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covers and a face shield and/or goggles. If available, N-95 or N-100 respi rators may be used to further limit infection risk. Positive-air-pressure respirators should be considered for high-risk medical procedures, such as intubation or suctioning. Medical equipment used in the care of an infected patient, such as gloves or syringes, should never be reused. Because filovirions are enveloped, disinfecting with detergents (e.g., 1% sodium deoxycholate, diethyl ether, or phenolic compounds) is relatively straightforward. Bleach solutions are recommended at 1:100 for surface disinfection and 1:10 for application to excreta or corpses. Whenever possible, potentially contaminated materials should be auto claved, irradiated, or destroyed. Emerging from research conducted during the 2013–2016 EVD outbreak in Western Africa, a vaccine based on a recombinant vesicu lar stomatitis Indiana virus expressing EBOV GP1,2 (rVSV-ZEBOV/ Ervebo) was the first filovirid vaccine approved for use in the United States and the European Union (EU). It is now widely deployed in both a reactive-ring vaccination strategy, targeting close contacts and their contacts in EVD outbreak settings, and for the preexposure vaccination of health care workers in at-risk regions. More recently, a heterologous dose vaccine candidate incorporating EBOV GP1,2 into an adenovirus vector (Ad26.ZEBOV-GP/Zabdeno) followed by a vaccinia virus vec tor incorporating multiple filovirid antigens (MVA-BN-filo/Mvabea) has been shown to be safe and immunogenic in humans. Though evaluation of efficacy in a clinical trial has not been possible, immu nobridging data gained during nonhuman primate experimentation led to regulatory authorization in the EU under “exceptional circum stances”; the two-dose requirement likely limits current use to proac tive preexposure prevention in “peri-outbreak” settings rather than reactive “in-outbreak” reactive strategies. Development and evaluation of this and other vaccine candidates continue toward complementary preventive approaches for non-outbreak or peri-outbreak settings, with emphasis on the durability of immune responses and increases in preventive breadth toward other filovirids. Even in the absence of high-level evidence, expert consensus informs the targeted use of EBOV-specific vaccine or postexposure prophylaxis (PEP) to prevent infection or disease in health care workers considered to have had a high-risk EBOV exposure (e.g., after needlestick injury). Evidence is needed to inform the use of PEP in high-risk contacts in the field outbreak

setting. For male survivors, abstinence from sexual activity with a partner for at least 12 months after disappearance of clinical signs is recommended, unless testing proves semen to be free of filovirid RNA. (The use of condoms is generally recommended for all sexual activities.) Reproductive tract and CNS tissues, including ocular tissues and fluids from survivors, should be handled with appropriate precautions until demonstrated to be filovirid-RNA free. The role of filovirid-specific therapeutics in the prevention or treatment of filoviral persistence is unclear. ■ ■FURTHER READING Cnops L et al: Essentials of filoviral load quantification. Lancet Infect Dis 16:e134, 2016. Crozier I et al: The evolution of medical countermeasures for Ebola virus disease: Lessons learned and next steps. Vaccines (Basel) 10:1213, 2022. Dudas G et al: Virus genomes reveal factors that spread and sustained the Ebola epidemic. Nature 544:309, 2017. Hoenen T et al: Therapeutic strategies to target the Ebola virus life cycle. Nat Rev Microbiol 17:593, 2019. Jacob ST et al: Ebola virus disease. Nat Rev Dis Primers 6:13, 2020. Kuhn JH et al: Filoviridae, in Fields Virology, Vol 1, 7th ed, PM Howley et al (eds). Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins, 2020, pp 449–503. Matz KM et al: Ebola vaccine trials: Progress in vaccine safety and immunogenicity. Expert Rev Vaccines 18:1229, 2019. Mulangu S et al: A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 381:2293, 2019. Regules JA et al: A recombinant vesicular stomatitis virus Ebola vaccine. N Engl J Med 376:330, 2017.

Section 16 Fungal Infections Michail S. Lionakis, John E. Edwards, Jr.

Pathogenesis, Diagnosis,

and Treatment of Fungal Infections DEFINITION AND ETIOLOGY In recent decades, human fungal infections have dramatically increased worldwide as a result of the AIDS pandemic, the widespread use of antibacterial agents, and the introduction of cytotoxic agents and precision medicine biologics for the treatment of autoimmune and neoplastic diseases and for use in patients undergoing solid organ transplantation or hematopoietic stem cell transplantation. Moreover, of great concern has been the recent rise in fungal infections caused by drug-resistant species, such as azole- and/or echinocandin-resistant Candida glabrata and Candida auris and azole-resistant Aspergillus fumigatus. Among the ~5 million fungal species, only a few cause human infections (Table 217-1). Fungal infections are classified as mucocutaneous and deep organ infections on the basis of anatomic location and as endemic and opportu nistic infections on the basis of epidemiology. Mucocutaneous infections can cause serious morbidity but are rarely fatal. Deep organ infections cause severe illness and often carry a high mortality rate. The endemic mycoses are caused by fungi that are not part of the normal human microbiota but are environmentally acquired. The opportunistic myco ses are caused by fungi (Candida, Aspergillus) that often are components of the human microbiota and whose ubiquity in nature renders them easily acquired by immunosuppressed hosts (Table 217-1). Opportunis tic fungi cause serious infections when impaired host immune responses allow the organisms to transition from commensals to invasive patho gens. Endemic fungi typically cause self-limited disease in immunocom petent hosts but severe illness in immunosuppressed patients. CHAPTER 217 Pathogenesis, Diagnosis, and Treatment of Fungal Infections Fungi are morphologically classified as yeast, mold, and dimorphic. Yeasts are seen as round single cells or budding organisms. Molds grow as filamentous forms called hyphae both at room temperature and in tissue. Aspergillus, Mucorales, and dermatophytes that infect skin and nails are mold fungi. Variations exist within this classification system. For instance, when Candida infects tissue, both yeasts and filamen tous forms (pseudohyphae) may be

present (except in the cases of C. glabrata and C. auris, which form only yeasts in tissue); in contrast, Cryptococcus exists only in yeast form. Dimorphic is the term used to describe fungi that have two forms; they grow as yeasts or large spheri cal structures in tissue but as filamentous forms at room temperature in the environment (Table 217-1). Patients acquire deep organ infection by molds and endemic dimorphic fungi via inhalation. Skin dermatophytes are primarily environmentally acquired, but human-to-human transmission may also occur. The commensal Candida invades deep tissues from sites of mucocutaneous colonization, usually in the gastrointestinal tract or the skin in the case of C. auris. In this chapter, we outline general principles of immunology, diagno sis, and treatment related to the most common human fungal infections. ■ ■PATHOGENESIS In the past decade, our understanding of fungal recognition pathways and of tissue-specific innate and adaptive antifungal host defense mechanisms has markedly expanded. A major breakthrough has been the discovery and functional characterization of the C-type lectin recep tor/spleen tyrosine kinase/caspase recruitment domain–containing

protein 9 (CLR/SYK/CARD9) signaling pathway, which mediates fungal polysaccharide recognition and orchestrates proinflamma tory mediator production, leukocyte recruitment, inflammasome

TABLE 217-1 Major Fungal Infections, Associated At-Risk Patient Populations, and Diagnostic Tests INFECTION (MOST COMMON FUNGAL GENERA AND SPECIES) CLINICAL SYNDROME(S) RISK FACTOR(S) DIAGNOSTIC TEST(S) Mold (Filamentous) Fungi Aspergillosis (Aspergillus fumigatus,

A. terreus, A. flavus, A. niger,

A. nidulansa) Pneumonia or disseminated infection ABPA Keratitis Neutropenia, glucocorticoids, HSCT, post-influenza or COVID-19, BTK inhibition Atopic individuals Direct inoculation Mucormycosis (Rhizopus, Rhizomucor,

Mucor, Cunninghamella, and Lichtheimia spp.) Sinopulmonary infection Rhinocerebral infection Necrotizing skin infection Neutropenia, HSCT Diabetic ketoacidosis Direct inoculation (e.g., tornado victims) Fusariosis (Fusarium solani, F. oxysporum) Pneumonia or disseminated infection Keratitis Neutropenia Direct inoculation Scedosporiosis (Scedosporium apiospermum) Pneumonia or disseminated infection Neutropenia, glucocorticoids, HSCT Phaeohyphomycosis (Cladophialophora, Alternaria, Phialophora, Rhinocladiella, Exophiala, and Exserohilum spp.) Sinopulmonary, CNS, or disseminated infection Skin infection Allergic sinusitis HSCT, neutropenia, glucocorticoids, healthy individuals (for CNS), TNF-α inhibition Direct inoculation Atopic individuals Dermatophytosis (Trichophyton, Microsporum, and Epidermophyton spp.) Skin and nail infections Healthy individuals Culture or microscopic examination of scrapings or clippings: chains of arthrospores (diagnostic) PART 5 Infectious Diseases Eumycetoma (Madurella mycetomatis) Skin and subcutaneous infections Healthy individuals Culture and macroscopic and histologic examination of grains harvested from biopsy or aspiration Yeast Fungi Mucosal candidiasisc Oropharyngeal or esophageal candidiasis Vulvovaginal candidiasis AIDS, glucocorticoids Antibiotic use (Candida albicans, C. glabrata) Invasive candidiasisc Candidemia Disseminated infection (spleen, liver, kidney, eye, heart, CNS) Critical illness (ICU) Neutropenia, glucocorticoids (C. albicans, C. glabrata,

C. parapsilosis, C. tropicalis,

C. auris) Cryptococcosis (Cryptococcus neoformans, C. gattii) Pneumonia Osteomyelitis Meningoencephalitis AIDS, glucocorticoids Sarcoidosis AIDS, AAbs to IFN-γ or GM-CSF, BTK or JAK inhibition Trichosporonosisd Superficial skin infection (white piedra) Disseminated infection (skin, eye) Healthy individuals Neutropenia, glucocorticoids, HSCT, SOT (Trichosporon asahii, T. mucoides, T. asteroides) Endemic Dimorphic Fungi Histoplasmosis (Histoplasma capsulatum, H. duboisii [in Africa]) Self-limited pneumonia Disseminated infection (liver, bone, bone marrow) Fibrosing mediastinitis Healthy individuals AIDS, SOT, glucocorticoids, AAbs to IFN-γ, JAK or TNF-α inhibition Blastomycosis (Blastomyces dermatitidis, B. gilchristii) Pneumonia Disseminated infection (skin, bone, mucosal surfaces, genitourinary tract) Healthy individuals AIDS, glucocorticoids, TNF-α inhibition Coccidioidomycosis (Coccidioides immitis, C. posadasii) Self-limited pneumonia Disseminated infection (CNS, bone) Healthy individuals AIDS, glucocorticoids, TNF-α inhibition Paracoccidioidomycosis (Paracoccidioides brasiliensis, P. lutzii) Pneumonia Disseminated infection (skin, bone, mucosal surfaces) Healthy individuals AIDS, glucocorticoids

Culture of BAL fluid: low sensitivity, nonspecific (colonization, contamination) Histologic examination of tissueb: acute-angle septate hyphae Biomarkers: GM (BAL > serum); serum BDG (nonspecific) Culture of BAL fluid or sinus tissue: very low sensitivity Histologic examination of tissue: ribbon-like aseptate hyphae Biomarkers: Negative Culture of tissue or blood: one of the few molds recovered from blood Histologic examination of tissue: acute-angle septate hyphae Biomarkers: GM can be positive; BDG (nonspecific) Culture of BAL: low sensitivity, nonspecific (colonization, contamination) Histologic examination of tissue: acute-angle septate hyphae Biomarkers: BDG can be positive Culture of ordinarily sterile site Histologic examination of tissue: cell walls may appear dark brown or golden on H&E; Fontana-Masson may stain fungal melanin Culture of mucosal surfaces Histologic examination of esophageal tissue or wet preparation (10% KOH) of vaginal discharge: yeast and/or pseudohyphae Culture of blood: low sensitivity Histologic examination of tissue: yeast and/or pseudohyphae Biomarkers/other tests: BDG (nonspecific); T2 magnetic resonance in whole blood Culture of CSF, BAL fluid, blood Microscopic examination of tissue or CSF: encapsulated yeast (GMS, India ink, mucicarmine stain) Biomarkers: Cryptococcus Ag (serum, CSF) is sensitive and specific Culture of tissue or blood Histologic examination of tissue: yeasts, hyphae, and arthroconidia Biomarkers: BDG can be positive Culture of blood or tissue: low sensitivity; weeks needed for growth Histologic examination of tissue: yeast with narrow-based budding Other tests: Histoplasma Ag (urine > serum > BAL); BDG can be positive; serology (CF) can be useful in non-AIDS patients Culture of BAL or tissue: low sensitivity; weeks needed for growth Histologic examination of tissue: yeast with broad-based budding Other tests: serology (CF, ID) has low sensitivity; Blastomyces Ag test cross-reacts with other endemic fungi; GM can be positive Culture is diagnostice Histologic examination: spherules Other tests: serology (CF, ID); Coccidioides Ag test can be useful in CNS infection; BDG can be positive Culture of tissue: active disease; several weeks needed for growth Histologic examination of KOH preparations or tissue: yeast with budding in steering-wheel pattern Other tests: serology (ID, CF); Paracoccidioides Ag test (Continued)

TABLE 217-1 Major Fungal Infections, Associated At-Risk Patient Populations, and Diagnostic Tests INFECTION (MOST COMMON FUNGAL GENERA AND SPECIES) CLINICAL SYNDROME(S) RISK FACTOR(S) DIAGNOSTIC TEST(S) Sporotrichosis (Sporothrix schenckii) Lymphocutaneous infection (ascending lymphangitis) Disseminated infection Direct inoculation AIDS, glucocorticoids Talaromycosis (Talaromyces marneffei) Pneumonia Disseminated infection (skin, bone, mucosal

surfaces) Healthy individuals AIDS, glucocorticoids, AAbs to IFN-γ Adiaspiromycosis (Emmonsia crescens, E. parva) Pneumonia Occupational dust exposure Culture: nonculturable Histologic examination: thick-walled adiaspore within granuloma Emergomycosis (Emergomyces africanus, E. pasteurianus) Disseminated infection (lungs, skin) AIDS, SOT Culture of infected tissue Histologic examination of tissue: yeast with narrow-based budding Biomarkers: Histoplasma Ag can be positive Chromoblastomycosis (Fonsecaea pedrosoi, F. monophora) Skin and subcutaneous tissue infections Healthy individuals Culture of infected tissue Histologic examination of scrapings (KOH) or tissue (GMS): sclerotic bodies (pathognomonic) Other Fungi Pneumocystosisf Pneumonia Disseminated infection (eye, CNS, skin, gastrointestinal tract) AIDS, glucocorticoids, BTK inhibition AIDS (Pneumocystis jirovecii) aA. nidulans is seen almost exclusively in chronic granulomatous disease. bGMS or PAS stains. cSome Candida species form pseudohyphae. dTrichosporon species are yeast-like fungi that also generate septate hyphae and arthroconidia. eCoccidioides is a laboratory hazard. It is important to notify the microbiology laboratory if this infection is suspected. fPneumocystis is present in cyst and trophozoite forms. Abbreviations: AAbs, autoantibodies; ABPA, allergic bronchopulmonary aspergillosis; Ag, antigen; BAL, bronchoalveolar lavage; BDG, β-D-glucan; BTK, Bruton’s tyrosine kinase; CF, complement fixation; CNS, central nervous system; CSF, cerebrospinal fluid; GM, galactomannan; GM-CSF, granulocyte-macrophage colony-stimulating factor; GMS, Gomori methenamine silver; H&E, hematoxylin and eosin; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; ID, immunodiffusion; IFN-γ, interferon γ; JAK, Janus kinase; KOH, potassium hydroxide; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; SOT, solid organ transplantation; TNF-α, tumor necrosis factor α. activation, and Th17 cell differentiation upon fungal invasion. Human inherited CARD9 deficiency causes severe mucocutaneous and inva sive fungal disease and is the only known primary immunodeficiency to feature fungus-specific infection susceptibility without a predispo sition to other infections, autoimmunity, allergy, or cancer. Notably, CARD9-deficient patients develop infections by certain fungi in cer tain tissues, including (1) chronic mucocutaneous candidiasis linked to defective interleukin (IL) 17 responses; (2) infections of the central nervous system (CNS) caused by Candida (but also by Aspergillus and phaeohyphomycetes) linked to impaired microglial-neutrophilic responses; and (3) deep dermatophytosis. Thus, the clinical use of SYK inhibitors for autoimmunity and cancer may cause opportunistic fun gal disease. Human inherited deficiency of Toll-like receptor (TLR) sig naling does not lead to spontaneous fungal disease, yet polymorphisms in TLR pathway molecules may increase the risk of fungal disease in critically ill or immunosuppressed persons, and TLR stimulation may boost protective CLR immunity, as has been shown with the TLR7 agonist imiquimod in chromoblastomycosis. The development of clinically relevant animal models of mycoses and the phenotypic characterization of fungal infections that develop in patients with primary immunodeficiencies and in recipients of immune pathway-targeting biologics have led to the delineation of fungus-, cell-, and tissue-specific requirements for antifungal host defense (Fig. 217-1). At the mucosal interface, IL-17-producing lymphoid cells play a critical role in protection by driving epithelial cell production of anti microbial peptides that restrict mucosal Candida invasion. Indeed, AIDS patients are at risk for mucosal—but not invasive—candidiasis. Concordantly, inherited deficiency of IL-17 signaling caused by muta tions in IL17F, IL17RA, IL17RC, or TRAF3IP2 (encoding the IL-17 receptor adaptor ACT1) or pharmacologic inhibition of IL-17 signal ing by biologics that target IL-12p40, IL-23p19, IL-17A, IL-17A/IL17F, or IL-17RA cause mucosal—but not invasive—candidiasis. Other conditions that underlie a predisposition to chronic mucocutaneous

(Continued) Culture of tissue (diagnostic) Histologic examination: cigar-shaped yeast, often with surrounding asteroid body Culture of tissue (diagnostic) Histologic examination of tissue: yeasts with transverse septa Biomarkers: GM is often positive Culture: nonculturable Histologic examination (gold standard): special (GMS, Diff-Quik) or immunofluorescence stains Biomarkers/other tests: BDG (nonspecific); BAL fluid PCR (sensitive; can be positive in colonized individuals) CHAPTER 217 Pathogenesis, Diagnosis, and Treatment of Fungal Infections candidiasis include primary immunodeficiencies due to mutations in STAT3, STAT1, DOCK8, JNK1, IRF8, RORC, and CARD9, all of which impair Th17 cells, as well as thymoma and autoimmune polyendocri nopathy–candidiasis–ectodermal dystrophy (APECED), which feature autoantibodies to IL-17A, IL-17F, and IL-22. In APECED, exacerbated

T cell–derived interferon γ (IFN-γ)/STAT1 responses disrupt the integrity of the oral epithelial barrier, thereby promoting mucosal fungal inva sion and infection; remission of candidiasis can be achieved with JAK inhibition in APECED and STAT1 gain of function (GOF). Of note, vaginal candidiasis (unlike oropharyngeal and esophageal candidiasis) develops in the setting of antibiotic treatment, not AIDS or IL-17–targeted biologics; this observation underscores the role of the microbiota in fungal control at the vaginal—but not the oral—mucosa. On the other hand, neutrophils—but not lymphocytes—are criti cal for control of invasive infections caused by Aspergillus (and other inhaled molds) and Candida (Fig. 217-1). Indeed, patients with che motherapy-induced neutropenia and patients undergoing allogeneic hematopoietic stem cell transplantation are at risk for invasive aspergil losis and candidiasis. Both oxidative and nonoxidative burst–dependent effector mechanisms are operational within neutrophils for fungal killing. Inherited deficiency in neutrophil superoxide generation due to mutations in the six subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex causes chronic granulomatous disease, a prototypic primary immunodeficiency that carries a lifetime risk for invasive aspergillosis of ~40%; infrequently (i.e., in <5% of cases, mostly infants), chronic granulomatous disease predisposes to invasive candidiasis. The unexpected development of invasive mold infections in recipients of Bruton’s tyrosine kinase (BTK) inhibitors has recently uncovered the critical role of BTK in promoting myeloid phagocyte-dependent antifungal effector functions. Host defenses against fungi that reside within macrophages, such as Cryptococcus, Pneumocystis, and endemic dimorphic fungi, depend on the interplay of IFN-γ–producing lymphoid cells and IL-12–producing macrophages that enable intramacrophagic fungal killing (Fig. 217-1).

IL6R IL23R Th17 cell Th1 cell Neutrophil JAK2 TYK2 STAT3 JAK2 TYK2 RORγT CXCL1 Nucleus fc T cell CXCR2 AAbs NADPH p22phox gp91phox IL-17A/IL-17F AAbs p67phox p47phox p40phox IL-17F IL-17A IL-22 IL-22R1 IL-10Rβ IL-17RA IL-17RC NADP+ PART 5 Infectious Diseases Candida yeast and pseudohyphae
Multilobed nucleus STAT3 ACT1 Epithelial cells Neutrophil Lung FIGURE 217-1 Host defense against fungi. Left: Production of IL-17A, IL-17F, and IL-22 by Th17 cells, Tc17 cells, γδ T cells, and innate lymphoid cells confers protection from mucosal Candida invasion. STAT3 promotes Th17 differentiation via RORγt induction. IL-17A and IL-17F bind to IL-17RA and IL-17RC on epithelial cells and signal via ACT1 to produce antimicrobial peptides that inhibit fungal growth. IL-22 binds to its receptor on epithelial cells and activates STAT3 to mediate epithelial proliferation and repair. Middle: Activation of CXCR2+ neutrophils recruited from blood in the Aspergillus-infected lung enables assembly of the six subunits of NADPH oxidase and superoxide generation that promotes fungal killing. Production of reactive oxygen species by neutrophils is facilitated by recruited

monocyte-derived and plasmacytoid dendritic cells via type I and type III IFNs and GM-CSF. Right: The interaction of Th1 cells with macrophages is protective against intramacrophagic endemic dimorphic fungi, Pneumocystis, and Cryptococcus. Upon fungal uptake, macrophages produce IL-12 that binds to its receptor on T cells and activates STAT4, with consequent release of IFNγ. IFN-γ binds to its receptor on macrophages and activates STAT1, thereby enabling fungal killing. TNF-α and GM-CSF are also critical for macrophage activation. AAbs, autoantibodies; IL, interleukin; IFN, interferon; JAK, Janus kinase; GM-CSF, granulocyte-macrophage colony-stimulating factor; NADPH, nicotinamide adenine dinucleotide phosphate; RORγt; RAR-related orphan receptor γ; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; TYK2, tyrosine kinase 2. Indeed, AIDS patients and those receiving glucocorticoids, which affect lymphocytes and macrophages both quantitatively and qualitatively, are at risk for severe infections by these fungi. Accordingly, inherited impair ment of the IL-12/IFN-γ signaling axis caused by mutations in IL12RB1, IFNGR1, IFNGR2, STAT1, IRF8, or GATA2 underlies susceptibility to severe infection by intramacrophagic fungi (and other intramacrophagic pathogens, such as mycobacteria and salmonellae). In addition, the IFN-γ–targeting monoclonal antibody emapalumab, JAK inhibitors that block IFN-γ–dependent cellular responses, and autoantibodies to IFN-γ predispose to infection with intramacrophagic fungi, as do biologics targeting tumor necrosis factor α (TNF-α) and autoantibodies to gran ulocyte-macrophage colony-stimulating factor (GM-CSF). The latter predisposing factors reveal the central role of these two Th1-associated cytokines—TNF-α and GM-CSF—in macrophage activation. Taken together, these observations show that the cellular and molec ular factors that drive protective antifungal immune responses vary greatly with the anatomic site of the infection, the offending fungus, and the patient population (Table 217-1). The growing body of data on human immunologic responses to fungi promises to inform precision medicine strategies for risk assessment, prophylaxis, immunotherapy, and vaccination of vulnerable patients.

Blood IFNγ CXCR2 Nucleus STAT4 STAT4 CXCL2 TYK2 JAK2 GM-CSF IL12Rβ1 IL12Rβ2 IFNγ IFN-λ Aspergillus conidia AAbs IL-12 IFNγ IFN-γR2 TNFα IFN-γR1 e– O2 – JAK2 STAT1 SOD JAK1 Phagosome STAT1 Phagosome H2O2 Yeast (Histoplasma, Cryptococcus) Macrophage IL-12 Nucleus GM-CSF ■ ■DIAGNOSIS The diagnostic modalities used for various fungal infections are out lined in Table 217-1 and are detailed in the chapters on specific myco ses that follow in this section. Definitive diagnosis of a fungal infection requires histopathologic identification of the fungus invading tissue with parallel culture of the fungus from the specimen. Certain fungi have dis tinctive morphologic features that facilitate diagnosis (Table 217-1). The stains most often used to identify fungi are periodic acid–Schiff (PAS) and Gomori methenamine silver (GMS). Candida, unlike other fungi, is visible on Gram-stained tissue smears. Hematoxylin and eosin stains define accompanying histologic features of fungal disease (granuloma formation, angioinvasion, necrosis) but are insufficient to reliably identify fungi in tissue. A positive India ink stain of cerebrospinal fluid (CSF) is diagnostic for cryptococcosis. Most laboratories use calcofluor white staining coupled with fluorescence microscopy to identify fungi in fluid specimens. A positive fungal culture of blood or tissue may signify either patient colonization or lab contamination instead of true infection, with the most likely scenario depending on the fungus and the anatomic site. In blood, Candida can be detected with any of the widely used automated blood culture systems, but the lysiscentrifugation technique increases the sensitivity of blood cultures for

both Candida and other less common fungi (e.g., Histoplasma). Matrixassisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) is now used extensively for detection and specia tion of fungi recovered from culture. The several available fungal-antigen and serologic tests vary in sen sitivity and specificity. The most reliable of these tests are the antibody to Coccidioides, Histoplasma antigen, and cryptococcal polysaccharide antigen. Serologic tests are also available for other endemic dimorphic fungi (Table 217-1). The galactomannan test—especially in the bron choalveolar lavage fluid—is useful for the diagnosis of aspergillosis; however, false-negative results are common, particularly in patients receiving antifungal prophylaxis, and false-positive results may occur with other fungal infections. The β-glucan test has a high negative pre dictive value for invasive candidiasis but lacks specificity. T2 magnetic resonance is now approved by the U.S. Food and Drug Administration (FDA) for detection of Candida in blood. Several polymerase chain reaction and nucleic acid hybridization assays exist for fungal detection but are not standardized and are not widely used in the clinic. ■ ■ANTIFUNGAL DRUGS This section provides a brief overview of available agents for the treat ment of fungal infections. Drug regimens and schedules are detailed in the chapters on specific mycoses that follow in this section. Since fungal organisms, like human cells, are eukaryotic, the identification of drugs that selectively kill or inhibit fungi but that are not toxic to human cells poses challenges. Indeed, far fewer antifungal than anti bacterial agents have been introduced into clinical medicine. Early initiation of appropriate antifungal therapy is a critical determi nant of favorable outcome, as has been shown for candidemia, aspergil losis, and mucormycosis. In addition, source control of the infection is important—e.g., with removal of the central venous catheter in candi demia, drainage of abdominal abscesses in intraabdominal candidiasis, and surgical debridement of sinus tissue in mucormycosis. Moreover, an essential factor in a favorable prognosis in patients with opportunistic mycoses is the achievement of immune reconstitution—e.g., with neu trophil recovery, tapering of glucocorticoids or other immunosuppres sive drugs, or initiation of combination antiretroviral therapy in AIDS. ■ ■AMPHOTERICIN B The advent of amphotericin B (AmB) in the 1950s revolutionized the treatment of deep-seated mycoses. Before the availability of AmB, cryptococcal meningitis and other disseminated fungal infections were nearly always fatal. AmB remains the broadest-spectrum antifungal agent. Its fungicidal mechanism of action involves forming extramem branous sponge-like aggregates that extract fungal ergosterol from lipid bilayers. AmB remains the preferred antifungal agent for the treatment of mucormycosis and fusariosis and for induction therapy for cryptococ cal meningitis and disseminated infections caused by endemic dimor phic fungi. However, AmB has several limitations, including lack of a licensed oral formulation and significant toxicity from the intravenous preparations, primarily renal and infusion-related (fever, chills, throm bosis). The introduction of lipid AmB formulations has ameliorated these toxicities, and the lipid formulations have largely replaced the original deoxycholate formulation in resource-rich settings. In develop ing countries, AmB deoxycholate is still widely used because of the high cost of the lipid formulations. The two lipid formulations commonly used in the clinic are liposomal AmB and AmB lipid complex, which exhibit comparable efficacy, toxicity, and tissue penetration profiles. ■ ■AZOLES Azoles offer important advantages over AmB, such as the availability of oral and IV formulations and a lack of renal toxicity. The mechanism of action of azoles involves inhibition of lanosterol 14α-demethylase and ergosterol synthesis in the fungal cell membrane, with a consequent accumulation of toxic sterol intermediates and growth arrest. Unlike AmB, azoles are considered fungistatic. Fluconazole Fluconazole plays an important role in the treatment of several fungal infections. Its major advantages are the availability of oral and IV formulations, a long half-life, penetration into most body

fluids (ocular fluid, CSF, urine), and minimal toxicity. This drug rarely causes liver toxicity; high doses may result in alopecia, dry mouth, and a metallic taste. Notably, the administration of even low doses of fluco nazole to pregnant women for the treatment of vaginal candidiasis was recently linked to miscarriage and stillbirth. Fluconazole has no activ ity against molds and most endemic dimorphic fungi and is less active than the newer azoles against C. glabrata and C. krusei.

Fluconazole is the preferred agent for the treatment of coccidioidal meningitis, although relapses may occur despite therapy. Fluconazole is also used as consolidation and maintenance therapy for cryptococcal meningitis and for the treatment of mucosal candidiasis. It is used for treating candidemia in patients who are not critically ill or immuno suppressed; in these patients, fluconazole was found to be as effica cious as AmB. Because of increasing rates of azole-resistant Candida strains, echinocandin treatment is preferred, which is then replaced by fluconazole once a susceptible Candida species is recovered. Flu conazole is effective as prophylaxis in recipients of high-risk liver and allogeneic bone marrow transplants, although many centers now use posaconazole in neutropenic patients, given its added activity against molds. Fluconazole prophylaxis in leukemic patients, in AIDS patients with low CD4+ T-cell counts, and in patients on surgical intensive care units is controversial. Itraconazole Itraconazole is available in oral (capsule, suspension) and IV formulations and has broader antifungal activity—i.e., against molds and endemic dimorphic fungi—than fluconazole. Itraconazole is the drug of choice for mild to moderate histoplasmosis and blasto mycosis and has also been used to treat chronic coccidioidomycosis, phaeohyphomycosis, sporotrichosis, and mucocutaneous mycoses such as oropharyngeal candidiasis, tinea versicolor, tinea capitis, and onychomycosis. Although it is approved by the FDA for use in febrile neutropenic patients, most centers now use newer azoles in such patients. Disadvantages of itraconazole include its poor CSF penetra tion, the use of cyclodextrin in its oral suspension and IV formulation, and its variable level of absorption in the capsule form, which requires monitoring of blood levels in patients receiving capsules for dis seminated mycoses. A new formulation of itraconazole, called SUBAitraconazole (for “super-bioavailability”), which results in improved absorption and less variable plasma levels, has recently been approved by the FDA. Itraconazole is a potent CYP3A4 inhibitor; this character istic leads to significant drug interactions. The drug causes hepatotox icity and cardiac toxicity that may manifest as congestive heart failure. CHAPTER 217 Pathogenesis, Diagnosis, and Treatment of Fungal Infections Voriconazole Voriconazole is also available in oral and IV formula tions, has far broader antifungal activity than fluconazole (including

C. glabrata, C. krusei, Aspergillus, Scedosporium, and endemic dimorphic fungi—but not Mucorales), and penetrates into most body fluids (ocular fluid, CSF). It is the preferred agent for the treatment of aspergillosis and also has been used to treat scedosporiosis and as step-down (but not pri mary) therapy for coccidioidomycosis, blastomycosis, and histoplasmo sis. Voriconazole is considerably more expensive than fluconazole, and as with itraconazole, its use is associated with numerous interactions with drugs typically used in patients at risk for fungal infections. Hepatotoxic ity, visual disturbances, and skin rashes (including photosensitivity) are relatively common, and long-term use requires skin cancer surveillance. A unique toxicity of voriconazole among azoles is fluorosis-associated periostitis. It is crucial to monitor drug levels because (1) voriconazole is metabolized in the liver by CYP2C9, CYP3A4, and CYP2C19; and (2) human genetic variation in CYP2C19 activity exists and can lead to sig nificant interpatient variability in drug levels. Dosages should be reduced in patients with hepatic, but not renal, failure; however, because the IV formulation is prepared in cyclodextrin, it should be given with caution to patients

with severe renal failure. Posaconazole Posaconazole has broader activity than voricon azole, including activity against Mucorales. Both oral (suspension, tablet) and IV formulations are available. Posaconazole is approved by the FDA for antifungal prophylaxis in neutropenic leukemic patients and allogeneic hematopoietic stem cell transplant recipients as well as for treatment of oropharyngeal candidiasis, including infections refractory

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Revision #1
Created 2026-01-06 16:32:38 UTC by Omar Ayman
Updated 2026-01-06 16:32:38 UTC by Omar Ayman