mg/kg/day as effective as but less toxic than 10 mg/kg/day as initial therapy for invasive aspergillosis in adults [68]

Antifungal drug	Dosing	Comments
Amphotericin B lipid complex	5 mg/kg daily	■ large non-randomized database for invasive aspergillosis [69]
Amphotericin B colloidal dispersion (ABCD)	5–6 mg/kg/day	■ ABCD (6 mg/kg/day) resulted in similar efficacy, lower nephrotoxicity, and greater infusional toxicity compared to Amb-D (1–1.5 mg/kg/day) as primary therapy for invasive aspergillosis [70]
Caspofungin	- FDA-approved dose: 70 mg × 1, then 50 mg daily; dose of 70 mg daily can be considered for invasive aspergillosis [71] - In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), a dose of 70 mg × 1, followed by 35 mg daily is advised by U.S. FDA. - Pediatric dose: 50 mg/m^2 (35 mg/m^2 in patients with moderate liver disease) [72]	■ Only echinocandin FDA-approved as salvage therapy for invasive aspergillosis
Micafungin	- Prophylaxis in adult HSCT recipients during neutropenia: 50 mg daily; no approved dose as therapy for aspergillosis	■ Non-randomized trial showed safety of micafungin alone and in combination in patients with invasive aspergillosis [73]
Anidulafungin	- no approved dose as therapy for aspergillosis	■ No clinical trial data as therapy for invasive aspergillosis ■ randomized trial underway comparing voriconazole + anidulafungin with voriconazole alone as primary therapy for invasive aspergillosis