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The goal of maintenance is to prevent recurrent disease, and its duration depends on the immune status of the patient. Individu als who remain deeply immunocompromised, such as those with HIV whose CD4+ T lymphocyte counts remain <200/μL or have not attained control of HIV with ART may need to remain on flu conazole indefinitely. Newer triazoles like voriconazole, posaconazole, and isavuconazole are highly active against cryptococcal strains and appear to be clinically effective, but clinical experience with these agents is limited. An oral formulation (cochleated) of AmB is in development. The echinocandins are not effective against Cryptococcus species. Addition of a short course of interferon γ to antifungal therapy in patients with HIV infection increases clear ance of cryptococci from the CSF. Antifungal drug resistance has not been a major problem with cryptococcal strains, but there are increasing reports of drug-resistant strains, including some emerging during the prolonged therapy needed for cryptococco sis. Hence, cryptococcosis that is refractory to antifungal therapy should prompt an investigation into the susceptibility of the clinical isolates in question.

Cryptococcal meningoencephalitis may be associated with increased ICP, which can damage the brain and cranial nerves. CSF pressure should be measured and increased ICP diligently man aged in such patients. The mechanism leading to increased ICP is often excess CSF fluid. Neurologic symptoms, including headache, blurred vision, cranial nerve abnormalities, and altered mental sta tus, are typical clues to increased ICP. Management requires reduc tion of pressure by repeated therapeutic lumbar punctures and the placement of shunts. Neither mannitol nor acetazolamide is effec tive. Glucocorticoids are not helpful unless the elevated ICP is from a brain lesion with associated mass effect and edema. PART 5 Infectious Diseases Several clinical syndromes in cryptococcosis are driven by an overactive immune response. In people with HIV disease who are treated with ART, an immune reconstitution inflammatory syndrome (IRIS) occurs when immunity rebounds in the setting of treated cryptococcosis (or an undiagnosed asymptomatic infec tion). Similar syndromes can occur in transplant recipients whose immunosuppressive regimens have been reduced to help control the infection and even in non-immunocompromised people with infection that had appeared to be resolving. The immune response triggers an inflammatory reaction that can be difficult to distin guish from a relapsing infection. Symptoms can include fevers, headache, lymphadenopathy, and pulmonary, CNS, and cutaneous manifestations. Administration of prophylactic dexamethasone in HIV-associated cryptococcosis is not recommended because it has been associated with reduced fungal clearance and increased mor tality. The approach to patients that have already developed IRIS and the related immune-driven syndromes must attempt to balance resurgent immunity against immune-mediated damage. Manage ment is individualized and can involve the use of glucocorticoids to reduce inflammation. Apart from the difficulties in distinguishing these inflammatory syndromes from cryptococcal

relapse, their management is complex because the cause is often triggered by the desirable outcome of improving immunity, which is important in controlling cryptococcal infection and preventing relapses. A major consideration for clinicians treating symptomatic AIDSrelated cryptococcosis is when to begin ART, which can trigger rebounding immunity. Current recommendations are to start ART 4−6 weeks after initiating antifungal therapy. Screening with serum CRAg is recommended for asymptomatic people with HIV and CD4+ T lymphocyte counts of <100–200/μL. Positive tests should be followed up with careful evaluation for active disease including CSF analysis. For those with antigenemia but no evidence of active disease, a preemptive fluconazole regimen is recommended with 14 days of induction dosing at 800 mg daily and up to 1200 mg daily when fungal burden is high (e.g., CRAg titers exceed 1:80) followed by consolidation and maintenance dosing. Initiation of ART should start 2 weeks after initiation of antifungal therapy in such circumstances.

■ ■PROGNOSIS AND COMPLICATIONS Even with antifungal therapy, cryptococcosis is associated with high rates of morbidity and death. For most patients with cryptococcosis, the most important prognostic factors are the extent and the dura tion of the underlying immunologic deficits that predisposed them to develop the disease. Cryptococcosis is often curable with antifungal therapy in individuals with no apparent immunologic dysfunction, but in patients with irreversible immunosuppression, the best that can be hoped for is that antifungal therapy will induce remission, which can then be maintained with lifelong suppressive therapy. Before the advent of ART, the median overall survival period for AIDS patients with cryptococcosis was <1 year. Cryptococcosis in patients with underlying neoplastic disease has a particularly poor prognosis. For CNS crypto coccosis, poor prognostic markers are a CSF assay positive for yeast cells on initial India ink examination (evidence of a heavy fungal bur den), high CSF pressure, low CSF glucose levels, low CSF pleocytosis (<2/μL), recovery of yeast cells from extraneural sites, absence of anti body to capsular polysaccharide, a CSF or serum cryptococcal antigen level of ≥1:32, and concomitant glucocorticoid therapy or hematologic malignancy. A response to treatment does not guarantee cure since relapse of cryptococcosis is common even among patients with rela tively intact immune systems and immune reconstitution syndromes can occur in patients who had been improving with antifungal therapy. Complications of CNS cryptococcosis include cranial nerve deficits, vision and hearing loss, and cognitive impairment. ■ ■PREVENTION No vaccine is available for cryptococcosis. Primary prophylaxis with fluconazole 100–200 mg daily is an approach in high-risk HIV patients (e.g., CD4+ T lymphocyte count <100/μL) and can be used in places where cryptococcal antigen testing is not readily available. Since ART raises the CD4+ T lymphocyte count, it constitutes an immunologic form of prophylaxis. ■ ■FURTHER READING Alanio A: Dormancy in Cryptococcus neoformans: 60 years of accu mulating evidence. J Clin Invest 130:3353, 2020. Boyer-Chammard T et al: Recent advances in managing HIV-associated cryptococcal meningitis. F1000Res 8:F1000 Faculty Rev-743, 2019. Kwon-Chung KJ et al: The case for adopting the “species complex” nomenclature for the etiologic agents of cryptococcosis. mSphere 2:e00357, 2017. Robertson EJ et al: Cryptococcus neoformans ex vivo capsule size is associated with intracranial pressure and host immune response in HIV-associated cryptococcal meningitis. J Infect Dis 209:74, 2014. Ssebambulidde K et al: Treatment recommendations for non-HIV associated cryptococcal meningoencephalitis including management of post-infectious inflammatory response syndrome. Front Neurol 13:994396, 2022. Tugume L et al: Cryptococcal meningitis. Nat Rev Dis Primers 9:62, 2023. Michail S. Lionakis, Shakti Singh,

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Candidiasis The genus Candida encompasses >150 species, only a few of which cause disease in humans. With rare exceptions (although the excep tions are increasing in number), the human pathogens are C. albicans, C. guilliermondii (recently revised to Meyerozyma guilliermondii), C. krusei (recently revised to Pichia kudriavzevii), C. parapsilosis,

C. tropicalis, C. lusitaniae (recently revised to Clavispora lusitaniae),

C. dubliniensis, C. glabrata (recently revised to Nakaseomyces glabratus), and the emerging, multidrug-resistant C. auris, which has been respon sible for several outbreaks in health care facilities in recent years. Ubiq uitous in nature, they inhabit the gastrointestinal tract (including the mouth and oropharynx), the female genital tract, and the skin in the majority of healthy persons. Although cases of candidiasis have been described since antiquity in debilitated patients, the advent of Candida species as common human pathogens dates to the introduction of modern therapeutic approaches that suppress normal host defense mechanisms. Of those advances, the most important are the use of antibacterial agents that alter the normal human microbiota and allow nonbacterial species to become more prevalent in the commensal flora, the use of indwelling intravenous catheters, and the use of cytotoxic, immunosuppressive treatments for malignant and autoimmune disor ders. With the introduction of antifungal agents, the causes of Candida infections shifted from an almost complete dominance of C. albicans to the common involvement of C. glabrata and the other species listed above. The non-albicans species now account for approximately half of all cases of candidemia and hematogenously disseminated candidiasis. Recognition of this change is clinically important since the various spe cies differ in susceptibility and are increasingly resistant to the newer antifungal agents. Candida is a small, thin-walled, ovoid yeast that measures 4–6 μm in diameter and reproduces by budding. Organisms of this genus occur in three forms in tissue: blastospores, pseudohyphae, and hyphae. Candida grows readily on simple media; lysis centrifugation enhances its recovery from blood. Species are identified by biochemi cal testing (currently with automated devices) or on special agar (e.g., CHROMagar). ■ ■EPIDEMIOLOGY Candida are present in humans as commensals, in animals, in foods, and on inanimate objects. In developed countries, where contemporary medical therapeutics are commonly used, Candida species are now among the most common nosocomial pathogens. In the United States, these species are among the four most common pathogens isolated from the blood of hospitalized patients. In fact, in a recent pointprevalence study in the United States, Candida species were the most common organisms infecting the bloodstream of hospitalized patients. In regions where advanced medical care is not readily available, muco cutaneous Candida infections, such as thrush, are more common than deep-organ infections, which rarely occur. However, the incidence of deep-organ candidiasis has been increasing steadily as advances in health care—such as therapy with broad-spectrum antibiotics, more aggressive treatment of cancer, and the use of immunosuppression for sustaining organ transplants—have been implemented. In aggregate, the global incidence of infections due to Candida species has risen over the past few decades. C. auris is an emerging species of Candida that has spread rapidly in recent years to >50 countries and is a major public health concern. It was designated an urgent threat in the 2019 Centers for Disease Con trol and Prevention (CDC) Antimicrobial Resistance Threat Report, and it was included within the critical priority group in the 2022 World Health Organization (WHO) fungal priority pathogens list. This concern stems from its occurrence in health care facilities, its ability to adhere to and

persist long term on inanimate objects (in hospitals) and the human skin despite decolonization efforts, its association with substantial mortality, its propensity for misidentification as other Candida species, the incomplete understanding of its environmental reservoirs, and its multidrug resistance to the current antifungal thera peutic armamentarium, with some C. auris strains being resistant to all antifungal drug classes currently available for treatment. C. auris (auris meaning ear in Latin) was first identified in 2009 from the ear drain age of a patient with an ear infection in Japan. However, subsequent retrospective analysis of Candida strain collections identified the earli est known C. auris strain to date back to 1996 in South Korea. Notably, whole genome sequencing analysis of C. auris strains from South Asia, East Asia, South America, South Africa, and Iran found that although

strains within each geographic region are closely related to each other, they are distinct compared to strains from other geographic regions. These findings indicate that C. auris emerged independently in mul tiple geographic locations around the same time; the epidemiologic reasons for this emergence remain poorly understood but may relate to the increasing use of antifungal drugs and climate change.

The presence of a central venous catheter and/or other invasive medical devices and recent residence in nursing homes are major risk factors for C. auris colonization and infection. Screening of selected patients who are in a hospital or nursing home where C. auris has been cultured and are at risk for dissemination from a colonization site may help in implementing effective infection control measures. Hand hygiene with an alcohol-based hand sanitizer is recommended when hands are not visibly soiled, in which case washing with soap and water is preferred. Identifying the source of contamination, if possible, and using an Environmental Protection Agency (EPA)-registered hospitalgrade disinfectant effective against Clostridioides difficile spores are desirable. If a patient develops an invasive or bloodstream infection, it is recommended that the health care facility informs the CDC, or a similar agency in other countries, and adheres to recommendations for infection control, including isolation of patients (contact or enhanced barrier precautions), use of proper personal protective coverings, enforcement of hospital environment hygiene, and communicating with other health care facilities if the patient is being transferred. ■

■PATHOGENESIS In the most severe form of Candida infection, the organisms dis seminate hematogenously and form microabscesses and small mac roabscesses in major organs. Although the exact mechanism is not known, Candida probably enters the bloodstream from mucosal surfaces after growing to large numbers as a consequence of bacterial suppression by antibacterial drugs and breaches in the integrity of the mucosal barrier; alternatively, in some instances, the organism may enter the bloodstream from the skin via central venous catheters. A change from the blastospore stage to the pseudohyphal and hyphal stages is generally considered integral to Candida’s penetration into tissue. However, C. glabrata and C. auris can cause life-threatening infection, even though they do not transform into pseudohyphae or hyphae. Adherence to both epithelial and endothelial cells is thought to be the first step in invasion and infection; several adhesins have been identified as well as a mucosal toxin, candidalysin. Biofilm formation also is considered important in pathogenesis. Numerous reviews of cases of hematogenously disseminated candidiasis have identified the predisposing factors or conditions associated with disease (Table 222-1). CHAPTER 222 Candidiasis Several genes that are involved in the pathogenesis of other Candida species—such as those responsible for biofilm formation, proteinases, lipases, phospholipases, hydrolases, adhesins, secreted aspartyl prote ases, and

transporters involved in azole resistance—are also present in C. auris. Unlike other Candida species, several C. auris strains exhibit aggregate-forming properties in vivo, which may enable immune eva sion. In addition, C. auris shows a unique tolerance to high temperature and saline concentrations and can grow optimally at up to 42°C and in a 10% saline concentration, making it possible to exist and persist in harsh environments. Furthermore, C. auris has significant affinity for TABLE 222-1 Well-Recognized Factors and Conditions Predisposing to Hematogenously Disseminated Candidiasis Antibacterial agents Indwelling intravenous catheters Hyperalimentation fluids Indwelling urinary catheters Parenteral glucocorticoids Severe burns CARD9 deficiency (central nervous system) Abdominal and thoracic surgery Cytotoxic chemotherapy Immunosuppressive agents for organ transplantation Respirators Myeloperoxidase deficiency Neutropenia Low birth weight (neonates) Diabetes

abiotic surfaces such as plastic materials and medical devices, as well as human skin and nasal and ear cavities, which may account for its persistent colonization capabilities. The C. auris–specific adhesin sur face colonization factor 1 (SCF1) was recently identified as a key fungal factor governing biofilm formation, colonization of skin and medical devices, and virulence during invasive infection.

Innate immunity is the most important defense mechanism against hematogenously disseminated candidiasis, and the neutrophil is the most potent component of this defense. Macrophages also play an important host defense role. On the other hand, interleukin (IL) 17– producing innate and adaptive lymphoid cells contribute significantly to defense against mucocutaneous candidiasis as evidenced by several monogenic disorders of IL-17 receptor signaling that manifest with chronic mucocutaneous candidiasis (CMC) (see “Clinical Manifestations,” below). Although many immunocompetent individuals have antibodies to Candida, the role of these antibodies in defense against the organism is not clear. Multiple genetic polymorphisms in host immune-related genes that predispose to both disseminated and focal candidiasis have been identified and may contribute to patient susceptibility. ■ ■CLINICAL MANIFESTATIONS Mucocutaneous Candidiasis Thrush is characterized by white, adherent, painless, discrete or confluent patches in the mouth, on the tongue, or in the esophagus, occasionally with fissuring at the corners of the mouth. This form of disease caused by Candida can also occur at points of contact with dentures (called “denture sore mouth”). Organisms are identifiable in gram-stained scrapings from lesions. The occurrence of thrush in a young, otherwise healthy-appearing person should prompt an investigation for underlying HIV infec tion. More commonly, thrush is seen as a nonspecific manifestation of severe debilitating illness. Vulvovaginal candidiasis is accompanied by pruritus, pain, and vaginal discharge, which is usually thin but may contain whitish “curds” in severe cases. In contrast to oral thrush, HIV is not considered a major risk factor for vulvovaginal candidiasis. Instead, many women who receive antibiotics, particularly β-lactams, may develop vulvovaginal candidiasis. A subset of patients with recur rent vulvovaginitis may have a deficiency in the surface expression of Dectin-1, encoded by CLEC7A, a major recognition factor for β-glucan on the surface of Candida and/or in the downstream adaptor molecule CARD9, which ultimately increases the propensity for recurrent muco cutaneous (including vaginal) infections. PART 5 Infectious Diseases Other Candida skin infections include paronychia, a painful swelling at the nail–skin interface; onychomycosis, a fungal nail infection rarely caused by this genus; intertrigo, an erythematous irritation with red ness and pustules in the skin folds; balanitis, an erythematous-pustular infection of the glans penis; erosio interdigitalis blastomycetica, an infec tion between the digits of the hands or toes; folliculitis, with

pustules developing most frequently in the area of the beard; perianal candidia sis, a pruritic, erythematous, pustular infection surrounding the anus; mastitis; and diaper rash, a common erythematous, pustular perineal infection in infants. Generalized disseminated cutaneous candidiasis, another form of infection that occurs primarily in infants, is character ized by widespread eruptions over the trunk, thorax, and extremities. The diagnostic macronodular lesions of hematogenously disseminated candidiasis (Fig. 222-1) indicate a high probability of dissemination to multiple organs as well as the skin. While the lesions are seen predomi nantly in immunocompromised patients treated with cytotoxic drugs, they may also develop in patients without neutropenia. CMC is a heterogeneous infection of the hair, nails, skin, and mucous membranes that persists despite intermittent antifungal therapy. The onset of disease usually comes in infancy or within the first two decades of life, but in rare cases, it occurs in later life. The condition may be mild and limited to a specific area of the skin or nails, or it may take a severely disfiguring form (Candida granuloma) characterized by exophytic outgrowths on the skin. CMC is usually associated with specific immunologic dysfunction; most frequently reported is a failure of lymphocytes to secrete or respond to type-17 cytokines following stimulation by Candida antigens in vitro. A subset of the affected

FIGURE 222-1 Macronodular skin lesions associated with hematogenously disseminated candidiasis. Candida organisms are usually but not always visible on histopathologic examination. The fungi grow when a portion of the biopsied specimen is cultured. Therefore, for optimal identification, both histopathology and culture should be performed. (Image courtesy of Dr. Noah Craft and the Victor Newcomer collection at UCLA, archived by Logical Images, Inc.; with permission.) patients has mutations in the IL-17 receptors IL-17RA or IL-17RC, its adaptor molecule ACT1 (TRAF3IP2), or, more often, in STAT1. Approximately half of patients with CMC have associated endocrine abnormalities either in the setting of gain-of-function mutations in STAT1 or in the context of autoimmune polyendocrinopathy–candidiasis– ectodermal dystrophy (APECED) syndrome. This syndrome is due to mutations in the autoimmune regulator (AIRE) gene and is most prevalent among Finns, Iranian Jews, and Sardinians. Conditions that usually follow the onset of the disease include hypoparathyroidism, adrenal insufficiency, autoimmune thyroiditis, autoimmune hepatitis, autoimmune pneumonitis, alopecia, pernicious anemia, intestinal mal absorption, and primary hypogonadism. In addition, dental enamel dysplasia, vitiligo, nail dystrophy, asplenia, and calcification of the brain and tympanic membranes may occur. Patients with CMC rarely develop hematogenously disseminated candidiasis, reflecting their intact neutrophil function. Deeply Invasive Candidiasis Deeply invasive Candida infections may or may not be due to hematogenous seeding. Deep esophageal infection may result from penetration by organisms from superficial esophageal erosions; joint or deep-wound infection from contiguous spread of organisms from the skin; kidney infection from catheterinitiated ascending spread of organisms through the urinary tract; infection of intraabdominal organs and the peritoneum from perfora tion of the gastrointestinal tract; and gallbladder infection from retro grade migration of organisms from the gastrointestinal tract into the biliary drainage system. However, more commonly, deeply invasive candidiasis results from hematogenous seeding of various organs as a complication of candi demia. Once the organism gains access to the intravascular compart ment (either from the gastrointestinal tract or, less often, from the skin through the site of an indwelling intravascular catheter), it may spread hematogenously to a variety of deep organs. The brain, chorioretina (Fig. 222-2), heart, and kidneys are most commonly infected and the liver and spleen are less commonly affected in nonneutropenic hosts (but most often involved in neutropenic patients). In fact, nearly

any organ can become involved, including the endocrine glands, pancreas, heart valves (native or prosthetic), skeletal muscle, joints (native or prosthetic), bones, and meninges. Candida organisms can also spread hematogenously to the skin and cause classic macronodular lesions (Fig. 222-1). Frequently, painful muscular involvement is evident beneath the area of affected skin. Chorioretinal involvement and skin involvement are highly significant since both findings are associ ated with a very high probability of abscess formation in multiple

FIGURE 222-2 Hematogenous Candida endophthalmitis. A classic off-white lesion projecting from the chorioretina into the vitreous causes the surrounding haze. The lesion is composed primarily of inflammatory cells rather than organisms. Lesions of this type may progress to cause extensive vitreal inflammation and eventual loss of the eye. Partial vitrectomy, combined with IV and possibly intravitreal antifungal therapy, may be helpful in controlling the lesions. (Image courtesy of Dr. Gary Holland; with permission.) deep organs as a result of generalized hematogenous seeding. Ocular involvement (Fig. 222-2) may require specific treatment (e.g., partial vitrectomy or intraocular injection of antifungal agents) to prevent per manent blindness. An ocular examination is indicated for patients with candidemia, whether or not they have ocular manifestations. C. auris invasive infections are similar to those of other Candida species and are most frequently associated with recent surgical procedures, immu nosuppression, invasive devices such as catheters or various support or drainage tubes, and extended hospital stays. In the majority of invasive infections, C. auris has been isolated from the blood, but invasion of the kidney or spleen, and its recovery from cerebrospinal, bile, perito neal, and pleural fluids demonstrate its invasiveness and dissemination potential. C. auris–associated candidemia can be life-threatening, with a crude mortality rate of 30–60%. ■ ■DIAGNOSIS The diagnosis of Candida infection is established by visualization of pseudohyphae or hyphae on wet mount (saline and 10% KOH), tis sue Gram stain, periodic acid–Schiff stain, or methenamine silver stain in the presence of inflammation. Absence of organisms on hematoxylin-eosin staining does not reliably exclude Candida infec tion. The most challenging aspect of diagnosis is determining which patients with Candida isolates have hematogenously disseminated A B C FIGURE 222-3 C. auris colony morphology and color on CHROMagar plates. A. Candida mixed culture: culture of C. glabrata (purple), C. tropicalis (navy blue), and C. auris (white, circled in red). B. C. auris showing multiple colony morphologies. C. C. auris after Salt SAB Dulcitol Broth enrichment. (From CDC: Identification of Candida auris. Available at: https://www.cdc.gov/fungal/candida-auris/identification.html.)

candidiasis. For instance, recovery of Candida from sputum, urine, or peritoneal catheters may indicate mere colonization rather than deepseated infection, and Candida isolation from the blood of patients with indwelling intravascular catheters may reflect inconsequential seeding of the blood from or growth of the organisms on the catheter. Despite extensive research into both antigen and antibody detection systems, there is currently no widely available and validated diagnostic test to distinguish patients with inconsequential seeding of the blood from those whose positive blood cultures represent hematogenous dissemi nation to multiple organs. Many studies have examined the utility of the β-glucan test; at present, its greatest utility is its negative predictive value (~90%). Meanwhile, the presence of ocular or macronodular skin lesions is highly suggestive of widespread infection of multiple deep organs. Despite extensive diagnostic tests for hematogenous dissemi nation, such as polymerase chain reaction and T2 technology, no test is fully validated or widely available at present. Matrix-assisted laser desorption–ionization–time-of-flight mass spectrometry (MALDITOF MS) is now being used extensively for detection and speciation and is

useful for the correct diagnosis of C. auris.

C. auris can be misdiagnosed in the microbiology laboratory, often leading to inappropriate treatment and delay in the implementation of appropriate infection control measures. Preliminary testing by culturing the fungus and examination of colony morphology may help in the initial identification, but this must be confirmed with more advanced diagnos tic methods. For example, features such as budding yeast morphology, absence of hyphal growth or germ tubes, and growth at 40–42°C (unlike other Candida species) on CHROMagar that may appear white, pink, red, or purple should raise suspicion for C. auris (Fig. 222-3). CHAPTER 222 Several advanced molecular techniques accurately identify C. auris strains and therefore are being used for the follow-up testing and confirmation of the specimens that failed to be identified by tradi tional methods. MALDI-TOF equipment with upgraded libraries, such as Bruker Biotyper MALDI-TOF (CA System library version claim 4 or research use only [RUO] libraries versions 2014 [5627] and more recent), and using the bioMérieux VITEK MALDI-TOF MS (IVD v3.2 or RUO libraries with Saramis Ver 4.14 database and Sac charomycetaceae update), are the most common methods of C. auris identification. Other supplemental MALDI-TOF databases, such as MicrobeNet, which include additional C. auris strains from the four phylogenetic clades (i.e., South Asian, East Asian, South American, and South African) also can be used for the identification of C. auris strains. Sequencing of the D1–D2 region of the 28s rDNA or the internal transcribed region (ITS) of rDNA can also correctly identify C. auris. Recently, an automated, qualitative nucleic acid multiplex in vitro diagnostic test by GenMark called ePlex Blood Culture Identifica tion Fungal Pathogen (BCID-FP) Panel was approved by the U.S. Food and Drug Administration for C. auris testing. Also, several polymerase chain reaction–based detection methods have been reported to identify

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TABLE 222-2 Typical Decision-Making Steps in the Diagnosis of C. auris NO. METHOD DATABASE/SOFTWARE INITIAL FINDING CONFIRMATION 1. Bruker Biotyper MALDI-TOF RUO libraries C. auris C. auris CA System library C. auris C. auris 2. bioMérieux VITEK MS MALDI-TOF RUO library C. auris C. auris IVD library (v3.2) C. auris C. auris Older IVD libraries C. haemulonii C. auris possible: Needs further workup C. lusitaniae C. auris possible: Needs further workup No identification C. auris possible: Needs further workup 3. VITEK 2 YST Software version 8.01 C. auris C. auris confirmed C. haemulonii C. auris possible: Needs further workup C. duobushaemulonii C. auris possible: Needs further workup Candida spp. not identified C. auris possible: Needs further workup Older versions C. haemulonii C. auris possible: Needs further workup C. duobushaemulonii C. auris possible: Needs further workup Candida spp. not identified C. auris possible: Needs further workup 4. API 20C Rhodotorula glutinis, if characteristic red color absent C. auris possible: Needs further workup C. sake C. auris possible: Needs further workup Candida spp. not identified C. auris possible: Needs further workup 5. API ID 32C C. intermedia C. auris possible: Needs further workup C. sake C. auris possible: Needs further workup Saccharomyces kluyveri C. auris possible: Needs further workup 6. BD Phoenix C. catenulata C. auris possible: Needs further workup C. haemulonii C. auris possible: Needs further workup Candida spp. not identified C. auris possible: Needs further workup PART 5 Infectious Diseases 7. MicroScan C. lusitaniae No hyphal growth present Can rule out C. lusitaniae, C. guilliermondii, and C. parapsilosis. C. auris possible: Needs further workup C. guilliermondii C. parapsilosis C. lusitaniae Hyphal growth present Possibly C. lusitaniae, C. guilliermondii, C. parapsilosis, or C. auris: Needs further workup C. guilliermondii C.

parapsilosis C. famata C. auris possible: Needs further workup Candida spp. not identified C. auris possible: Needs further workup 8. RapID Yeast Plus C. parapsilosis → Test on corneal agar Candida spp. not identified C. auris possible: Needs further workup 9. GenMark ePlex BCID-FP Panel C. auris C. auris confirmed Abbreviations: IVD, in vitro diagnostic; RUO, research use only. Source: Adapted from CDC: Identification of Candida auris. Available at: https://www.cdc.gov/fungal/candida-auris/pdf/Testing-algorithm_by-Method_508.pdf. C. auris in various specimens. Table 222-2 outlines the typical decision-making steps in the diagnosis of C. auris by using different methods. A suspicious C. auris specimen is usually sent to a regional reference laboratory for further testing and confirmation of C. auris. TREATMENT Candida Infections MUCOCUTANEOUS CANDIDA INFECTION The treatment of mucocutaneous candidiasis is summarized in Table 222-3. CANDIDEMIA AND SUSPECTED HEMATOGENOUSLY DISSEMINATED CANDIDIASIS All patients with candidemia are treated with a systemic anti fungal agent. A certain percentage of patients, including many of those who have candidemia associated with an indwelling intra vascular catheter, probably have “benign” candidemia rather than

No hyphal growth present Can rule out C. parapsilosis. C. auris possible: Needs further workup Hyphal growth present Possibly C. parapsilosis or C. auris: Needs further workup deep-organ seeding. However, because there is no reliable way to distinguish benign candidemia from deep-organ infection, and because antifungal drugs less toxic than amphotericin B are avail able, antifungal treatment for candidemia—with or without clinical evidence of deep-organ involvement—has become the standard of practice. In addition, if an indwelling intravascular catheter is TABLE 222-3 Treatment of Mucocutaneous Candidal Infections DISEASE PREFERRED TREATMENT ALTERNATIVES Cutaneous Topical azole Topical nystatin Vulvovaginal Oral fluconazole (150 mg) or ibrexafungerp (300 mg twice daily for 1 day) or azole cream or suppository Nystatin suppository Oral (thrush) Fluconazole tablets (100–200 mg/d) Clotrimazole trashes, nystatin Esophageal Fluconazole tablets (100–200 mg/d) or itraconazole solution (200 mg/d) Caspofungin, micafungin, or amphotericin B

TABLE 222-4 Agents for the Treatment of Disseminated Candidiasis ROUTE OF ADMINISTRATION DOSEa COMMENT AGENT Amphotericin B deoxycholate IV only 0.5–1.0 mg/kg daily Mostly replaced by lipid formulations Amphotericin B lipid formulations Not approved as primary therapy by the U.S. Food and Drug Administration, but used commonly because they are less toxic than amphotericin B deoxycholate Liposomal (AmBiSome, Abelcet) IV only 3.0–5.0 mg/kg daily Lipid complex (ABLC) IV only 3.0–5.0 mg/kg daily Colloidal dispersion (ABCD) IV only 3.0–5.0 mg/kg daily Associated with frequent infusion reactions Azolesb Posaconazole IV and oral 300 mg/d (IV) 200 mg tid (oral) Fluconazole IV and oral 400 mg/d Most commonly used Voriconazole IV and oral 400 mg/d Multiple drug interactions, visual hallucinations, fluorosis, phototoxicity Approved for candidemia in nonneutropenic patients Echinocandins Broad spectrum against Candida species; approved for disseminated candidiasis; less toxic than amphotericin B formulations Caspofungin IV only 50 mg/d Anidulafungin IV only 100 mg/d Micafungin Rezafungin IV only IV only 100 mg/d 400 mg loading dose, 200 mg once weekly thereafter aFor loading doses and adjustments in renal failure, see Pappas PG et al: Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62:e1, 2016. The recommended duration of therapy is 2 weeks beyond the last positive blood culture and the resolution of signs and symptoms of infection. bAlthough ketoconazole is approved for the treatment of disseminated candidiasis, it has been replaced by the newer agents listed in this

table. Posaconazole has been approved for prophylaxis in neutropenic patients and for oropharyngeal candidiasis. present, it is best to remove or replace the device whenever feasible. Moreover, an infectious disease consultation is recommended as it has been associated with improved patient outcomes. The drugs used for the treatment of candidemia and suspected disseminated candidiasis are listed in Table 222-4. Various lipid formulations of amphotericin B, four echinocandins, the azoles fluconazole and voriconazole, and in some instances, the newer triazole posaconazole are used; no agent within a given class has been clearly identified as superior to the others. Most institutions choose an agent from each class on the basis of their own specific microbial epidemiology, strategies to minimize toxicities, and cost considerations. An echinocandin is the first choice of treatment. The U.S. Food and Drug Administration (FDA) recently approved the new-generation echinocandin rezafungin for the treatment of candidemia and invasive candidiasis in adult patients; rezafungin has a prolonged half-life, which allows for once-weekly 200-mg dos ing following a 400-mg front-loading dose. Echinocandin treatment continues until sensitivities or speciation is determined. In stable patients, many centers then switch to fluconazole if a sensitive strain is identified and there is no evidence of hematogenous dissemina tion. For hemodynamically unstable or neutropenic patients, initial treatment with echinocandins is warranted, and once the clinical response has been assessed and the pathogen specifically identified, the regimen can be altered according to the sensitivities. At present, the vast majority of C. albicans isolates are sensitive to fluconazole. Isolates of C. glabrata and C. krusei are less sensitive to fluconazole and more sensitive to polyenes and echinocandins. C. parapsilosis is less sensitive to echinocandins in vitro; however, this lesser sen sitivity is considered clinically insignificant. Posaconazole has been approved for prophylaxis, including against Candida, in neutropenic patients. Itraconazole is rarely used for Candida nowadays, and isa vuconazole is not recommended for this indication. Antifungal drug resistance is one of the hallmarks of C. auris infections. Some C. auris strains have multidrug resistance with elevated minimal inhibitory concentrations (MICs) to all three major antifungal classes—azoles, echinocandins, and polyenes—resulting in limited treatment options. A CDC study reported antifungal resistance in C. auris strains obtained from 54 patients

Approved for prophylaxis in India, Pakistan, South Africa, and Venezuela: 93% were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% of the tested strains were resistant to two antifungal classes, and, alarmingly, 4% of the tested strains were resistant to all three classes of antifungal drugs. A 2023 CDC report indicated that rates of C. auris echinocandin resistance tripled in 2021 compared to the prior 2 years. Almost all C. auris strains that have been identified have elevated MICs for fluconazole with variable susceptibilities to other triazoles (Table 222-5), associated with mutations in ERG11encoded lanosterol demethylase and/or overexpression of drug transporters/efflux pumps. Candidiasis Due to the high rates of azole resistance among C. auris strains, the use of echinocandins is recommended as first-line therapy for

C. auris infection. By contrast, the CDC discourages the use of antifungal drugs for the treatment of colonization of C. auris in the absence of invasive or bloodstream infection. A history of patient travel or residence in a health care or nursing facility with a known TABLE 222-5 Typical MICs of Available Antifungal Drugs for C. auris TENTATIVE RESISTANCE BREAKPOINTSa MIC RANGE, µg/mL DRUG MIC MIC50 MIC90 Amphotericin B ≥2 0.06–8 0.5–1 2–4 Fluconazole ≥32 0.12–≥64 ≥64 ≥64 Itraconazole N/A 0.032–2 0.06–0.5 0.25–1 Voriconazole N/A 0.032–16 0.5–2 2–8 Posaconazole N/A

0.015–16 0.016–0.5 0.125–2 Isavuconazole N/A 0.015–4 0.125–0.25 0.5–2 Caspofungin ≥2 0.03–16 0.25–1 1–2 Anidulafungin ≥4 0.015–16 0.125–0.5 0.5–1 Micafungin ≥4 0.015–8 0.125–0.25 0.25–2 aTentative resistance breakpoints per Centers for Disease Control and Prevention (CDC) (www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html). Abbreviations: MIC, minimum inhibitory concentration; N/A, not available. Source: Adapted from CDC: Antifungal susceptibility testing and interpretation. Available at: www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.

TABLE 222-6 List of CDC-Recommended Echinocandin Doses for the Treatment of C. auris Infections CHILDREN

(>2 MONTHS) INFANTS

(<2 MONTHS) DRUG ADULTS Caspofungin Loading dose 70 mg IV, then 50 mg IV daily Loading dose 70 mg/m2 per day IV, then 50 mg/m2 per day IV 25 mg/m2 per day IV Anidulafungin Loading dose 200 mg IV, then 100 mg IV daily Not approved for use in children Not approved for use in children Micafungin 100 mg IV daily 2 mg/kg per day IV with option to increase to 4 mg/ kg per day IV in children at least 40 kg 10 mg/kg per day IV Abbreviation: CDC, Centers for Disease Control and Prevention. Source: Adapted from CDC: Treatment and management of infections and colonization. Available at: www.cdc.gov/fungal/candida-auris/c-auris-treatment.html. outbreak of C. auris infection, as well as drug susceptibility data of identified strains, act as a guide for the effective choice of treatment of invasive and bloodstream infections. C. auris is known to develop antibiotic resistance during treatment. Therefore, the emergence of antifungal resistance should be closely monitored with follow-up cul tures and repeat susceptibility testing. Antibiotic stewardship should be implemented to ameliorate the risk of development of drug resis tance. Patients may remain colonized with C. auris during or after the successful treatment of invasive C. auris infection. Therefore, infec tion control measures should be implemented throughout patient care. Table 222-6 outlines CDC-recommended echinocandin doses for the initial antifungal treatment for C. auris infections. PART 5 Infectious Diseases In cases of echinocandin resistance, liposomal amphotericin B (5 mg/kg per day) can be considered. For neonates and infants (<2 months old), amphotericin B deoxycholate (1 mg/kg per day) treatment can be initiated. If this fails, liposomal amphotericin B (5 mg/kg per day) can be given. In very severe cases, if all treat ment options fail, echinocandins per CDC recommendations can be given (Table 222-6). Other considerations for C. auris infection management can be referenced from the 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Man agement of Candidiasis. Some generalizations exist regarding the management of specific Candida infections. Recovery of Candida from sputum is almost never indicative of underlying pulmonary candidiasis and does not by itself warrant antifungal treatment. Similarly, Candida in the urine of a patient with an indwelling bladder catheter may represent colonization only, rather than bladder or kidney infection. However, the threshold for systemic treatment is lower in general in severely ill patients in this category since it is impossible to distinguish colo nization from lower or upper urinary tract infection. If the isolate is

C. albicans, most clinicians use oral fluconazole rather than a bladder washout with amphotericin B, which was more commonly used in the past. Although echinocandins are poorly excreted into the urine, they may be an option, especially for non-albicans isolates. The doses and duration are the same as for disseminated candidiasis. The sig nificance of the recovery of Candida from abdominal

drains in post operative patients is unclear, but again, the threshold for treatment is generally low because most of the affected patients have been sub jected to risk factors predisposing them to disseminated candidiasis. In addition, there has been a considerable increase in the recognition and diagnosis of intraabdominal candidiasis. Removal of the infected valve and long-term antifungal admin istration constitute appropriate treatment for Candida endocardi tis. Although definitive studies are not available, patients usually are treated for weeks with a systemic antifungal agent (Table 222-4) and then given chronic suppressive therapy for months or years (sometimes indefinitely) with an oral azole (usually fluconazole at 400–800 mg/d). Hematogenous Candida endophthalmitis is a special problem requiring ophthalmologic consultation. When lesions are expanding

or are threatening the macula, an IV polyene combined with flucy tosine (25 mg/kg four times daily) has been the regimen of choice, although comparative studies with other regimens have not yet been reported. As more data on the newer triazoles (e.g., voriconazole) and the echinocandins become available, new strategies involving these agents are developing, although it is important to note that echinocandins exhibit low penetration in ocular tissue. Of para mount importance is the decision to perform a partial vitrectomy. This procedure debulks the infection and can preserve sight, which may otherwise be lost due to vitreal scarring. All patients with can didemia should undergo ophthalmologic examination because of the relatively high frequency of this ocular complication (up to 15–20% in some case series). This examination can detect a developing eye lesion early in its course; in addition, identification of a lesion signi fies a probability of ~90% of deep-organ abscesses and may prompt prolongation of therapy for candidemia beyond the recommended 2 weeks after the last positive blood culture. Although the basis for the consensus is a very small data set, the recommended treatment for Candida meningitis is a polyene (Table 222-4) plus flucytosine (25 mg/kg four times daily). Development of Candida meningo encephalitis in an otherwise immunocompetent individual should raise suspicion for deficiency in the C-type lectin receptor adaptor molecule CARD9 and should prompt genetic testing to rule out this monogenic disorder. Successful treatment of Candida-infected pros thetic material (e.g., an artificial joint) nearly always requires removal of the infected material followed by long-term administration of an antifungal agent selected on the basis of the isolate’s sensitivity and the logistics of administration. ■ ■PROPHYLAXIS The use of antifungal agents to prevent Candida infections has been controversial, but some general principles have emerged. Most centers administer prophylactic fluconazole (400 mg/d) to recipients of alloge neic hematopoietic stem cell transplantation. High-risk liver transplant recipients are also given fluconazole prophylaxis in most centers. The use of prophylaxis for neutropenic patients has varied considerably from center to center; many centers that elect to give prophylaxis to this population use either fluconazole (200–400 mg/d) or a lipid formula tion of amphotericin B (AmBisome, 1–2 mg/d). Caspofungin (50 mg/d) also has been used. Posaconazole (200 mg three times daily) has been approved by the FDA for prophylaxis in neutropenic patients; it is gain ing in popularity and may replace fluconazole in settings when mold activity is desired. Prophylaxis is sometimes given to surgical patients at very high risk for candidiasis. The widespread use of prophylaxis for nearly all patients in general surgical or medical intensive care units is not—and should not be—a common practice for three reasons: (1) the incidence of disseminated candidiasis is relatively low, (2) the cost–benefit ratio is suboptimal, and (3) increased resistance with widespread prophylaxis is a valid concern. Prophylaxis for oropharyngeal or esophageal candidiasis in HIVinfected patients is not recommended unless there are frequent recurrences. ■ ■FURTHER READING Lionakis MS, Edwards JE jr: Candida species, in Mandell, Douglas, and Bennett’s Principles of Infectious Diseases, 10th ed. Blaser MJ et al (eds).

Philadelphia, Elsevier, 2025. Pappas PG et al: Invasive candidiasis. Nat Rev Dis Primers 62:e1, 2018. Pechacek J, Lionakis MS: Host defense mechanisms against Candida auris. Expert Rev Anti Infect Ther 21:1087, 2023. Proctor DM et al: Integrated genomic, epidemiologic investigation of Candida auris skin colonization in a skilled nursing facility. Nat Med 27:1401, 2021. Santana DJ et al: A Candida auris-specific adhesin, Scf1, governs sur face association, colonization, and virulence. Science 381:1461, 2023. Tsai SV et al: Burden of candidemia in the United States, 2017. Clin Infect Dis 71:e449, 2020.

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