REVIEW ARTICLE

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Aspergillus Infections

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N Engl J Med 2021;385:1496-509.
DOI: 10.1056/NEJMra2027424

CME at NEJM.org

Aspergillus conidia (spores) are ubiquitous in the environment and thus unavoidable. In soil and on other vegetative or moist material, aspergillus species exist as saprobes, digesting dead or dying organic material. This highly competitive environment requires aspergillus species to survive under variable temperature, pH, water, and nutrient conditions. Oxidative damage and environmental antifungal exposure also drive fungal adaptation, and these factors together account for numerous aspects of aspergillus virulence.[1,2] The vast majority of human encounters with inhaled conidia do not result in measurable colonization. For persons who do acquire and retain conidia, a spectrum of clinically significant outcomes can occur, from asymptomatic colonization to invasive infection (i.e., disease).[3]

Spores from this genus of mold have the appropriate surface charge, hydrophobicity, and size (2 to 5 μm) to propagate by transfer in air, colonizing airways in the pulmonary tree and sinuses or leading to cutaneous or ocular infection. After inhalation of airborne fungal conidia, clinical manifestations of disease are largely dependent on the host immune response. A wide range of clinical syndromes can be observed (Table 1). Hypersensitivity to inhaled airborne conidia causes allergic bronchopulmonary aspergillosis or asthma with fungal sensitization, whereas an aspergillus fungus ball (aspergilloma) or chronic pulmonary aspergillosis develops more frequently in persons with structural lung disease. Invasive infection is the most devastating form of disease and is primarily observed in persons with clinically significant immunosuppression.[1,4] Small foci of growth are unchecked, and vegetative hyphae penetrate tissue planes and blood vessels, with the opportunity for hematogenous spread and dissemination to multiple organ systems. New risk factors, such as a stay in the intensive care unit (ICU), influenza or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection,[5-7] and chimeric antigen receptor T-cell (CAR-T) therapy, have recently been observed.

Despite advances in antifungal prophylactic strategies, diagnostic tests, and treatments, morbidity and mortality related to invasive aspergillosis remain high. With this review, we report progress in the understanding of this infection, building on the 2009 review in the *Journal*.[8]

Mycologic Features

Invasive infection of humans is most frequently caused by members of the *Aspergillus fumigatus* complex, followed by *A. flavus*, *A. niger*, and *A. terreus*. *A. fumigatus* is most common in the lung, whereas *A. flavus* more commonly causes infection of the larger passageways and sinuses. In contrast, burn wounds are commonly colonized by *A. niger* and *A. flavus*.[9] These organisms were previously identified solely by phenotypic methods; however, molecular methods[10]

Table 1. Risk Factors for and Clinical Manifestations of Aspergillus Infections.*

Clinical Syndrome	Risk Factors	Clinical Elements of Infection
Allergic bronchopulmonary aspergillosis	Reactive airway conditions, cystic fibrosis	Hypersensitivity to inhaled airborne conidia causes allergic bronchopulmonary aspergillosis or asthma exacerbations with fungal sensitization
Aspergilloma	Structural lung disease	Fungus balls develop inside lung cavities (e.g., from tuberculosis)
Colonization of the pulmonary tree	Inhaled glucocorticoids, bronchiectasis, cystic fibrosis	Recurrent recovery in culture without compatible symptoms or radiographic findings
Cutaneous disease	Tissue damage, traumatic inoculation, burn wounds	Primary site or secondary dissemination; iatrogenic infection of wounds (e.g., through contamination in an operating room or contaminated medical products)
Eye disease	Tissue damage, surgery, foreign body	Topical keratitis, endophthalmitis, or extension of sinus disease
Tracheobronchitis	Develops most commonly in lung-transplant recipients but may be seen in other patient groups as well	Cough, hemoptysis, wheezing, and dyspnea are observed clinically, although radiographic imaging may be normal or show only airway thickening; various patterns have been described: obstructive tracheobronchitis with prominent mucous plugs and hyphae in the airways, ulcerative tracheobronchitis with focal invasion of the mucosa, and a pseudomembranous form with extensive inflammation and necrosis of the tracheobronchial tree; in lung-transplant recipients, invasion by hyphae may develop at the site of anastomosis and suturing
Chronic pulmonary aspergillosis	Structural lung disease, underlying cancer, receipt of glucocorticoids, malnutrition, impaired mucociliary clearance after recent pulmonary infection, ICU stay	Fever, cough, and shortness of breath, with or without chest pain and hemoptysis (signs of angioinvasion)
Sinus disease	Neutropenia, diabetes, excessive alcohol use, tropical residence, prolonged immunocompromised state	Sinus disease may be difficult to differentiate from other infections, including mucormycosis; clinical findings may be subtle in patients who have neutropenia, with nasal congestion, fever, and facial pain most commonly encountered; cacosmia is a concerning signal, suggesting necrosis of the nasal or sinus tissue and requiring urgent evaluation; extension from the sinus into the surrounding bony or soft tissues may develop, requiring surgical débridement; patients with the orbital apex syndrome, characterized by impairment of extraocular muscles, present with ophthalmoplegia and visual loss
Disease of the central nervous system	Develops with hematogenous dissemination from a primary site (pulmonary or cutaneous inoculation) or contiguous extension from a sinus source; common with ibrutinib therapy	Neurologic deficits consistent with the region of involvement are seen on examination, and imaging studies show mass lesions or nodules
Invasive infection	Exogenous immunosuppression, often related to chemotherapy, transplantation, or small-molecule kinase inhibitors Severe respiratory viral infection (SARS-CoV-2 infection or influenza)	Small foci of growth are unchecked, and vegetative hyphae invade through tissue planes into blood vessels (i.e., angioinvasion), with the opportunity for contiguous or hematogenous spread and fatal infection of multiple organ systems, including endocarditis

* ICU denotes intensive care unit, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

have revealed a substantial number of new species. Phenotypically similar to more well-known pathogens, these organisms are termed "cryptic" species. In multicenter surveillance investigations of fungal disease in populations in the United States[11] and Spain,[12] 11 to 15% of all aspergillus isolates were identified as cryptic species. These species are frequently resistant to antifungal agents, underscoring the importance of accurate identification.

IMMUNE RESPONSE

The pulmonary system is exposed to aspergillus conidia daily, and a highly coordinated immune response has evolved for rapid pathogen elimi-

nation. The proximal airways remove conidia through mucociliary clearance, and if this process is impaired (e.g., in cystic fibrosis and bronchiectasis), colonization or infection may develop. Airway epithelial cells and alveolar macrophages are the first line of defense against potential aspergillus infection. They must kill phagocytosed conidia while minimizing the surrounding inflammatory reaction and maintaining immune homeostasis. The bronchial epithelium can internalize conidia; however, hyphae are able to pass through the epithelium without disturbing its integrity.[13] Dectin-1, DC-SIGN (dendritic-cell–specific ICAM 3 [intercellular adhesion molecule 3]–grabbing nonintegrin), and pentraxin 3 have been identified as key macrophage receptors assisting in the recognition and phagocytosis of these conidia.[14,15] Polymorphisms in the host genome in these sites and others have been found to predispose patients to invasive aspergillosis.[16]

After phagocytosis, killing occurs through generation of NADPH-dependent reactive oxidant species (ROS). Patients with defects in this pathway (e.g., those with chronic granulomatous disease) have invasive infection with aspergillus and other pathogens. Additional signaling pathways regulating aspergillus immunity have also been identified recently, although they are incompletely characterized. These include the calcium–calcineurin–NFAT (nuclear factor of activated T cells) pathway, which is disrupted by calcineurin inhibitors commonly used during the care of patients who have received stem-cell or solid-organ transplants, and Bruton's tyrosine kinase inhibitors such as ibrutinib, which is increasingly used in patients with lymphoproliferative cancer.[1,17]

Neutrophils have long been recognized as the most important immune cell with activity against aspergillus. Neutrophil recruitment depends on chemokine release from lung epithelial cells[18] and CARD9 (caspase recruitment domain–containing protein 9) signaling, and defects in this latter pathway lead to extrapulmonary aspergillosis. The process of recognition is similar to that for alveolar macrophages and downstream NADPH oxidase–induced ROS production, causing fungal cell death. Host neutrophils release antimicrobial peptides (e.g., defensins) and proteases and attempt to sequester iron availability in response to fungal invasion.[19]

T cells are also essential in the host defense, with both CD4 and CD8 cells providing protective immunity.[20] Chronic noninvasive forms of aspergillosis, such as asthmatic exacerbations, allergic bronchopulmonary aspergillosis, and chronic pulmonary aspergillosis, are also defined by aberrant T-cell responses. A dominant type 2 helper T-cell response is observed in allergic diseases, whereas a proinflammatory phenotype has been described in chronic forms of pulmonary aspergillosis.

EPIDEMIOLOGIC FEATURES AND RISK FACTORS

The number of aspergillosis cases continues to increase yearly.[21] The growing immunosuppressed population is largely the result of improvements in cancer therapy that prolong the duration of risk, the development of new immunotherapeutic agents that increase susceptibility to infection, and improved diagnostics. An increased risk of aspergillosis has been recognized for decades among patients who have undergone hematopoietic-cell transplantation (HCT), particularly in the early period of neutropenia and during treatment of graft-versus-host disease (GVHD), and among solid-organ transplant recipients treated with systemic glucocorticoids or other immunosuppressive agents.[22,23]

More recently, nontraditional risk factors for invasive aspergillosis have been identified (Table 1). Patients in the ICU frequently have a multitude of overlapping risk factors conferring a predisposition to invasive aspergillosis, including structural lung disease, underlying cancer, receipt of glucocorticoids for the treatment of chronic obstructive pulmonary disease or acute respiratory distress syndrome, and impaired mucociliary clearance after a recent pulmonary infection. The incidence of aspergillosis in the ICU varies substantially according to the geographic region,[24] and ongoing prospective studies are further delineating the risk.

Patients with severe respiratory viral infections are also at increased risk for the development of invasive aspergillosis. Severe infection with influenza virus, respiratory syncytial vi-

rus, or SARS-CoV-2 damages the pulmonary epithelium, providing a potential portal of entry for colonizing aspergillus species.[6,7] In addition, the use of glucocorticoids and other immunomodulating medications during treatment of severe SARS-CoV-2 infection may confer a predisposition to pulmonary mold infections.[25,26]

The diagnosis may be difficult to establish in patients who have tracheobronchitis in the absence of radiographic manifestations. Patients with parenchymal involvement may have consolidation or other nonspecific signs of infection.

As noted above, Bruton's tyrosine kinase inhibitors, such as ibrutinib, have emerged as risk factors, not only for invasive aspergillosis but also for the development of disseminated or central nervous system disease,[17] and antifungal prophylaxis during ibrutinib therapy is provided at some centers. Fludarabine, a purine analogue that causes quantitative and qualitative T-cell defects that persist for 1 to 2 years, has been associated with aspergillosis. Treatment with venetoclax, a B-cell lymphoma 2 (BCL2) inhibitor that is prescribed for some hematologic cancers, may also be a risk factor for invasive aspergillosis and other opportunistic infections. However, venetoclax is often used in combination with other chemotherapeutic agents, making the specific risk attributable to this agent difficult to define; additional data are needed to make this determination definitively.[27]

CAR-T therapy, which is used to reprogram autologous or allogeneic T cells to express chimeric antigen receptors, directing them at specific tumor antigens, has also emerged as a risk factor for invasive aspergillosis. After infusion, this T-cell population expands and remains viable for months to years, providing a useful treatment option for some refractory or relapsed leukemias and lymphomas. Cytokine release syndrome may develop as a complication of CAR-T therapy, and most infectious complications develop shortly after therapy, during the early period of neutropenia or soon after the development of cytokine release syndrome. (When infection develops shortly after the development of cytokine release syndrome, the infection is probably secondary to the initiation of immunosuppressive therapy with tocilizumab plus a glucocorticoid for the treatment of the cytokine release syndrome.)

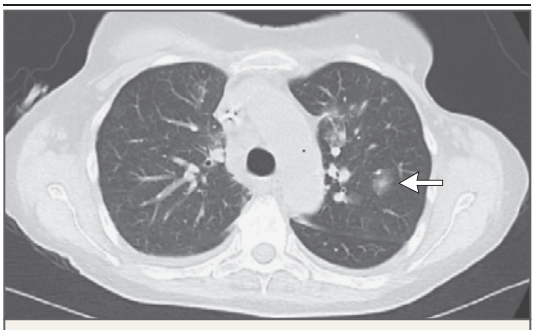

Figure 1. Halo Sign Suggestive of Invasive Fungal Infection.

The halo sign (arrow) is a focal nodule or consolidation with surrounding attenuation.

The role of the lung microbiome in the pathogenesis of invasive aspergillosis remains unclear but is the subject of ongoing work. Microbiome-mediated mechanisms of resistance and alteration of the host immune response may increase fungal colonization rates and cause infection during periods of immunosuppression.[28] The effects of mycoviruses or other viruses on aspergillus infections also have yet to be determined.

A large number of new agents that affect numerous immunologic pathways have become available over the past decade and pose theoretical risks of invasive fungal diseases, as recently reviewed.[29] Agents involving monocyte–macrophage function appear to pose the highest risk of invasive aspergillosis, and agents that impair type 1 helper T-cell immunity also confer a predisposition to infection, according to sporadic reports.

CLINICAL MANIFESTATIONS

Table 1 shows the spectrum of clinical presentations of aspergillosis, defined by the site of involvement. The severity of invasive infection correlates inversely with the immune status of the host. A high index of suspicion is required for the diagnosis of invasive disease, since an immunocompromised patient may be relatively asymptomatic, precluding early diagnosis. Imaging is a critical component in the diagnostic

evaluation of pulmonary and sinus infections in particular. Radiographically, computed tomographic imaging of the chest shows focal consolidations, and in the case of invasive pulmonary infection, consolidation may be characterized by nodules with surrounding ground-glass infiltrates (halo sign) (Fig. 1) or cavitating lesions. Patients with tracheobronchial infection may have no parenchymal lung changes, but debris may be visible in large airways. Noninvasive disease, such as allergic bronchopulmonary aspergillosis, is suggested by central bronchiectasis or parenchymal opacities and prompts testing such as measurement of IgE levels and examination of the peripheral-blood eosinophil count. Central nervous system lesions[30] are more common in patients with an underlying genetic immunodeficiency (e.g., CARD9)[31] and are seen with immunosuppressive therapy that targets the pathways involved.

DIAGNOSIS

Allergic bronchopulmonary aspergillosis is diagnosed when testing establishes sensitization to aspergillus antigens, with compatible clinical and radiographic findings.[1] Blood test results that are compatible but nonspecific include a total eosinophil count of more than 500 cells per microliter in patients not receiving glucocorticoids and a total serum IgE level of more than 1000 IU per milliliter. Specific tests include serum aspergillus-specific IgE or IgG levels, serum precipitating antibodies, and skin testing for aspergillus sensitivity.

The difficulty in obtaining samples for culture or histopathological assessment[32] for the diagnosis of local or systemic invasive infection has spurred interest in noninvasive diagnostic testing (Table 2). Components of the fungal cell wall, including galactomannan and 1,3-β-D-glucan, can be detected in some patients with invasive aspergillosis (Fig. 2).[34,35] A polymerase-chain-reaction (PCR) assay has more recently become available, although primarily at reference laboratories.[33] The sensitivity of these tests is variable and depends on the immune status of the host, the site of involvement, status with respect to prior antifungal prophylaxis or treatment, the sample type, and the laboratory performing the testing. The sensitivity of serum galactomannan testing increases with lower neutrophil counts, whereas galactomannan testing in bronchoalveolar lavage (BAL) fluid is less dependent on host factors. Galactomannan from serum and galactomannan from BAL are used as biomarkers during the conduct of clinical trials.[36]

The serum galactomannan optical density index at baseline (i.e., at the time of diagnosis) and galactomannan kinetics have both been found to be prognostic.[34] A serum galactomannan index that is higher than the baseline level[37] and an index that remains elevated over time have been associated with increased mortality. Increases in the galactomannan optical density index of more than 0.25 from baseline have also been suggestive of poor outcomes.[35] False positive galactomannan results have been previously attributed to concurrent piperacillin–tazobactam administration, although serial changes in product development suggest that this cross-reactivity is now uncommon.[38] Cross-reactivity with other fungi (e.g., fusarium or penicillium) may also occur. A direct comparison of 1,3-β-D-glucan testing with galactomannan testing has suggested a higher sensitivity for 1,3-β-D-glucan testing and a higher specificity for galactomannan.[39]

Combining diagnostic assays may help overcome the limitations of any individual test. A meta-analysis showed that when weekly serum galactomannan testing or a serum or whole-blood PCR assay was used in high-risk patients, a single positive result had modest sensitivity (serum galactomannan testing, 92%; PCR assay, 84%), although when the two tests were used concurrently and either one was positive, the sensitivity increased to 99%.[40] When both tests were positive in the same patient, the specificity increased to 98%.

ANTIFUNGAL RESISTANCE

When cultures are positive for aspergillus species, antifungal susceptibility testing could be considered for patients in certain geographic locations where the increase in antifungal resistance in these genera is known to be problematic. Resistance may occur de novo or may de-

velop during therapy. New *A. fumigatus* resistance can result from the use of agricultural antifungal agents that are structurally similar to mold-active triazoles.[41] A tandem repeat in the gene promoter with a substitution of leucine for histidine at codon 98 (TR_{34}/L98H) causes pan-triazole resistance,[42] and other mechanisms may also contribute to resistance.[43] Some species are known to have variable susceptibility to antifungal agents. *A. terreus* is infrequently susceptible to amphotericin B, whereas *A. calidoustus* and *A. lentulus* are resistant to multiple antifungal agents, including amphotericin B and voriconazole. Since clinical outcomes depend largely on recovery from defects in host immunologic factors, the results of susceptibility testing are used to optimize antifungal therapy so that host-specific variables can be addressed in an infected patient.[44]

TREATMENT

Management of aspergillosis requires early recognition of infection so that attention can be focused on the question of whether to provide antifungal therapy. In addition to antifungal agents, allergic forms of infection may require glucocorticoids, anti-IgE therapy (omalizumab), or potentially, anti–interleukin-5 monoclonal antibodies. Fungus balls and wound or topical infections may require surgical débridement in addition to systemic antifungal therapy. Initiation of antifungal therapy requires medication that has a mechanistic application to the identified species of aspergillus that is causing infection (Fig. 2). Clinicians should decrease the dose or stop immunosuppressive therapy when feasible.

A number of professional societies have published guidelines for treatment, with voriconazole or isavuconazole recommended as first-line therapy (Table 3). A trial reported in 2021 supports the use of posaconazole as first-line therapy.[45] Amphotericin B was previously the mainstay of treatment but was supplanted by voriconazole on the basis of a randomized study, reported in 2002, comparing voriconazole with amphotericin B deoxycholate as primary therapy.[46] Voriconazole, which undergoes extensive hepatic metabolism by cytochrome P-450 (CYP) enzymes CYP2C19, CYP2C9, and CYP3A4, interacts with a number of other medications that share these metabolic pathways. Genetic polymorphisms in *CYP2C19* also contribute to the observed variations in serum drug levels among patients treated with voriconazole. Adverse events during voriconazole treatment include photopsia (flashing lights), central nervous system disturbance (associated with serum drug levels >5.5 μg per milliliter), photosensitivity, periostitis, prolongation of the corrected QT interval, and hair and nail changes.[47]

Isavuconazole is an alternative primary therapeutic option for invasive aspergillosis. This agent was evaluated in a phase 3, double-blind, noninferiority trial reported in 2016.[48] All-cause mortality at day 42 was similar for isavuconazole and voriconazole (19% and 20%, respectively), although drug-related adverse events were less common in the isavuconazole group (42%, vs. 60% in the voriconazole group; P<0.001). Isavuconazole is a moderate inhibitor of CYP3A4, and drug–drug interactions may occur. Therapeutic drug monitoring is not necessary with isavuconazole treatment in most cases[49]; however, additional data are needed for definitive recommendations to be made. In contrast to other triazoles, isavuconazole causes a shortening of the QT interval, although this is of unclear clinical significance.[47]

Posaconazole was compared with voriconazole for the primary treatment of aspergillosis in a phase 3, prospective, double-blind study reported in 2021.[45] Mortality among patients with proven or probable aspergillosis at day 42 was the same in the two treatment groups (19%). Posaconazole is also an inhibitor of CYP3A4, and combined use with medications metabolized by this same pathway may result in drug–drug interactions. Therapeutic drug monitoring is recommended for posaconazole. Serum drug levels above 1 μg per milliliter are recommended during treatment; with long-term use, levels exceeding 4 μg per milliliter may be associated with toxic effects.[47,50]

Combination therapy with voriconazole and an echinocandin may provide a benefit over monotherapy in some patient groups.[51] A benefit of combination therapy has been seen in animal models of infection and retrospective studies.

Table 2. Diagnostic Testing for Aspergillosis.*

Diagnostic Method	Degree of Certainty of Infection	Key Issues	Limitations
Imaging: the lungs are the most commonly affected site, followed by the sinuses	May indicate only possible infection, if diagnosis is based on imaging alone	Supplement with noninvasive testing	CT (with more radiation exposure than plain radiography); plain radiographs of the chest are generally unhelpful Radiographic findings must be interpreted in conjunction with the neutrophil count, since radiographic lesions may increase in size and later cavitate (air crescent sign) with recovery from neutropenia
Invasive methods			
Histopathological evaluation, tissue culture	Traditional standard for proof of invasion; with tissue culture, a sterile site must be sampled to provide proof of invasion	Historical reference standard	Site of suspected infection may be difficult to sample, blood culture not useful
Cytologic assessment of BAL fluid and GMS staining or fluorescent staining (calcofluor white), as well as fungal culture and GM testing†	Probable infection	When infection is suspected, imaging of the presumed site of infection is warranted to assess the extent of disease and any contiguous structures involved	In patients with peripheral lung lesions, needle biopsy may be performed, although biopsy is precluded in patients at risk for thrombocytopenia or coagulopathy
Noninvasive methods			
Specific tests for allergic forms of aspergillosis: serum aspergillus-specific IgE or IgG level, serum precipitating antibodies, and skin testing	Obligatory criteria and predisposing criteria must be present‡	Proper clinical context (often asthma or cystic fibrosis) and radiographic context; CT often shows underlying bronchiectasis	No individual test establishes the diagnosis of allergic bronchopulmonary aspergillosis
GM testing, performed by EIA and read as a ratio relative to the optical density of a control (OD index)	May indicate only probable or possible infection; GM may be obtained from serum or BAL fluid samples	An OD index ≥0.5 is considered positive in serum; with this cutoff of 0.5, sensitivity is 82% (95% CI, 73 to 90) and specificity is 81% (95% CI, 72 to 90)	The performance characteristics of GM testing are most favorable in patients who have hematologic cancer or have undergone HCT, as compared with recipients of solid-organ transplants and other populations; these differences may be related to the burden of disease or to individual host immune factors that aid in GM elimination§
BDG testing	BDG is a cell-wall component of many clinically relevant fungi and is thus not specific for aspergillosis	The appropriate cutoff to optimize BDG performance in the diagnosis of invasive aspergillosis has not been determined According to cutoffs defined for other invasive mycoses, a positive result is generally considered to be >80 pg/ml; sensitivity ranges from 55–96% and specificity from 77–96% (there is substantial variation in the cutoff values used in these studies)	False positive results are seen in patients undergoing hemodialysis (cellulose membranes) and those receiving intravenous immune globulin or albumin and some antibiotics

PCR	Unknown	PCR testing has been evaluated in numerous studies; a meta-analysis of 25 studies with 2595 patients showed a sensitivity of 85% with a specificity of 76%; serial samples were shown to improve specificity (two positive PCR tests increased specificity to 95%)[33]	DNA may be found in the case of nonviable organisms or colonization; sensitivity improves when PCR is used concurrently with GM testing

* BAL denotes bronchoalveolar lavage, BDG 1,3-β-D-glucan, CI confidence interval, EIA enzyme immunoassay, CT computed tomography, GM galactomannan, HCT hematopoietic-cell transplantation, and PCR polymerase chain reaction.
† According to one study, Gomori methenamine silver (GMS) staining of BAL fluid samples was positive in 42% of cases.[32] In contrast, only 2 of 67 BAL fluid samples (3%) were positive in direct smears stained with calcofluor white. Positive GMS staining results were significantly more frequent in invasive pulmonary aspergillosis with cavitary lesions and invasive pulmonary aspergillosis caused by more than one aspergillus species, but the proportions of positive cytologic results did not differ among aspergillus species.
‡ Either asthma or cystic fibrosis is usually present as a predisposing criterion, but sometimes the criterion is chronic obstructive pulmonary disease, a post-tuberculous cavity, bronchiectasis, chronic granulomatous disease, hyperimmunoglobulinemia E syndrome, or lung transplantation, to name some possibilities.
§ The performance of GM testing has also been shown to vary among aspergillus species, with a higher sensitivity for non–*A. fumigatus* species than for *A. fumigatus* (49% vs. 13%; P<0.001).

However, a large, randomized trial comparing voriconazole alone with voriconazole plus anidulafungin, reported in 2015, showed no significant difference in mortality at 6 weeks between patients receiving monotherapy and those receiving combination therapy.[52] A post hoc analysis of the study data showed a significant reduction in 6-week mortality with combination therapy in the subgroup of patients with a diagnosis of probable aspergillosis (defined by positive galactomannan testing and radiographic abnormalities). This group may represent a more homogeneous patient population than prior, smaller reported groups of patients, although additional studies are needed to further explore the benefit of combination therapy. For now, combination therapy is recommended only in selected patient groups.

Lipid formulations of amphotericin B (liposomal amphotericin B or amphotericin B lipid complex) can be used in patients in whom first-line therapy is associated with an unacceptable adverse-event profile or who have refractory disease.[51] However, in centers with a substantial number of de novo triazole-resistant aspergillus infections, lipid formulations of amphotericin B may be used as first-line therapy. Dose escalation results in increased toxic effects.[53] Because of the low response rates and the nephrotoxic effects associated with intravenous treatment, nonlipid amphotericin (i.e., amphotericin B deoxycholate) is used as intrathecal therapy or as a component of surgical irrigant solutions more often than as intravenous treatment of invasive infection, unless other agents are not available (e.g., in developing countries).

Itraconazole should not be used as first-line therapy for invasive aspergillosis, although it is a potential treatment option in patients with other forms of disease. In a study evaluating itraconazole therapy for chronic cavitary pulmonary aspergillosis, improvement or stabilization of disease was seen in 71% of the study participants.[54] Patients with allergic bronchopulmonary aspergillosis in whom oral glucocorticoids cannot be tapered also benefit from itraconazole therapy, and although other mold-active azoles are probably similar in efficacy for these noninvasive forms of disease, data from prospective studies are lacking. A new itraconazole formulation (SUBA-itraconazole [SUBA is a proprietary technology denoting superbioavailability]), which

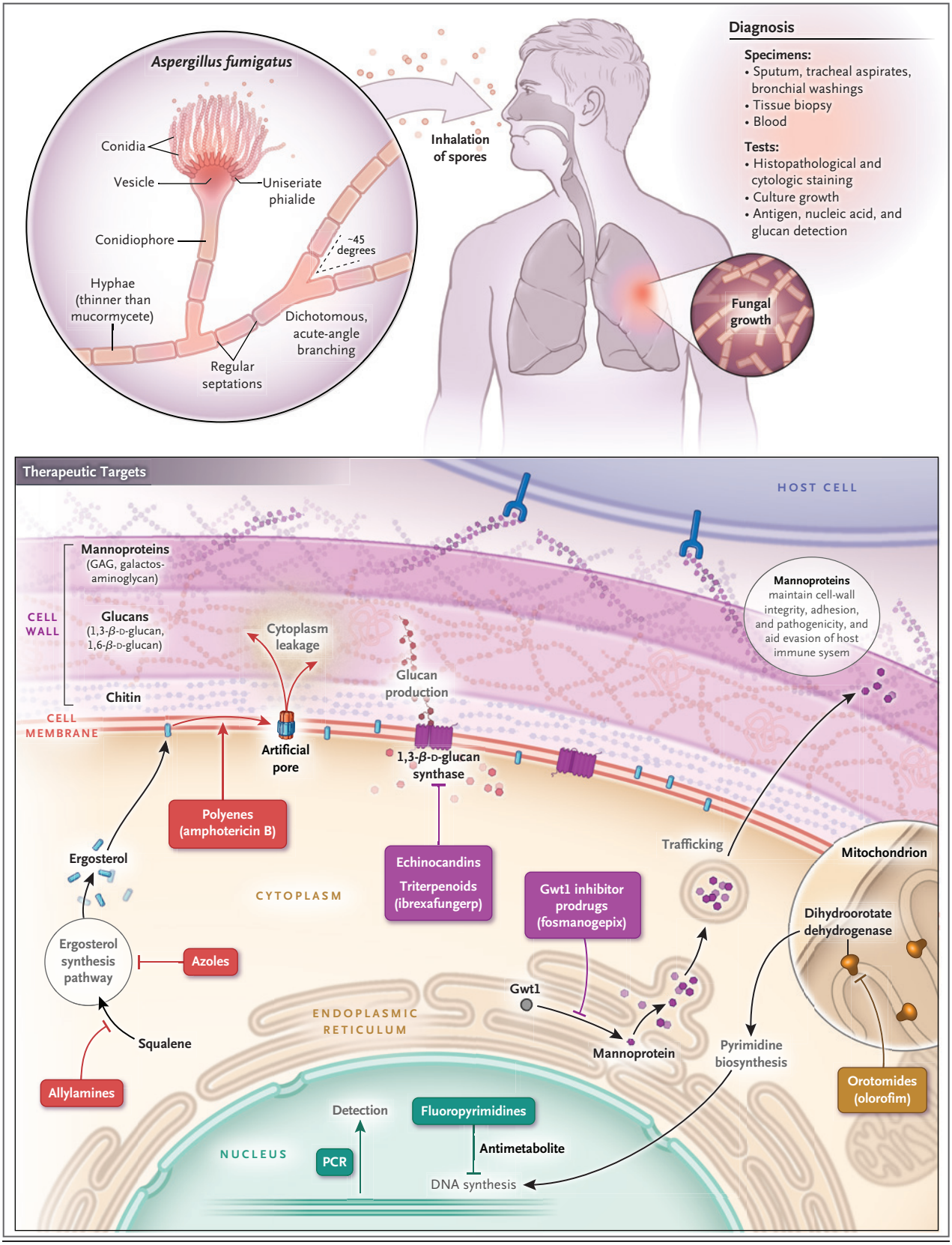

Figure 2 (facing page). Invasive Aspergillosis, from Inhalation to Diagnosis and Treatment.
GAG denotes galactopyranose, *N*-acetylgalactosamine, and galactosamine; and PCR polymerase chain reaction.

offers improved pharmacokinetics as compared with conventional itraconazole, is also a treatment option.[55] Therapeutic drug monitoring during itraconazole therapy is recommended.[56]

Other treatment options include the echinocandins. Echinocandins should not be used as monotherapy except in the case of patients in whom alternative antifungal therapy is associated with an unacceptable adverse-event profile or who have disease that is refractory to it.[51]

In addition to a reduction in exogenous immunosuppressive medications, adjunctive therapy such as granulocyte or granulocyte–macrophage colony-stimulating factor can be used on a case-by-case basis. Granulocyte transfusions are sometimes recommended, primarily if there are no other reasonable options; however, no benefit of this approach has been shown.[57]

PREVENTION

Hospitalized patients who are undergoing or have undergone HCT should ideally be placed in protective environment rooms that have high-efficiency particulate air (HEPA) filters with 99.97% efficiency for removing particles that are 0.3 μm or more in diameter.[58] Allocation of these rooms should be prioritized for patients who are at highest risk for invasive mold infections (e.g., patients in whom neutropenia is expected to be prolonged and those receiving treatment for GVHD). Plants and dried or fresh flowers should not be allowed in hospital rooms during conditioning or after HCT, because aspergillus species and other molds have been isolated from these items. Education regarding additional exposures is also of paramount importance, and extensive guidance has been published.[59] More recently, cannabis use has been identified as a potential source of infection. Cannabis contains fungal and bacterial pathogens, even when sourced from dispensaries, and is directly inhaled in nonfiltered form; it therefore poses a serious risk for immunocompromised patients.[60,61]

Despite rigorous attempts to mitigate environmental factors, patients at highest risk for invasive mold infections benefit from pharmacologic antifungal prophylaxis. Posaconazole is effective in the prevention of aspergillosis in patients undergoing chemotherapy for acute myeloid leukemia and is associated with improved survival.[62] Similarly, posaconazole is effective in patients with severe GVHD after HCT.[63] Voriconazole has been evaluated as long-term prophylaxis (for 100 to 180 days) but was not associated with a survival benefit, as compared with fluconazole, during this extended period.[64] Because of the interactions between triazoles and newer oncologic agents (e.g., venetoclax), short-term prophylactic regimens increasingly use echinocandins, although breakthrough infections during prophylaxis with echinocandins may occur, given their relatively limited spectrum of activity.[65,66]

Antifungal prophylaxis has also proved to be beneficial in patients with chronic granulomatous disease[67] and is recommended as lifelong therapy unless curative treatment (e.g., transplantation) is undertaken. The need for prophylaxis in nontraditional hosts (i.e., patients without a compromised immune system) in the ICU has not been defined, and trials assessing the potential benefit of targeted prophylaxis in this patient population are ongoing.

FUTURE DIRECTIONS

Despite the extensive work done in this field and advances in antifungal therapy, outcomes for patients with invasive infections must be improved, since mortality rates at 6 weeks remain close to 20%.[45,48,52] Drug–drug interactions during clinical care are a serious problem, and adverse events limit current therapeutic regimens. The search for alternative agents has prompted interest in agents with improved pharmacokinetic characteristics (SUBA-itraconazole, with its superbioavailable drug-delivery system, and the long-acting echinocandin rezafungin)[68,69] and novel mechanisms of action (fosmanogepix, a glycosylphosphatidylinositol-anchor biosynthesis inhibitor; ibrexafungerp, a glucan synthesis inhibitor [triterpenoid][55]; and olorofim, a dihydroorotate dehydrogenase inhibitor),[70,71] and phase 2 and 3 trials are ongoing.[55]

As with the development of CAR-T therapy for

Table 3. Current Medication Options for the Treatment of Aspergillosis.*

Antifungal Agent	Advantages	Disadvantages	Comments
Voriconazole	Superior to amphotericin B deoxycholate†; treatment with voriconazole is based on decades of data and experience with multiple clinical forms of invasive aspergillosis	Need for therapeutic drug monitoring; trough drug levels should be monitored within the first 7 days after initiation of therapy, with a goal of 1 to less than 5.5 μg/ml Multiple drug–drug interactions Risk of periostitis or cutaneous cancer with long-term use Hepatotoxicity, transient visual disturbance or visual hallucinations, rash, alopecia and nail changes, QTc prolongation	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Isavuconazole	Noninferior to voriconazole in a randomized, prospective trial, with fewer side effects; no clear indication for therapeutic drug monitoring; no QTc prolongation	Common adverse effects are nausea, vomiting, and diarrhea Multiple drug–drug interactions Hepatotoxicity QTc shortening of unclear clinical relevance Infusion reactions with IV administration	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Posaconazole	Noninferior to voriconazole in a randomized, prospective trial, with fewer side effects	Need for therapeutic drug monitoring Multiple drug–drug interactions Hepatotoxicity, potential for QTc prolongation Possibility of hypertension during treatment	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Itraconazole	Associated with good clinical responses in patients with ABPA when itraconazole was the only oral azole available; it decreased the fungal burden and reduced the need for glucocorticoid courses	A strong inhibitor and substrate of CYP3A; drug–drug interactions occur	Drug–drug interactions during therapy with mold-active triazoles require a careful review of concurrent medication use to ensure that toxic effects can be minimized; serious drug interactions, including bidirectional interactions, may occur, warranting caution with the use of other medications metabolized through these CYP isoenzymes
Lipid amphotericin B formulations (liposomal amphotericin B, amphotericin B lipid complex)	Release of amphotericin from synthetic phospholipids at the site of infection, based on affinity for fungal ergosterol rather than exposure of kidney tissues to amphotericin, which occurs with IV administration of nonlipid amphotericin B deoxycholate	With dose escalation of liposomal amphotericin B, a dose that exceeds 5 mg/kg/day results in increased toxic effects	Dose-related reactions: nephrotoxicity and electrolyte disturbances Infusion-related reactions: fever, rigors, and nausea Both dose-related and infusion-related reactions are much less frequent with lipid formulations than with amphotericin B deoxycholate

Amphotericin B deoxycholate	IV administration is limited to situations in which lipid formulations of amphotericin B or mold-active azole antifungals are unavailable; inhaled or nebulized antifungal therapy may be an option in patients with neutropenia and lung-transplant recipients; agent of choice for intrathecal or irrigant use	Clinical outcomes severely limited by toxic effects that preclude robust IV dose escalation	Dose-related reactions: nephrotoxicity and electrolyte disturbances Infusion-related reactions: fever, rigors, and nausea Both dose-related and infusion-related reactions are much less frequent with lipid formulations than with amphotericin B deoxycholate
Echinocandin (anidulafungin, caspofungin, micafungin)	Daily IV infusion has an acceptable side-effect profile	Sporadic cases of aminotransferase elevations Sporadic cases of infusion or hypersensitivity reactions	Should not be used as initial monotherapy

* APBA denotes allergic bronchopulmonary aspergillosis, CYP cytochrome P-450, IV intravenous, and QTc corrected QT interval.
† In a 2002 randomized trial, primarily involving patients treated with allogeneic HCT and those with hematologic diseases,[46] successful outcomes at 12 wk were more common in the voriconazole group than in the amphotericin B group (53% vs. 32%), with a survival benefit in the voriconazole group (71% vs. 58%); voriconazole-treated patients also had fewer severe drug-related adverse events.

oncologic conditions, T cells genetically modified to render cytotoxic T cells specific for fungi have been developed and are being explored as treatment options.[72] The pattern-recognition receptor dectin-1 is adapted to activate T cells through chimeric CD28 and CD3-ζ on binding with carbohydrate in the cell wall of aspergillus. These cells have specificity for β-glucan, which can lead to damage and inhibition of hyphal growth of aspergillus in vitro and in vivo. Preclinical development is ongoing.[72]

Novel diagnostics, including point-of-care assays with rapid turnaround times[73] and analysis of fungal metabolites in patient breath,[74] are also in development. Improvements in radiographic technology may help shorten the time to diagnosis. Imaging studies performed before chemotherapy may also be of use to identify infection acquired even before diagnosis of the underlying disease (e.g., neutropenia from previously undiagnosed myelodysplastic syndrome).[75]

SUMMARY

Aspergillus infections affect persons with various levels of immune system competence or compromise. Since 2009, molecular studies have identified new polymorphisms that predispose some persons to disease. New risk factors for aspergillosis include ICU stays and respiratory viral infections. Clinicians are linking new diagnoses of invasive aspergillosis to evolving therapies for various medical conditions. For example, monoclonal antibodies and tyrosine kinase inhibitors have been developed to treat underlying disease and avoid glucocorticoid-induced immunosuppression. If invasive infection is suspected, clinicians can perform noninvasive diagnostic testing to supplement radiographic imaging, so that treatment can be initiated as early as possible in the course of infection. Clinicians can add prophylaxis against a new aspergillus infection in high-risk situations. With multiple classes of antifungal agents available for treatment, clinicians have options to assist infected patients with recovery. Good outcomes depend largely on reversal of immunosuppression, early administration of antifungal therapy, and surgical drainage in selected cases.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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