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# G Mycoses

# 255 Introduction to Mycoses

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The advent of the human immunodeficiency virus epidemic and the ever-increasing use of immunosuppressive drugs has dramatically increased the incidence of deep mycoses and substantially broadened the range of fungi causing potentially lethal disease. Clinicians caring for highly immunosuppressed patients are rarely able to ignore a fungal isolate because the species is not "pathogenic." An additional complication is that the rapidly moving field of diagnostic microbiology is providing names of species that clinicians have not encountered before (see "Cryptic Species" later), and centralization of facilities has moved the laboratory away from where the clinician works, complicating communication.

## CHANGES IN HOW FUNGI ARE IDENTIFIED

### Identification by DNA Sequence

DNA sequence is replacing appearance (morphology) for identifying fungi and showing relatedness between different fungal genera.[1] Sequencing has provided a powerful tool for discovering new relationships (e.g., *Penicillium marneffei* should be in the genus *Talaromyces*), for identifying newly discovered infections (*Emergomyces* species; see Chapter 268),[2] and for discovering unexpected groups, called "cryptic species," within existing single species. For example, cryptic species have been found in *Aspergillus, Coccidioides, Cryptococcus, Paracoccidioides, Sporothrix,* and many other genera. Despite these important contributions to taxonomy, limitations to basing phylogeny on DNA sequences alone include the following: (1) less than 1% of an estimated 1.5 million fungal species have been sequenced; (2) the extent of variability *within* a monophyletic species is not known for many fungi pathogenic for humans because too few isolates have been sequenced; (3) the distinction between one species and another based on sequence alone is fundamentally arbitrary; (4) no single area of the genome is suitable to distinguish all fungi; (5) published sequences of species are known to contain errors in species identification and sequence; (6) instability of fungal names is detrimental to medicine, making it difficult for the clinician to find precedent for managing an infection with a fungus given a new name; and (7) sequence-derived distinctions do not necessarily translate into differences in biology of medical importance, such as epidemiology, pathogenesis, or response to treatment.[3]

### Cryptic Species

New fungal species are being described by their DNA sequence alone. Although sequences between the genes coding for ribosomal RNA (internal transcribed spacer [ITS] region, D1/D2 region) are most commonly used, genes coding for proteins, such as β-tubulin or calmodulin, are added, depending on the genus. These species are called "cryptic species" because they cannot be identified by their appearance in culture or by biochemical tests. An increasing number are also being identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, which compares the spectrum of small proteins extracted from the organism with a database of many other organisms.[4–6] The machine reports what species matches the spectrum of the isolate being analyzed, with a number indicating how similar the spectra are. A lower number may indicate the genus is correct but the species may not be. As more correctly identified fungi are put into the database, this technique is more useful. Despite the high cost of the machine, laboratories like the simplicity of sample preparation and analysis, inexpensive reagents, and rapid completion. The end result is that more cryptic species will be appearing in culture reports.

Frequency of cryptic species within isolates of a genus depends on the genus and geographic location. For example, cryptic species within *Aspergillus* isolates vary from 10% to 26%.[7] Laboratories not equipped to identify cryptic species will report the identification using traditional techniques, so that *Aspergillus lentulus* will be reported as *Aspergillus fumigatus* or, more correctly, *Aspergillus fumigatus* complex.[8] As data accumulate, it will become more clear if some cryptic species differ significantly from other species in the complex in terms of response to specific antifungal drugs, virulence, or habitat. For example, *A. lentulus* is more resistant to azoles in vitro than some other species in the *A. fumigatus* complex, though it is unclear if this impacts response to azole treatment.

### One Fungus, One Name

For decades, fungi could have had one name for the fungus sporulating in its "sexual state," called its teleomorph, and another name when it was growing only "asexual" spores (anamorph). Sexual spores are formed when the fungus mates (combines haploid DNA), usually with another isolate; forms a diploid structure; and then undergoes meiosis, producing haploid spores that are recombinants of the parental isolates. There are a few species in which an isolate can mate with itself and form sexual spores. Most cultures in the diagnostic laboratory form only asexual spores, which are produced by mitosis. Almost all the fungal names that clinicians recognize come from the anamorph rather than the teleomorph, such as *Aspergillus,* not *Neosartorya,* and *Blastomyces dermatitidis,* not *Ajellomyces dermatitidis.* Now, medical mycologists have agreed that each fungal species should have a single name and that the old schema of having a different name for the sexual form and the asexual form was unnecessarily confusing. Which of the two names should be retained is still a matter of debate for some species. A more contentious issue for medical mycologists is whether sequence differences alone should be used to carve out a new "cryptic" species from within an existing species. Some mycologists believe that sequence differences alone are not enough to define a cryptic species and believe that evidence of biologic differences is needed. Some of the more recently identified cryptic species do differ from other isolates formerly in the same species. *Sporothrix brasiliensis,* isolates of which were formerly assigned to *Sporothrix schenckii,* appears to be more geographically confined and more virulent than isolates still classified as *S. schenckii* (see Chapter 259). There are epidemiologic differences between *Coccidioides immitis* and *Coccidioides posadasii* and between *Paracoccidioides brasiliensis* and

[a]The chapter was written by Dr. Bennett in his personal capacity. The views expressed herein do not necessarily represent the views of the National Institutes of Health, the Department of Health and Human Services, or the United States.

*Paracoccidioides lutzii* (see Chapters 265 and 267). In these three examples, the clinical disease is similar enough that clinical information about the older species is sufficient to guide diagnosis and management.

## COMMON FEATURES OF PATHOGENIC FUNGI

Some specialized terms used in this chapter are listed in Table 255.1.

**TABLE 255.1 Lexicon of Mycology Terms for the Clinician**

**Aleurioconidia/aleuriospore**—spore growing at the end of a specialized hypha. The spore is released by breakage of the hypha adjacent to the spore.
**Anamorph**—a fungus forming only asexual spores.
**Arthrospore**—a spore formed by a hypha breaking at a septum.
**Asexual spores**—spores formed by mitosis, a form of cell division that creates an exact copy of the original cell.
**Basidiomycete**—one of the four major classes of fungi; includes mushrooms and *Cryptococcus neoformans.*
**Basidiospore**—a sexual spore that arises on a specialized structure, usually club shaped, in a basidiomycete (e.g., *C. neoformans* forms basidiospores in its sexual state).
**Blastospore**—an asexual spore formed by budding (e.g., *C. neoformans, Candida* spp.).
**Conidiophore**—specialized hyphae that bear a conidium (spore) on the end.
**Conidium** (plural, conidia)—an asexual spore usually produced at the tip or side of a hypha.
**Dematiaceous mold**—dark-colored mold. Same as phaeohyphomycetes.
**Dimorphic**—capable of producing both hyphae and yeast (e.g., the agents of coccidioidomycosis, blastomycosis, histoplasmosis, sporotrichosis, and chromoblastomycosis).
**Diploid**—having two sets of chromosomes.
**Endemic fungi**—fungi having a limited geographic distribution (e.g., blastomycosis, histoplasmosis, and coccidioidomycosis).
**Endospore**—spore formed within a larger cell, such as a *Coccidioides* spherule.
**Entomophthoramycosis**—infections caused by molds of the order Entomophthorales, including species of *Conidiobolus* and *Basidiobolus.*
**Germ tube**—a hypha emerging from a yeastlike structure, characteristic of *Candida albicans* cells placed on specialized culture medium.
**Haploid**—having a single set of chromosomes.
**Heterothallic**—a fungus that can mate only between different colonies of an opposite mating type.
**Homothallic**—a fungus in which mating can take place within the same colony (e.g., *Pseudallescheria boydii*).
**Hyaline**—colorless, transparent.
**Hyalohyphomycosis**—infection caused by molds with light-colored colonies. This term includes most of the pathogenic molds and is so broad that it has not proven useful.
**Hypha** (plural, hyphae)—the tubular element that forms the body of a fungus.
**Imperfect state**—fungus producing only asexual spores.
**Meiosis**—process in a dividing cell that allows reassorting of chromosomes and reduces the number of chromosomes by half, from diploid to haploid.
**Mitosis**—process in a dividing cell that produces two genetically identical copies of the original cell.
**Mold**—filamentous fungus. A colony on agar generally appears fuzzy, rather than smooth.
**Morphology**—appearance of the fungus.
**Mucormycosis**—infection by molds of the subphylum Mucormycotina.
**Mycelium** (pleural, mycelia)—the mass of hyphae making up a fungal colony.
**Perfect state**—fungus capable of producing sexual spores.
**Phaeohyphomycosis**—infection caused by molds with dark-colored colonies caused by pigmentation in the hyphae. Individual hyphae may not have enough pigment to be dark colored under the microscope. A colony can be dark colored because of the spores, such as *Sporothrix schenckii,* and may not be an agent of phaeohyphomycosis.
**Phenotype**—genetically determined properties that help distinguish an organism from otherwise similar organisms (e.g., requirement for exogenous uracil is a useful phenotype in some yeast mutants).
**Pseudohyphae**—a string of budding cells (e.g., those formed by most *Candida* spp.).
**Sexual spores**—spores formed by meiosis, a form of division in which the number of chromosomes is reduced by half.
**Spherule**—large round cell of *Coccidioides* species that forms spores inside.
**Sporangium**—a sacklike structure with asexual spores (sporangiospores) inside. Spores are released when the sack breaks.
**Spp.**—abbreviation for species (plural).
**Teleomorph**—a fungus forming sexual spores.
**Thallus**—the vegetative body of a fungus, such as a fungal colony.
**Yeast**—technically, a fungus of the family Saccharomycetaceae, including *Saccharomyces cerevisiae* (baker's yeast). The terms *yeast form* or *yeastlike* are generally used to denote fungi that reproduce by budding.

### Yeasts and Molds

It is important for all infectious disease specialists to understand the distinction between yeasts and molds. Even at the first recognition in a diagnostic laboratory that a fungus has been found in a smear or culture, the laboratory can distinguish between a yeast and a mold. Yeasts are typically round or oval; generally form smooth, flat colonies; and reproduce by budding. Biochemical tests are important for identification of yeasts, although MALDI-TOF mass spectrometry is increasingly being used. Molds are composed of tubular structures called hyphae and grow by branching and longitudinal extension. Mold colonies typically appear fuzzy. However, not all pathogenic fungi can be categorized neatly by their appearance in tissue as yeasts or molds. *Coccidioides* species, *Rhinosporidium seeberi*, and *Pneumocystis jirovecii* are round in tissue but do not bud. Instead, the cytoplasm divides to form numerous internal spores that, on rupture of the "mother" cell, are released to form new spherical structures.

### Dimorphic Fungi

Some fungi can grow either as a yeast or as a mold. In candidiasis and tinea versicolor, the fungus is often seen in both tubular and rounded forms but is not commonly considered to be dimorphic. The so-called dimorphic fungi grow in the host as yeastlike forms but grow at room temperature in vitro as molds. These fungi include the agents of histoplasmosis, blastomycosis, sporotrichosis, coccidioidomycosis, paracoccidioidomycosis, chromoblastomycosis, talaromycosis (see Chapter 268), and emergomycosis (see Chapter 268).

## DIAGNOSIS OF MYCOSES

Fungi can often be identified in tissue, even in the absence of culture, by taking into account the clinical findings, body site, inflammatory response, and fungal appearance (Fig. 255.1; Table 255.2). Culture diagnosis is potentially more accurate than diagnosis by histologic features, but many smaller laboratories encounter difficulties in isolating and identifying fungi. The histologic features of a biopsy specimen can be more rapidly diagnostic than culture when mycoses are caused by slow-growing fungi. Biopsy slides are more readily mailed to consultants than cultures, which may arrive nonviable or contaminated. Finally, biopsy may provide proof that the fungus is invading tissue and is not just a contaminant or saprophyte growing on debris in a lung cavity or skin ulcer. Ideally, both histologic examination and culture should be done together. Detection of fungal DNA by polymerase chain reaction has proved useful for identifying fungi in tissue and clinical specimens, such as bronchoalveolar lavage, although currently that is most often confined to research settings. Also, luminescent DNA probes for hybridization to fungal RNA are commercially available and valuable for identifying colonies of *Histoplasma capsulatum, Coccidioides* spp., *B. dermatitidis*, and *Cryptococcus neoformans.* Identification of fungi in tissue by immunohistochemistry remains experimental.

## MICROSCOPIC APPEARANCE OF FUNGI

### Tissue Stains

*Brown and Brenn* stain (tissue Gram stain) results in fungi that may appear gram-positive or gram-negative. *Actinomyces* and *Nocardia* are gram-positive, but other stains are preferred for visualizing fungi in clinical material.

*Grocott-Gomori methenamine silver* (GMS) stains all fungal walls brownish-black and is the most sensitive stain for fungal cells. As an exception, some agents of mucormycosis, such as *Mucor velutinosus,* do not stain or stain poorly with GMS. The usual counterstain in GMS, such as fast green, does not allow adequate visualization of the inflammatory response but shows the fungi in strong contrast. *Leishmania,* which does not stain with GMS and has a cytoplasmic dot (a kinetoplast), should be distinguished from *H. capsulatum* and *P. jirovecii.* A black dot is sometimes visible in the cell wall of *Pneumocystis* cysts on GMS. Artifacts caused by deposition of silver oxide around other structures can resemble yeasts or hyphae and are a common source of diagnostic confusion with GMS. *Actinomyces* may stain with GMS in a grain from a patient with actinomycosis or actinomycetoma, although the Brown and Brenn stain is preferred for these organisms in tissue.

*Hematoxylin and eosin* (H&E) stains some fungal cells purple, but other fungal cells may be visible only as refractile clear structures. H&E is most valuable for studying the inflammatory response in the tissue.

*Mayer mucicarmine* stains cryptococcal cells burgundy red. Staining ranges from deep to negligible in the same section and may not be detectable at all in some tissues. *Rhinosporidium seeberi* also stains positive, but the huge size, endospores, and lack of budding prevent confusion. Although *B. dermatitidis* sometimes takes up mucicarmine faintly, a positive mucicarmine stain is helpful in distinguishing cryptococci from other yeasts. Although mucicarmine stains only the capsule, the capsule shrinks around the cryptococcal cell wall during fixation so that the cell wall may appear to be stained.

*Masson-Fontana* (or Fontana-Masson) stains melanin brown in fungal cell walls. This stain is not highly specific but can be useful for distinguishing hyphae of agents of phaeohyphomycosis from hyphae of agents of hyalohyphomycosis, such as *Aspergillus, Fusarium,* and *Scedosporium. Cryptococcus neoformans* and *Cryptococcus gattii* usually stain positive by Masson-Fontana. Mucicarmine is a more specific but less sensitive stain for cryptococci.

*Periodic acid–Schiff* (PAS) stains all fungal cell walls red. PAS also stains some microsporidia, *Tropheryma whipplei,* and many polysaccharide-containing structures within tissue. In the Splendore-Hoeppli phenomenon of basidiobolomycosis and sporotrichosis, the concretions around the hyphae stain with PAS. *Histoplasma* within old caseous foci may stain with GMS and not PAS.

## Fresh Clinical Specimens

*Calcofluor white* stains chitin-containing structures so that they fluoresce bright white under ultraviolet light in a fluorescent microscope. This stain in the microbiology laboratory has replaced the KOH (potassium

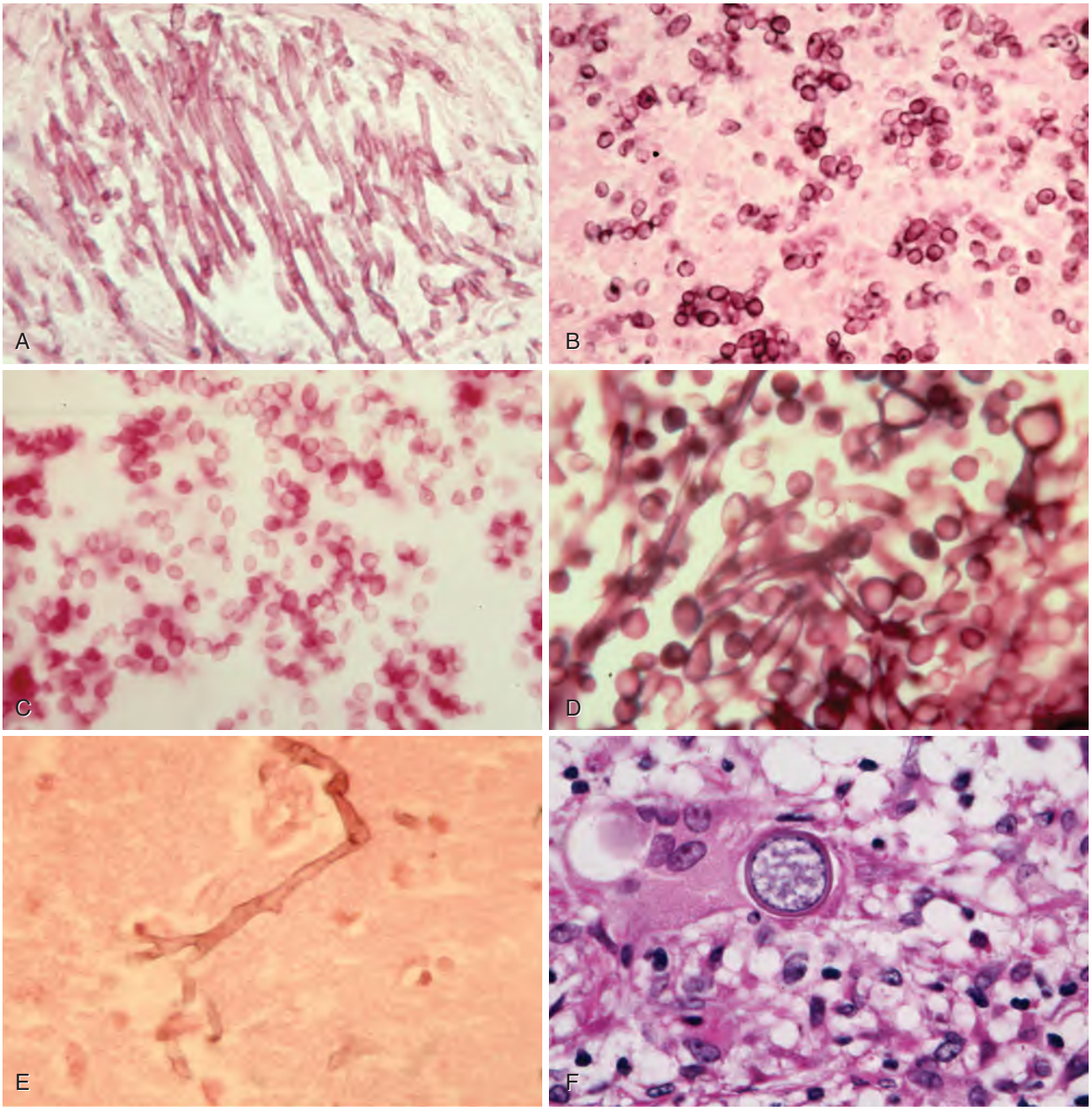


**FIG. 255.1 Appearance of fungi in tissue.** (A) *Aspergillus* sp.; periodic acid–Schiff (PAS) stain. (B) *Histoplasma capsulatum;* Gomori methenamine silver (GMS) stain. (C) *Candida glabrata* yeast cells; PAS stain. (D) *Candida albicans;* GMS stain. (E) *Rhizomucor* sp.; GMS stain. (F) *Coccidioides* sp.; hematoxylin and eosin (H&E) stain.

*Continued*

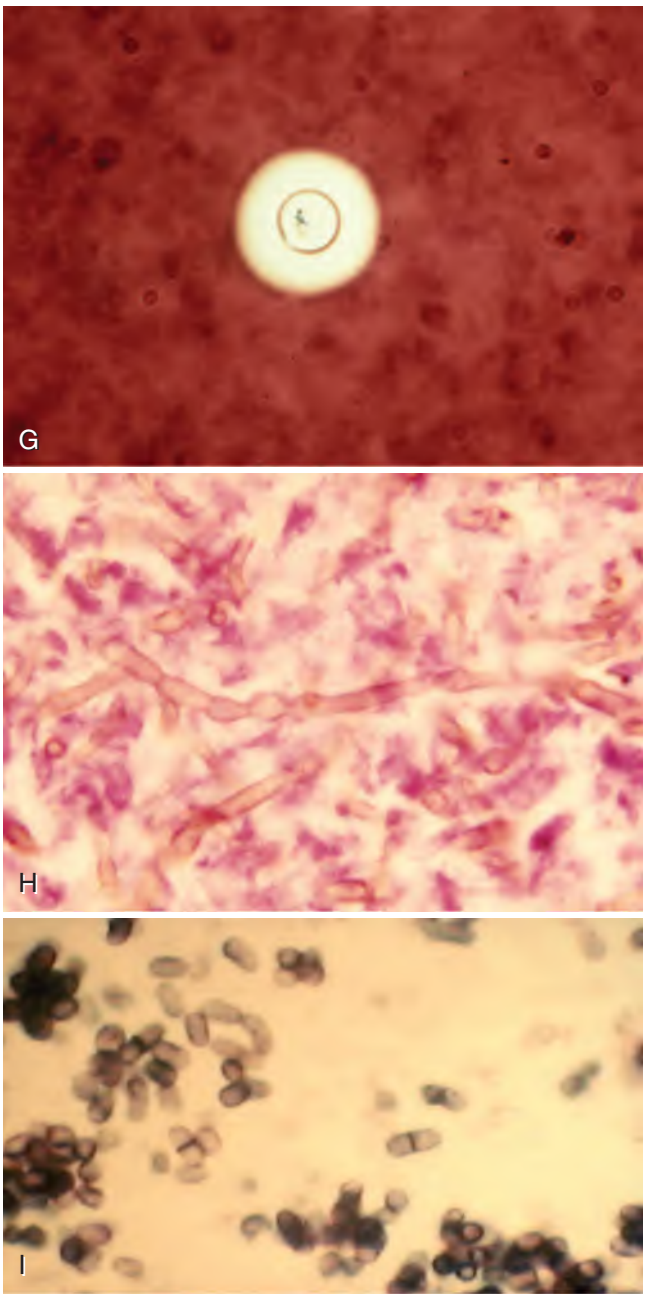


**FIG. 255.1, cont'd** (G) *Cryptococcus neoformans;* India ink smear of cerebrospinal fluid. (H) *Cladophialophora bantiana;* H&E stain. (I) *Talaromyces marneffei;* GMS stain.

hydroxide) wet mount because the contrast speeds examination. *Pneumocystis,* microsporidia, *Cryptosporidium,* and some parasitic cysts also are calcofluor positive.

With *Gram stain, Candida* yeast cells and pseudohyphae often appear gram-positive on clinical specimens. Some technologists can identify cryptococci in cerebrospinal fluid (CSF) by Gram stain, but Gram positivity may be only a few dots on the cell or not seen at all.

With *India ink,* suspension of colloidal carbon particles mixed with CSF will show the capsule around a cryptococcal cell. Capsule size may be too small to be visible on cultured cells. India ink staining should not be done on pus, sputum, or bronchial lavage specimens because viscous material surrounds many structures and can resemble a capsule.

## SEROLOGIC DIAGNOSIS

Despite a rich history of serologic studies of mycoses, the only mycosis for which serodiagnosis has an established role is coccidioidomycosis (see Chapter 265). Even with this infection, lack of standardization of tests among laboratories and among methods has made it difficult for the clinician to interpret the results. The situation is even worse for histoplasmosis and blastomycosis, for which the most promising test in the literature, complement fixation, has been considered too labor intensive and has been replaced in commercial laboratories by tests of unknown significance. Serodiagnosis for any mycosis should be used with great caution and with knowledge of the technique and laboratory performing the test.

Diagnosis by antigen detection has proved very useful in disseminated histoplasmosis and cryptococcosis. Severe cases of aspergillosis, coccidioidomycosis, and blastomycosis may also be amenable to diagnosis by antigen detection. An enzyme immunoassay using a rat monoclonal antibody that detects fungal polysaccharide in serum and bronchoalveolar lavage specimens has been used in the diagnosis of invasive aspergillosis and talaromycosis[9] (see Chapters 257 and 268). Sensitivity and specificity depend on the cutoff used for positivity, the patient population being tested, and prior use of mold-active antifungals. However, in high-risk

**TABLE 255.2 Typical Appearance of Fungi in Tissue**

| FUNGI | DESCRIPTION |
|---|---|
| **Yeastlike Fungi** | |
| *Histoplasma capsulatum* | 2–3 × 3–4–μm oval, budding uninucleate cells; often intracellular; granulomatous inflammation. Caseous necrosis can occur. Cells in African histoplasmosis (var. *duboisii*) are 6–15 μm in diameter. |
| *Talaromyces marneffei* | 2–3 × 2–6–μm oblong yeasts, some with central cross septum; often intracellular except in areas of necrosis. |
| *Pneumocystis jirovecii* | 3.5- to 7-μm cysts stain black on methenamine silver and may show a central black dot. White on calcofluor. No budding. Clusters of cysts occur in alveoli surrounded by eosinophilic amorphous material. |
| *Candida glabrata* | 2.5–3 × 4–5–μm oval budding cells; pyogenic necrosis. |
| *Cryptococcus neoformans/C. gattii* | 4- to 6-μm round uninucleate cell with large surrounding capsule; narrow pore between mother and daughter cell; daughter cell detached while small. Stains red with mucicarmine. |
| *Sporothrix schenckii/S. brasiliensis/ S. mexicana* | 1–3 × 3–10–μm cigar-shaped cell or 2- to 10-μm round budding cell; pyogenic and granulomatous inflammation. |
| *Blastomyces dermatitidis/B. gilchristii* | 8- to 15-μm round multinucleated cell with large pore between mother and daughter cell; daughter cell remains attached until almost the size of mother cell; pyogenic and granulomatous inflammation. |
| *Paracoccidioides brasiliensis/P. lutzii* | 2- to 30-μm multiply budding, round cells with tiny pore between mother and daughter cell; daughter cell released when small. |
| *Coccidioides posadasii/C. immitis* | 5- to 60-μm thick-walled, nonbudding, round cells that may contain endospores. Lung cavities may contain hyphae. |
| Agents of chromoblastomycosis | 4- to 12-μm round or oval, brown, thick-walled cells, often in clumps; hyphal forms may be seen in superficial crusts. |
| **Molds** | |
| *Aspergillus* spp. | 2- to 5-μm–wide hyphae, frequently septate, even diameter, Y-shaped branching; propensity for vascular invasion; necrosis. |
| Agents of mucormycosis | 4- to 15-μm–wide hyphae, rarely septate, uneven diameter, often branch at broad angles; propensity for vascular invasion; necrosis. |

patients with prolonged neutropenia or allogeneic stem cell transplantation, the galactomannan test has proven useful in preemptive treatment strategies, often in conjunction with high-resolution chest computed tomography (see Chapter 307). Tests are commercially available for detecting β-glucan in serum. β-Glucan is a cell wall component of many different molds and yeasts, including *P. jirovecii*. Problems of insensitivity and false-positive tests have complicated interpretation of this test, and it has yet to find its niche in the armamentarium of diagnostic tests.

## EPIDEMIOLOGY

Mycoses are acquired through two major routes: inhalation of airborne fungal spores into the lungs and paranasal sinuses, or direct contact. *Malassezia* spp. become part of the skin microbiome during infancy through contact with colonized humans. *Candida albicans* is acquired in the intestinal and mucosal microbiome from passage through the birth canal or later in life by contact with colonized persons. Ringworm is acquired by contact with infected animals, infected persons, or soil. Inoculation of saprophytic fungi on vegetation or soil through minor trauma can lead to sporotrichosis, mycetoma, or chromoblastomycosis. Ingestion has not proven to be a portal for pathogenic fungi, although that has been suspected for gastrointestinal basidiobolomycosis. Contact with water is suspected to transmit rhinosporidiosis.

Agents of histoplasmosis, blastomycosis, coccidioidomycosis, and cryptococcosis grow in natural sites, are inhaled, and initiate infection in the lung. A restricted reservoir in nature accounts for the geographic restriction of these mycoses. *Talaromyces marneffei* probably is acquired by inhalation, although the reservoir in nature is not well understood. Molds that infect immunosuppressed patients, such as those causing aspergillosis, mucormycosis, and fusariosis, are saprobes that are widely distributed in nature.

High-efficiency particulate air (HEPA) filtration of air in hospital rooms is used to protect highly immunosuppressed patients from invasive mold infections. The necessity of moving such patients out of the protected air for imaging and other procedures has limited the efficacy of air filtration. Anecdotal evidence has connected hospital construction with clusters of aspergillosis cases in immunosuppressed patients.

With rare exception, mycoses are not transmissible from patient to patient. Standard precautions for hospitalized patients are all that is indicated. Ringworm of the scalp in children is transmissible to other children, so caps and combs should not be shared by infected children and playmates. Airborne transmission of *P. jirovecii* has been documented, but reactivation also accounts for a large percentage of cases. Bandages or casts that become contaminated with draining pus from patients with coccidioidomycosis require care to ensure that the fungus does not remain on the fomite for several days because, at room temperature, the fungus will grow as the infectious, spore-bearing mold form.

The diagnostic laboratory should be alerted when specimens from patients suspected of having coccidioidomycosis or histoplasmosis are sent for culture. Once these cultures grow in the mold form, they can be hazardous to laboratory personnel.

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# 256 *Candida* Species

*Michail S. Lionakis and John E. Edwards, Jr.*

## SHORT VIEW SUMMARY

### Microbiology
- Budding yeast found abundantly in nature worldwide.
- Normal human commensals.
- Human-to-human transmission of disease is rare.
- Multiple species are pathogenic: *Candida albicans* and *Candida glabrata* most common.

### Epidemiology and Pathogenesis
- Normally not pathogenic in humans until host defense mechanisms become compromised.
- Disease of modern medicine: broad-spectrum antibiotics, indwelling intravenous catheters, prosthetic devices, hyperalimentation fluids, cancer treatment with cytotoxic agents, use of immunosuppressives for organ transplantation.
- Has emerged as the fourth most common organism recovered from blood in hospitalized patients. A health care–associated infection. Can disseminate widely when entering the bloodstream.
- Emerging incidence, especially in developing countries where modern advances in medical therapeutics are being introduced.
- Organism can infect nearly every organ and nearly all types of prosthetic materials. Female genital tract and oral mucosa are the most common mucocutaneous sites infected. Kidney, brain, heart, and eye are most commonly infected with dissemination.

### Diagnosis
- Diagnosis is by culture in normally sterile body fluids or by visualizing the organism in specimens of mucosa or skin using Gram stain, calcofluor white, or fungal stains, preferably confirmed by culture.

### Treatment
- Topical agents exist for mild to moderate mucosal or cutaneous candidiasis. For deep tissue infections, systemic treatment with amphotericin B, an azole, or an echinocandin is used (see Tables 256.3 to 256.5).

Written descriptions of oral lesions that were probably thrush date to the time of Hippocrates and Galen. Langenbeck, in 1839, found fungi in oral lesions of a patient.[1] In 1861, Zenker described the first well-documented case of deep-seated *Candida*. The first case of *Candida*-induced endocarditis was described in 1940.[2]

The most interesting period in the history of *Candida* infections began in the 1940s, when the widespread use of antibiotics was introduced. Since then, the incidence of practically all forms of *Candida* infections has risen abruptly. *Candida* spp. have been the fourth most common organisms recovered from blood of hospitalized patients in the United States during recent decades.[3] Between 2000 and 2005 the incidence of candidemia-related hospitalizations per 100,000 population rose by 52%.[4] A subsequent decrease in the incidence of candidemia has been noted in the late-2000s and early-2010s in the United States, which may reflect the successful implementation of prevention strategies for the decrease of central line–associated bloodstream infections.[5,6] The decreased incidence may also reflect a decrease in blood cultures. The burden of this illness in terms of morbidity, mortality, and expense is considerable. Estimates of the cost of candidemia in the United States are at least 2 billion dollars per year.[5,7] A small sample of the numerous reviews detailing the continued emergence of *Candida* as a common pathogen, the evolution of the disease in developing countries, the shift to non-*albicans* species, and antifungal resistance is available.[8–13] The emerging *Candida* infections include not only bloodstream infection but also arthritis, osteomyelitis, endophthalmitis, myocarditis, pericarditis, pacemaker-induced endocarditis, ventricular assist device infection, meningitis, peritonitis, myositis, pancreatitis, and others that are elaborated upon in detail in their respective sections of this chapter. The increasing incidence of human immunodeficiency virus type 1 infection, the use of therapeutic modalities for advanced life support, and certain surgical procedures, such as organ transplantation and the implantation of prosthetic devices, have expanded the incidence of *Candida* infections (Table 256.1).

Two interesting trends are continuing to develop with the extensive, rapidly evolving literature on *Candida* infections. First, as developing countries have introduced advanced medical care, including primarily more complex surgical procedures and more comprehensive cancer treatments, their increasing reports of the epidemiology and predisposing factors for *Candida* infections have recapitulated those that have been noted during the past two decades from countries with advanced medical care. Second, there has been a steady and significant increase in reports on the incidence and manifestations of *Candida* infections caused by non-*albicans* species.[8]

## PATHOGEN

*Candida* organisms are yeasts, that is, fungi that exist predominately in a unicellular form. They are small (4–6 μm), thin-walled, ovoid cells (blastospores) that reproduce by budding. They grow well in vented routine blood culture bottles and on agar plates and do not require special fungal media for cultivation. Several automated blood culture methods offer more rapid detection of *Candida*. Yeast forms, pseudohyphae, and hyphae may be found in microscopic examination of clinical specimens; identification of the hyphae and pseudohyphae is facilitated with 10% potassium hydroxide, which clears the epithelial cells, and with fluorescent microscopic examination of calcofluor white–stained smears.[14] The organism also stains gram-positive (Fig. 256.1).

*Candida* organisms form smooth, creamy white, glistening colonies that may resemble staphylococcal colonies. A rapid, presumptive identification of *C. albicans* can be made by placing the organism in serum and observing formation of germ tubes, small projections from the cell surface that appear within 90 minutes. However, both false-negative and false-positive germ tube formation may occur. The remainder of the identification and speciation procedures are based primarily on physiologic parameters rather than on morphologic characteristics. Metabolic tests include carbohydrate assimilation and fermentation reactions, nitrate utilization, and urease production. Chlamydospore formation is also used to identify *C. albicans*. Because of variation in species pathogenicity, speciation is desirable. There are more than 150 species of *Candida*, but only a small percentage are regarded as frequent pathogens for humans. They are *C. albicans, C. guilliermondii, C. krusei,*

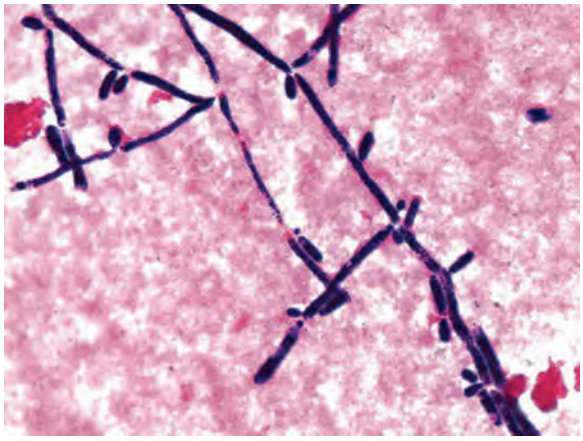

**FIG. 256.1 Morphology of *Candida* seen on Gram stain.** *(From Anaissie EJ, McGinnis MR, Pfaller MA. The laboratory and clinical mycology. In: Anaissie EJ, McGinnis MR, Pfaller MA, eds.* Clinical Mycology. *2nd ed. New York: Churchill Livingstone; 2009:55–77.)*

**TABLE 256.1 Predisposing Factors for Disseminated Candidiasis**

| |
|---|
| Exposure to broad-spectrum antibiotics |
| Indwelling intravenous catheters |
| Hyperalimentation fluids |
| Gastrointestinal surgery |
| Thoracic surgery |
| Neutropenia |
| Low-birth-weight neonates |
| Burn patients |
| Intravenous heroin use |
| Solid-organ transplant patients on immunosuppressives |

*C. parapsilosis*, *C. tropicalis, C. pseudotropicalis, C. lusitaniae, C. dubliniensis,* and *C. glabrata* (formerly classified as *Torulopsis glabrata*). *C. dubliniensis* is a relatively newly described species that was formerly included within *C. albicans.*[15] *C. dubliniensis* forms germ tubes and chlamydospores and is identified as *C. albicans* by the most common methods. However, it will not grow at 45°C, is darker green when initially isolated on CHROMagar Candida (BD Diagnostics, Heidelberg, Germany), and hybridizes poorly to the Ca3 probe. Because it is not yet clear how the clinical features may differ from those of *C. albicans,* if at all, the two are considered synonymous in this chapter. Infections by other species are being reported with increasing frequency, such as the azole-resistant species *Candida inconspicua* and newer *Candida* species such as *C. orthopsilosis* and *C. metapsilosis.*[16] The API 20C AUX yeast strip (bioMérieux, Durham, NC) is a commercial kit that gives accurate identification of most *Candida* spp. in 2 to 5 days. Rapid methods have been developed for speciation, such as the AdvanDx PNA FISH (OpGen, Gaithersburg, MD), but they are not widely used at present.[17]

Nucleotide sequencing and protein analysis by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) are identifying different groups within some *Candida* spp., now being described as potentially different species within a larger species complex. Examples are *Candida africana* within the *C. albicans* complex, *C. nivariensis* and *C. bracarensis* within the *C. glabrata* complex, *C. metapsilosis* and *C. orthopsilosis* within the *C. parapsilosis* complex, and *C. duobushaemulonii* and *C. haemulonii* var. *vulnera* in the *C. haemulonii* complex.[18,19] These cryptic species are not identified by most routine testing, and their clinical relevance is as yet unclear.[18,19] Problems in defining these cryptic species include inadequate definition of variability within the cryptic species, both in nucleotide sequence and in protein patterns, as well as the need to develop an efficient and reproducible means of identifying cryptic species. Two commercially developed MALDI-TOF MS systems are now available.[20]

Of extreme importance is the evolution of the species of *Candida* designated as *C. auris,* which was recovered from the ear of a patient in Japan in 2009 and has now spread globally. Multiple excellent reviews are now available, the details of which are beyond the scope of this chapter.[21–25] The following selected practical points can be made at this time:

1. The organism has now been found on five continents and appears to be spreading relatively rapidly.
2. It arises from separate clades.
3. Certain strains of the species are resistant to all classes of antifungal drugs.
4. Candidemia with *C. auris* has been associated with mortality rates greater than 50%.
5. Current fungal speciation methods have been associated with misidentification and classified as incorrect *Candida* species.
6. In-hospital outbreaks have occurred, and eradication of the organism from fomites in patients' rooms has been difficult to impossible.
7. The precise epidemiology of this species is not known at this time.

Many authors have named this organism the "*Candida* Superbug."

## EPIDEMIOLOGY AND ECOLOGY

*C. albicans* organisms have been recovered from soil, animals, hospital environments, inanimate objects, and food. Non-*albicans* species may live in animal as well as non-animal environments. Only rarely are *Candida* spp. laboratory contaminants. That principle has not been generally appreciated historically, and interpretation of positive cultures as laboratory or skin contaminants has led to important errors in patient management.

The organisms are normal commensals of humans and are commonly found on skin, throughout the entire gastrointestinal (GI) tract, in expectorated sputum, in bronchoalveolar lavage fluid, in the female genital tract, and in the urine of patients with indwelling Foley catheters. There is a relatively high incidence of carriage on the skin of health care workers. Although the vast majority of *Candida* infections are of endogenous origin, human-to-human transmission is possible. Examples are thrush of the newborn, which may be acquired from the maternal vagina, and balanitis in the uncircumcised man, which may be acquired through sexual contact with a partner having *Candida* vaginitis. There is also important, emerging evidence that *Candida* infection can be acquired from the hospital environment. Molecular biology tools are improving considerably the understanding of *Candida* epidemiology.[26–29]

## PATHOGENESIS AND IMMUNOLOGY

The most important predisposing factors to *Candida* infections are iatrogenic. The introduction of newer therapeutic modalities for advanced life support into clinical medicine has been primarily responsible for the dramatic change in the incidence of nearly all forms of candidiasis in recent decades. Of these factors, probably the most important have been the introduction of antibiotics, the use of myeloablative chemotherapy for neoplastic diseases, and the widespread use of indwelling intravenous catheters. Antibiotics suppress normal bacterial flora and allow *Candida* organisms to proliferate, especially in the GI tract.[30] The factors that predispose patients to disseminated candidiasis, which have been mentioned in countless reviews, are listed in Table 256.1.

An extensive discussion of the virulence factors, pathogenesis, and immunity of *Candida* infections is beyond the scope of this chapter and can be only highlighted herein. Virulence factors responsible for the capability of the organism to damage the host have been studied and reviewed extensively.[14,31] Of these, the switch of *C. albicans* from yeast to hyphal phase, in vivo, has been the most intensively investigated trait through the years. In infected organs, the hyphal phase dominates. Locking the organism in yeast phase by genetic engineering renders it nonpathogenic.[32] Yet, the precise role of this phenotypic switch in conferring *Candida* pathogenicity in humans remains elusive, since *C. glabrata* can cause lethal infections but does not undergo hyphal transformation. Gene disruption studies have identified well over 150 factors that promote *Candida* virulence.[14] Biofilm formation has been studied extensively and is important for *Candida* pathogenicity on both human tissues and prosthetic materials.[33,34] Animal models of both deep visceral and mucocutaneous candidiasis have examined mechanisms of adherence to host constituents and prosthetic devices. *Hwp1* and genes within the *ALS* gene family have received the greatest attention for conferring

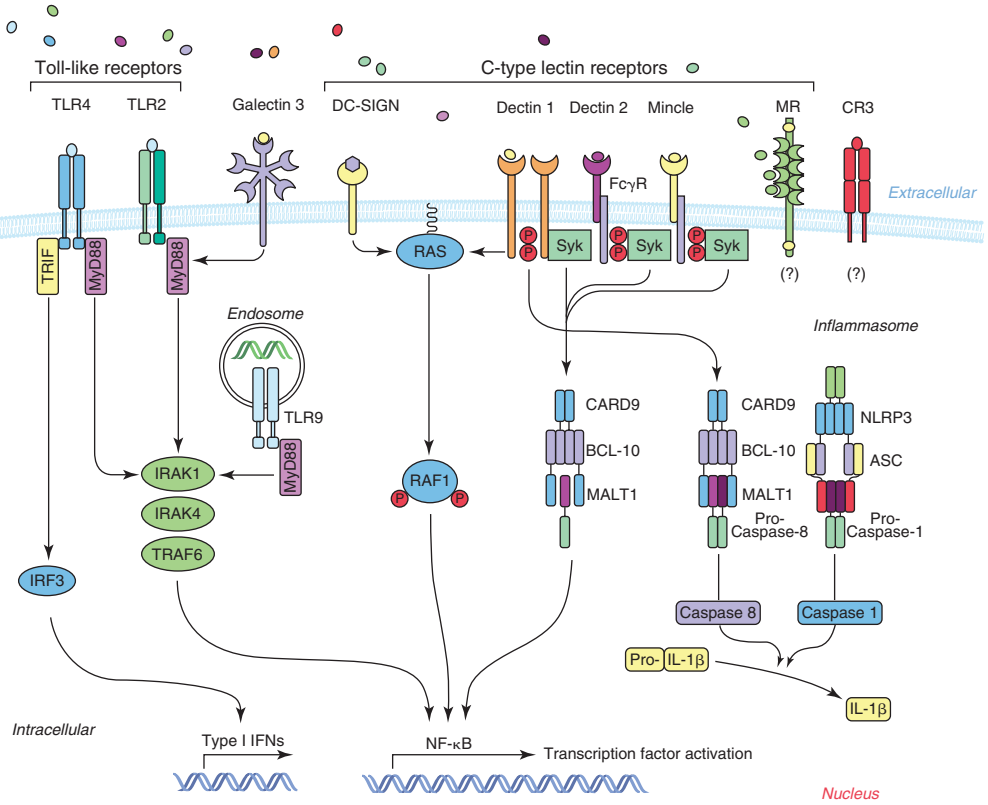


**FIG. 256.2 Pathways involved in immune defense against *Candida*.** *(Modified from Lionakis MS, Netea MG. Candida and host determinants of susceptibility to invasive candidiasis.* PLoS Pathog. *2013;9:e1003079.)*

adherence; however, several other genes also operate as adhesins.[35] Secreted aspartyl proteases and phospholipases,[36] capable of directly damaging tissue during invasion, have received considerable attention also.[37] Candidalysin, a cytolytic peptide toxin secreted by *C. albicans,* was recently shown to be critical for mucosal epithelial damage and host fungal recognition.[38]

Perhaps the greatest expansion in knowledge of *Candida* pathogenesis in recent years has been in the area of host defense mechanisms and genetic susceptibility to infection. *Candida* is a normal human commensal and becomes pathogenic mainly due to immune system perturbations. For a more complete review of this topic the reader is directed to comprehensive, contemporary, and excellent reviews (only a partial list).[39–43] An important concept in *Candida* host defense is that the constituents of effective immunity against mucosal and systemic disease cleanly segregate. Thus innate immunity via phagocytes is critical for control of systemic candidiasis, whereas adaptive immunity via T lymphocytes is important for control of mucosal candidiasis.

Fig. 256.2 summarizes current concepts regarding the pattern recognition receptors (PRRs) involved in *Candida* recognition by the innate immune system. Among PRRs, C-type lectin receptors (CLRs) have emerged as the most critical in humans. Dectin-1, the prototypic CLR, recognizes *Candida* β-glucan, while dectin-2 and dectin-3 recognize *Candida* mannans. The caspase recruitment domain–containing protein 9 (CARD9) signaling pathway, shown in Fig. 256.2, is downstream of CLR engagement and activates the immune system via production of cytokines and chemokines and via phagocyte recruitment and fungal uptake and killing.[43] Inherited deficiency in *CLEC7A,* which encodes dectin-1, is associated with recurrent vulvovaginitis and onychomycosis, but not systemic candidiasis.[44] Conversely, inherited deficiency in *CARD9* causes deeper immune defects and is the only known congenital immunodeficiency that predisposes to both mucosal and systemic candidiasis. The latter has a unique predilection for the central nervous system (CNS) due to impaired neutrophil recruitment to the *Candida*-infected CNS.[45] Beyond candidiasis, CARD9-deficient patients develop deep-seated dermatophytosis, extrapulmonary aspergillosis, and phaeohyphomycosis.[46–48]

A primary anti-*Candida* defense mechanism is intact skin and mucosal membranes. Any process causing skin maceration or mucosal damage leaves the involved site susceptible to *Candida* invasion, even in healthy individuals. In recent years, the importance of interleukin-17 (IL-17) signaling in protecting against *Candida* invasion at mucocutaneous barriers has become apparent. Mechanistically, IL-17 produced by $CD4^+$ Th17 cells, γδ T cells, and innate lymphoid cells protects via mediating the production of antimicrobial peptides that inhibit mucosal *Candida* growth. Several inherited disorders that impair human IL-17 immunity and cause chronic mucocutaneous candidiasis (CMC) have been discovered and are described later in this chapter.[49–51] Of note, IL-17 increases in humans in response to vaccination with the encoded product of the N-terminus of Als3.[52]

After *Candida* invades the bloodstream and disseminates into deep tissues, myeloid cells such as neutrophils, monocytes, and macrophages are key components of defense via effective uptake and killing of *Candida*.[43] Indeed, a strong predisposing factor for disseminated candidiasis is iatrogenic neutrophil deficiency, usually caused by cytotoxic chemotherapy. In addition, patients with defective oxidative cytotoxicity, such as those with chronic granulomatous disease due to NAPDH oxidase deficiency, or patients with complete myeloperoxidase deficiency are at risk for developing systemic (but not mucosal) candidiasis.[50] However, the majority of these patients do not develop candidiasis during their lifetime, underscoring the importance of nonoxidative fungal killing mechanisms that can compensate in the absence of oxidative burst. Importantly, recent studies have uncovered polymorphisms in immune-related genes in intensive care unit (ICU) patients that increase their risk for candidemia and disseminated candidiasis.[43,53–55] These studies show promise for identifying ICU patients at high risk for candidiasis, in whom personalized strategies for prophylaxis and treatment may help improve outcomes. Although well recognized for their protective roles, neutrophils may rarely cause tissue damage during candidiasis. Indeed, some *Candida*-infected patients develop worsening symptoms upon neutrophil recovery, necessitating corticosteroid administration.[56] Therefore identification of molecules that mediate neutrophil immunopathology in the mouse model of candidiasis, such as the chemokine

receptor Ccr1 and others, show promise for developing immune-based therapies for selected patients.[57]

## CLINICAL MANIFESTATIONS

As the frequency of diseases due to *Candida* has increased, a relatively large number of manifestations, which were previously either not recognized or extremely infrequent, have become well documented. The discussion of these clinical manifestations is facilitated by their subdivision into mucocutaneous and deep organ involvement.

### Mucous Membrane Infections

#### Thrush

Oral *Candida* infections are common and have been reviewed extensively.[58–62] The term *thrush* is applied to a specific form of oral candidiasis characterized by creamy white, curdlike patches on the tongue and other mucous membranes (Fig. 256.3); the patches are removable by scraping and leave a raw, bleeding, and painful surface. The patches are actually pseudomembranes consisting of *Candida,* desquamated epithelial cells, leukocytes, bacteria, keratin, necrotic tissue, and, in the mouth, food debris. The formation of *Candida* biofilm,[63] as well as epithelial cell invasion,[64] is important in the establishment of oropharyngeal candidiasis. The diagnosis is made by the clinical appearance of the lesion and confirmed by scraping, using either a potassium hydroxide smear or Gram stain to show masses of hyphae, pseudohyphae, and yeast forms. Simple culturing does not solidify the diagnosis because *Candida* grows easily from normal mouths. In addition to the classic lesions, which have been described by Lehner,[65] other manifestations include (1) acute atrophic candidiasis, a nonspecific atrophy of the tongue that is thought to be a sequela of acute pseudomembranous candidiasis; (2) chronic atrophic candidiasis or "denture sore mouth," which is a chronic inflammatory reaction and epithelial thinning under the dental plates; (3) angular cheilitis, an inflammatory reaction at the corners of the mouth (not due exclusively to *Candida*); and (4) *Candida* leukoplakia, which is firm, white plaques affecting the cheek, lips, and tongue that have a protracted course (and, in rare instances, may be precancerous). Since the introduction of inhaled steroids for the treatment of asthma, especially in children, oral thrush has been reported extensively in patients treated with these agents. The incidence has ranged from 0% to 77%. Thrush developing in patients who use inhaled steroids usually resolves spontaneously without a change in the dosage of the agent or is successfully managed with topical nystatin or clotrimazole. Other patients with a high incidence of thrush are cancer patients and those with acquired immunodeficiency syndrome (AIDS). Patients with thrush for no obvious reason should be evaluated for AIDS. Because of the introduction of potent antiretroviral therapy, the incidence of colonization and symptomatic infection with thrush has declined somewhat in patients with AIDS, but remains common.[66] Certain patients may have chronic thrush, and thrush may be a feature of inherited CMC syndromes (see later).

#### *Candida* Esophagitis

Although there have been a small number of reports of *Candida* esophagitis occurring in patients with no known underlying illness, it is more commonly associated with treatment of malignancy of the hematopoietic or lymphatic systems (Fig. 256.4) and in AIDS patients.[67,68] Additionally, omeprazole has been implicated as a risk factor. Esophageal disease was believed to occur by direct spread from oral disease (thrush), but reviews have shown that *Candida* esophagitis may occur frequently without thrush; this is an important clinical concept. The most common symptoms of *Candida* esophagitis include painful swallowing, a feeling of obstruction on swallowing, and substernal chest pain. Nausea and vomiting may also occur. The diagnosis is made definitively by biopsy during endoscopy (Fig. 256.5). However, the appropriate clinical settings, associated with the endoscopic appearance of white patches resembling thrush that show masses of hyphae and pseudohyphae on scraping, are enough evidence to initiate therapy without a histopathologic demonstration of the organisms invading the mucosa. It is important to recognize that *Candida* esophagitis can occur simultaneously with herpes simplex virus or cytomegalovirus infection in severely immunocompromised patients. Radiographic examination may be helpful in making a clinical diagnosis; irregularity of the esophageal mucosa as a result of ulcerations may be seen, as well as shoulder defects, diverticulae, fistulas, and dilatation of the esophagus from denervation. Endoscopy is the preferred procedure for definitive diagnosis, however. The pseudomembrane that forms may become so extensive that it causes intraluminal protrusions and partial esophageal obstruction. Perforation of the esophagus due to esophageal candidiasis is very rare. Generally, if perforation occurs, it is in the lower two-thirds of the esophagus. Some patients have had extensive esophageal disease and been almost asymptomatic, probably as a result of denervation of the esophagus from the disease. Other complications include bleeding and, presumably, dissemination.

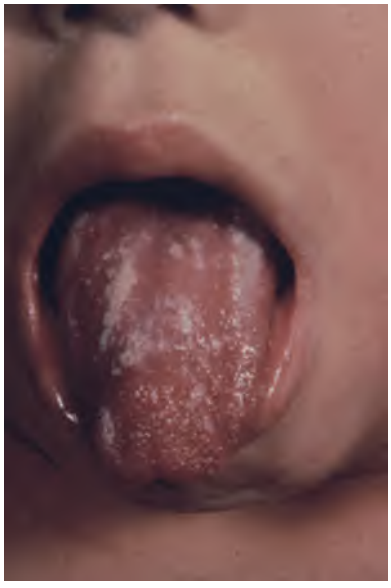

**FIG. 256.3 Typical oral thrush with curdlike white patches over the tongue.** *(Courtesy Dr. Arnold Gurevitch.)*


**FIG. 256.4 Severe *Candida* esophagitis at autopsy.**

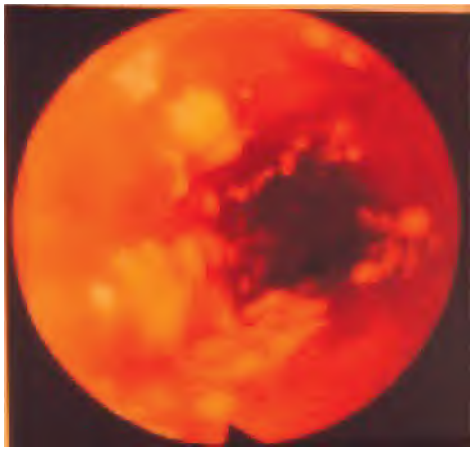

**FIG. 256.5 *Candida* esophagitis in an AIDS patient.** Numerous white plaques are seen.

## Nonesophageal, Mucous Membrane, Gastrointestinal Candidiasis

The most common clinical setting for GI tract candidiasis is in patients with neoplastic disease. The esophagus is the most common site, followed by the stomach and small intestines. The most frequent lesions are single or multiple ulcerations containing *Candida* deep in the ulcer beds. *Candida* can also invade ulcers caused by other diseases, such as peptic ulcer and malignant gastric ulcer. As in other mucous membrane *Candida* infections, white plaques may be seen on endoscopy of the duodenum, and there may be thickening of mucosal folds in the duodenum and jejunum. Equal in frequency to the involvement of the small bowel is involvement of the large bowel, which again may be characterized by ulceration, superficial erosions, pseudomembrane formation, penetrating ulcers, and, rarely, perforation.

Reviews of defensive mechanisms of mucosal candidiasis have been published.[69,70] It is highly likely that hematogenous dissemination from the GI tract occurs in neutropenic patients with GI mucosal damage due to cytotoxic chemotherapy (Fig. 256.6).[71,72]

## *Candida* Vaginitis

*Candida* has assumed the role of the most common cause of vaginitis, with higher frequency rates than those of *Trichomonas* or bacterial vaginosis. This common infection is most frequently seen in the setting of diabetes mellitus; antibiotic therapy, particularly with β-lactams; and pregnancy. In addition, although controversial, the use of certain birth control pills may be a predisposing factor. Estimates are that 75% of women have an episode of candidal vaginitis during their lifetime, 50% of them will have at least one recurrence, and 8% will have recurrent vulvovaginal candidiasis (>3 episodes/year).[73] Recent investigations have shown that certain polymorphisms in innate immune genes and the interleukin-22 (IL-22) signaling axis may account for recurrence in this subset of patients.[42,74,75]

Of interest, in contrast to oral and esophageal disease, vaginal candidiasis is not more common or more refractory to treatment in patients with AIDS, indicating that cells other than CD4 T lymphocytes are critical for local vaginal anti-*Candida* host defense. Conversely, use of antibiotic therapy is an important factor responsible for the emergence of *Candida*-induced vaginitis, whereas antibiotics do not predispose to oral or esophageal disease. Antibiotics can have effects by disrupting local IL-17/IL-22 protective immunity, via promoting biofilm formation by *Candida,* or both.[76,77] Excellent reviews of the current trends in the epidemiology and pathogenesis of vaginal candidiasis are available.[73,76–79] In these reviews, the rising incidences of non-*albicans Candida* species and of azole resistance in the species of *Candida* recovered are emphasized.[80,81]

Although *Candida*-induced vaginitis may be accompanied by a thick, curdlike discharge, scanty discharge may instead characterize the infection. Edema and intense pruritus of the vulva are almost always present. The discharge consists of epithelial cells and masses of hyphae and pseudohyphae, accompanied by lymphocytes and neutrophils.[82] The vagina and labia are usually erythematous, and extension onto the skin of the perineum can occur (Fig. 256.7). In addition, endometritis due to *Candida* has been reported, and the urethra may become secondarily infected.

## Cutaneous Candidiasis Syndromes

### Generalized Cutaneous Candidiasis

This condition is an unusual form of cutaneous candidiasis and is characterized by widespread eruptions over the trunk, thorax, and extremities with increased severity in the genitocrural folds, anal region, axillae, hands, and feet (Fig. 256.8). The process begins as individual

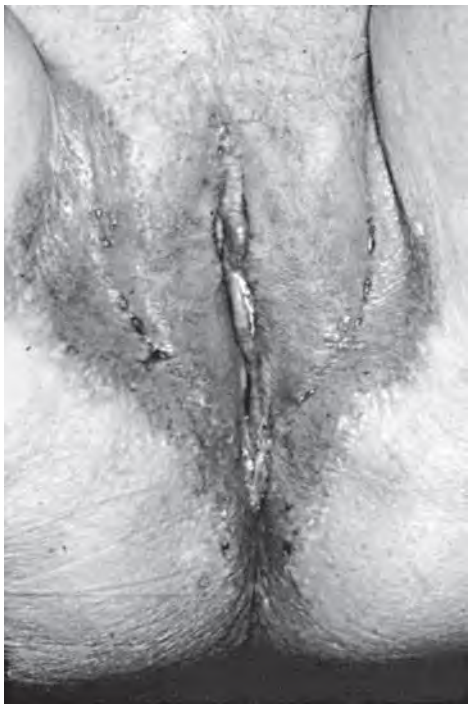

**FIG. 256.7 Extension of *Candida* vaginitis onto the perineum.**

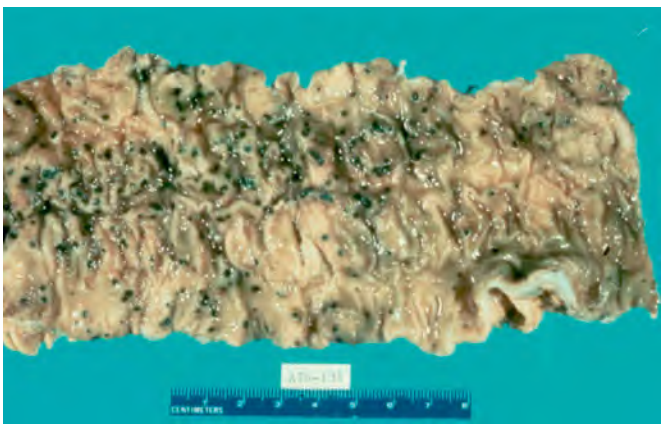

**FIG. 256.6 Numerous small intestine ulcerations with *Candida* and disseminated candidiasis in a neutropenic patient at autopsy.**

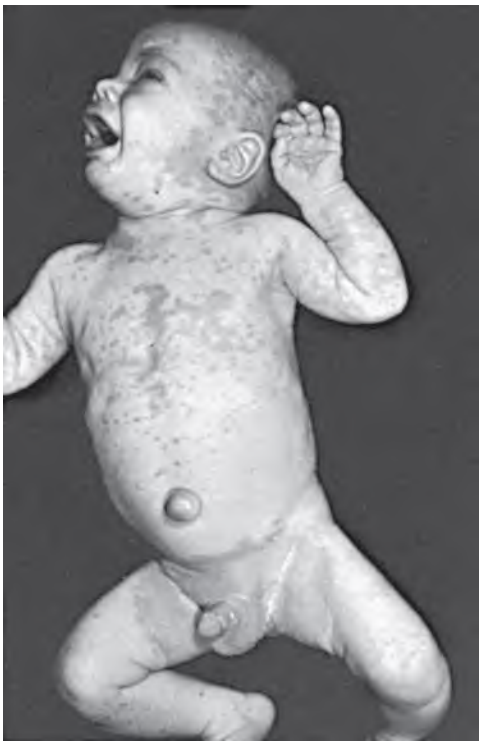

**FIG. 256.8 Generalized cutaneous candidiasis.** *(Courtesy Dr. Victor Newcomer.)*

lesions that spread into large confluent areas. It is more common in newborns and children but does occur in adults.[83,84] It should not be confused with *Candida* folliculitis or the cutaneous macronodular lesions of widespread hematogenously disseminated *Candida* (see later).

## Erosio Interdigitalis Blastomycetica

This term applies to *Candida* infection occurring between the fingers or toes (Fig. 256.9). It has a red base, may extend onto the sides of the digits, is painful, and is predisposed to by maceration.[85,86]

## *Candida* Folliculitis

Infection with *Candida* at the hair follicles can occur (Fig. 256.10). Rarely, the condition may become extensive. It must be distinguished from folliculitis caused by the dermatophytes and tinea versicolor. This folliculitis has been described in immunocompromised hosts and intravenous drug abusers. Its incidence is increased in obesity.[87,88]

## *Candida* Balanitis

This process begins as vesicles on the penis that develop into patches resembling thrush and are accompanied by severe itching and burning. *Candida* is one of the more common causes of balanitis.[89] It may spread to the thighs, gluteal folds, buttocks, and scrotum. It can be acquired through sexual intercourse with a partner who has vaginal candidiasis.[90]

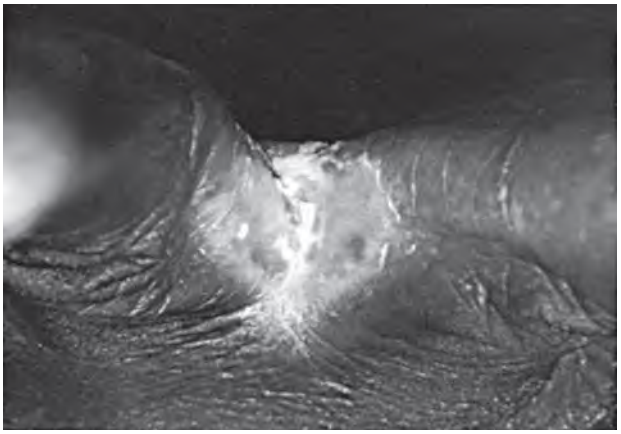

**FIG. 256.9 Erosio interdigitalis blastomycetica.** *(Courtesy Dr. Arnold Gurevitch.)*

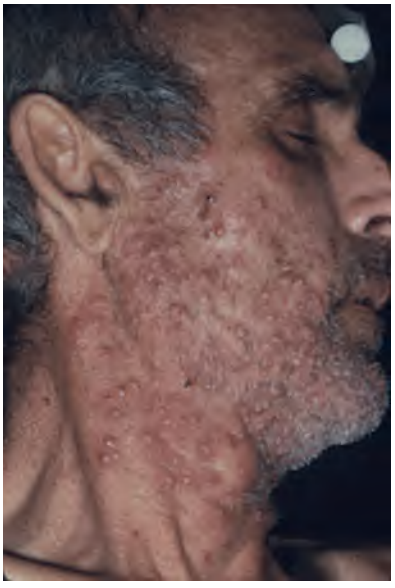

**FIG. 256.10 Severe *Candida* folliculitis in beard distribution.** *(Courtesy Dr. Victor Newcomer.)*

## Cutaneous Lesions of Disseminated Candidiasis

Four distinct types of lesions associated with disseminated candidiasis have been described. The macronodular lesions (Fig. 256.11) are 0.5 to 1 cm in diameter, are pink to red, and may either be single or occur widely distributed over the entire body. The most accurate method of making a specific diagnosis is by punch biopsy[91,92] and demonstration of organisms on histologic section. Most patients with these lesions are neutropenic, and all have disseminated candidiasis, not local inoculation. Additionally, lesions resembling ecthyma gangrenosum,[93,94] purpura fulminans,[95] and leukocytic vasculitis[96] have been described. Chronic lesions of pyoderma gangrenosa may become superinfected with *Candida* and delay their definitive diagnosis.

## Intertrigo

This common skin condition affects any site in which skin surfaces are in close proximity and provide a warm, moist environment.[97] It begins as vesicopustules, which enlarge and rupture, causing maceration and fissuring. The area of involvement has a scalloped border with a white rim consisting of necrotic epidermis, which surrounds an erythematous, macerated base. Frequently, satellite lesions are found that may coalesce and extend the affected area. A variant form of cutaneous candidiasis in the intertriginous region has a miliary appearance resembling miliaria rubra with erythematous macules or vesicopustules.

## Paronychia and Onychomycosis

*Candida* is one of the most common causes of paronychia. Species other than *albicans* may be causative and may cause osteomyelitis of the distal phalanx.[98,99] Many skin bacteria, as well as *Candida,* can usually be recovered by culture of the infected area. The appearance of the reaction is that of a relatively well-localized area of inflammation that becomes warm, glistening, and tense and may spread extensively under the nail (Fig. 256.12). Unless the disease process is stopped, secondary thickening, ridging, and discoloration occur, and nail loss may develop.

*Candida* paronychia occurs in association with frequent immersion of the hands in water. People who may contract paronychia include dishwashers, laundry workers, and parents of babies. There is also a higher incidence of paronychia among diabetic patients than in the nondiabetic population. Specific diagnosis is made by Gram stain or potassium hydroxide preparation and culture showing predominantly *Candida* organisms.

*Candida* can cause onychomycosis, usually in patients with paronychia.[100,101]

## Diaper Rash

*Candida* is a common cause of diaper rash in infants.[102] The condition generally starts in the perianal area and spreads over the perineum in the region of diaper contact (Fig. 256.13). The process is facilitated by maceration caused by wet diapers. The probable origin is the GI tract. Diagnosis is made by scraping the area and demonstrating the organisms on potassium hydroxide preparation.

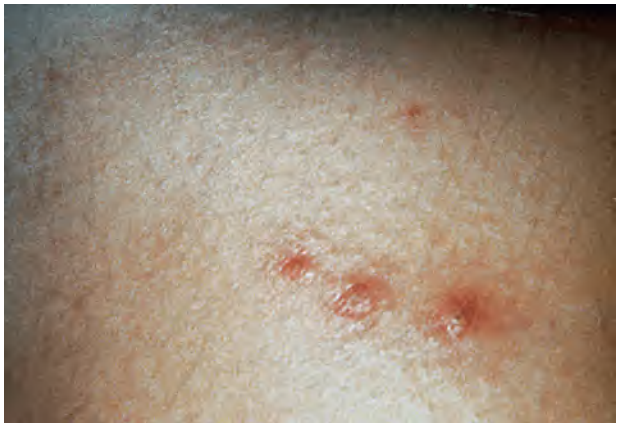

**FIG. 256.11 Macronodular lesions of disseminated candidiasis.** *(Courtesy Dr. Richard Meyer.)*

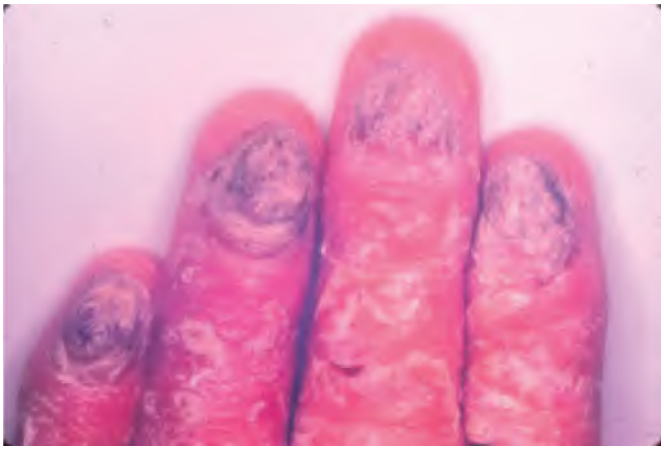

**FIG. 256.12** **Chronic mucocutaneous candidiasis of the fingers and nails.**

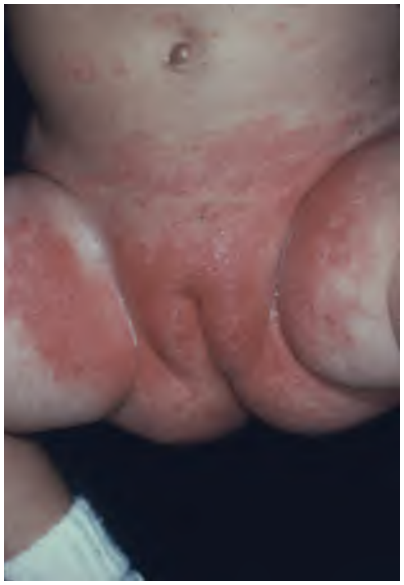

**FIG. 256.13** **Severe *Candida* diaper rash.** *(Courtesy Dr. Victor Newcomer.)*

## Perianal Candidiasis

Although numerous organisms and combinations of organisms have been associated with pruritus ani either alone or in combination, *Candida* is a frequent cause.[103] The perianal skin develops marked erythema and progresses to maceration (Fig. 256.14). Intense pruritus results. Complications include involvement of the anal canal and extensive spread over the perineum. It can occur among men who have sex with men.[104]

## Chronic Mucocutaneous Candidiasis

The term *chronic mucocutaneous candidiasis* (CMC) describes a heterogeneous group of *Candida* infections of the skin, mucous membranes, hair, and nails that have a protracted and persistent course despite what is usually adequate therapy. The major complication is disfiguring lesions of the face, scalp, and hands. *Candida* esophagitis can be a long-term complication, and can cause esophageal stenosis and, in some instances, carcinoma. Alopecia in areas of infection is common and may be permanent. The subject has been reviewed comprehensively in a classic publication.[105] Most forms of CMC begin in infancy or within the first 2 decades; rarely, the onset may be after the age of 30 years. The first manifestation is usually oral thrush followed by nail infections. There is a broad spectrum of severity, ranging from chronic involvement of an isolated nail to a severely disfiguring form (*Candida* granuloma) (Fig. 256.15).

In recent years, an explosion in the discovery of several inborn errors of IL-17 immunity has dramatically expanded our understanding of the pathogenesis of and genetic susceptibility to CMC. The topic has been reviewed comprehensively.[50] Briefly, deficiency in the following genes may present with CMC: *IL17RA, IL17RC, IL17F, ACT1, RORC, AIRE, STAT3, DOCK8, CARD9, CLEC7A, STAT1, IL12RB1,* and *STK4.* The direct defects of IL-17 signaling (i.e., mutations in *IL17RA, IL17RC, IL17F,* and *ACT1*) primarily manifest with CMC and staphylococcal skin infections without noninfectious manifestations. Other genetic perturbations result in CMC together with syndromic manifestations; two of these are sufficiently important to briefly highlight. Autoimmune polyendocrinopathy-candidiasis–ectodermal dystrophy (APECED) is an autosomal-recessive disease caused by *AIRE* mutations. Patients manifest with selective infection susceptibility to CMC (~85% prevalence) along with a variety of endocrine and nonendocrine autoimmune manifestations, and ectodermal dystrophy.[106] CMC is typically the first disease manifestation during infancy and is associated with the presence of neutralizing autoantibodies to IL-22, IL-17A, and IL-17F.[106] Job syndrome or autosomal-dominant hyperimmunoglobulin E syndrome is caused by *STAT3* mutations. Affected patients manifest with CMC

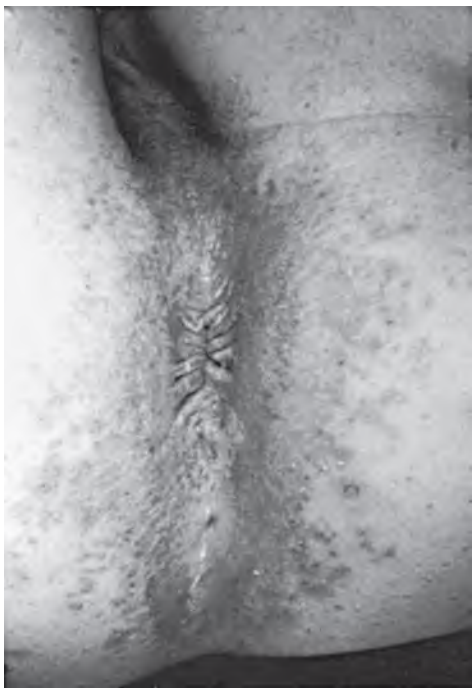

**FIG. 256.14** **Perianal candidiasis.** *(Courtesy Dr. Victor Newcomer.)*

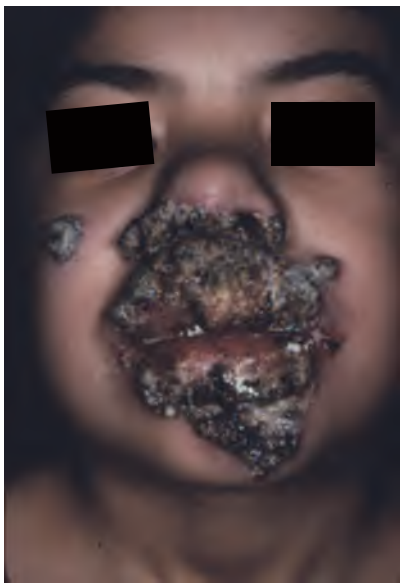

**FIG. 256.15** ***Candida* granuloma.** *(Courtesy Dr. Victor Newcomer.)*

(~70% prevalence), skin and pulmonary staphylococcal infections, skeletal abnormalities, and elevated serum immunoglobulin E. CMC develops in Job syndrome patients because *STAT3* is critical for the differentiation of CD4 T cells into the Th17 lineage.[107]

## Deep Organ Involvement

### Central Nervous System Candidiasis

*Candida* infects both parenchymal brain tissue and the meninges, usually as a complication of hematogenously disseminated candidiasis. Of note, CNS involvement is more frequent in neonates with candidemia. Approximately 50% of patients with *Candida* meningitis have had disseminated disease in other organs. When infection occurs in brain parenchyma, it generally forms multiple microabscesses and small macroabscesses scattered throughout the tissue. Rarely, larger abscesses have occurred and may be visualized by computed tomography. Mechanisms by which this organism localizes to the brain in the mouse model have been elucidated.[108] As mentioned previously, CARD9 deficiency predisposes to CNS candidiasis due to insufficient neutrophil recruitment into the brain. The diagnosis should be considered in putatively immunocompetent individuals who present with CNS *Candida* disease.[45]

Virtually all patients with *Candida* meningitis have had cerebrospinal fluid pleocytosis. Fifty percent have had a lymphocyte pleocytosis with an average count of 600 cells/mm$^3$. Sixty percent have had hypoglycorrhachia and elevated protein levels; organisms have been present on wet mount or Gram stain in approximately 40%. *C. albicans* has been the responsible pathogen in 90% of cases. Occasional cases due to *C. tropicalis* have been reported.

The clinical manifestations of CNS involvement with diffuse microabscesses may be variable. If the patient is comatose or noncommunicative, detection of abnormalities may be exceptionally difficult. When meningitis is present, the signs of meningeal irritation (headache, stiff neck, irritability), typical of any meningeal infection, are frequently present. In the newborn, particularly the very-low-birth-weight neonate, diagnosis is often difficult and delayed, leading to permanent neurologic sequelae. Lumbar puncture should be considered when the blood cultures of such infants contain *Candida*.

In addition to occurring as a complication of disseminated candidiasis, *Candida* meningitis may result from infection of a ventricular shunt, or may be introduced by lumbar puncture, trauma, or neurosurgery,[109] or may complicate bacterial meningitis. The signs and symptoms are nonspecific. Untreated, the mortality rate is very high; it is reduced substantially with antifungal therapy. Hydrocephalus is a frequently occurring complication of the infection. The number of cases of *Candida* meningitis reported in neonates has been increasing.

### Respiratory Tract Candidiasis

In general, *Candida* pneumonia occurs in two forms: (1) either local or diffuse bronchopneumonia originating from endobronchial inoculation of the lung, a very rare event; or (2) a hematogenously seeded, finely nodular, diffuse infiltrate that in its early stages may be difficult to distinguish from congestive heart failure or *Pneumocystis* pneumonia. Other forms of *Candida* pneumonia are very rare; those that have been described are necrotizing pneumonia, *Candida* as a fungus ball in the lung, and transient infiltrates due to *Candida*. Radiographic and computed tomographic findings are nonspecific, and definitive diagnosis depends on biopsy-proven fungal invasion of pulmonary tissue. Because of a relatively high prevalence of yeasts colonizing the respiratory tract, especially in ill patients, a definitive diagnosis of *Candida* pneumonia cannot be made on radiographic findings and recovery of yeasts from sputum, bronchoalveolar lavage, or endotracheal tube aspirate. A contemporary discussion of the significance of *Candida* in sputum in ill patients is now available.[110] *Candida* has also caused bronchial infection, laryngitis, epiglottitis, and infection of laryngeal prostheses. The entity of "fungal empyema thoracis" has been described as an emerging clinical entity, usually a combination of bacteria and *Candida* in the empyema.[111] Hospitalized patients who develop bacterial pneumonia, are treated with broad-spectrum antibiotics, and then begin growing *Candida* from the sputum only rarely have *Candida* pneumonia, that is, pneumonia that is predominantly caused by *Candida*.

### Cardiac Candidiasis

In addition to causing endocarditis, *Candida* infects both the pericardium and the myocardium. *Candida* myocarditis occurs as diffuse microabscesses scattered throughout the myocardium with normal intervening myocardial tissue. The relatively high incidence of myocarditis has been stressed by Franklin and coworkers,[112] who found that 62% of their 50 patients with disseminated candidiasis had myocardial involvement. Other retrospective autopsy studies have shown a range from 8.4% to 93%. *Candida* myocarditis has also occurred in AIDS patients. Autopsy series of disseminated candidiasis reveal a surprisingly high incidence of myocarditis (without associated valvular involvement) and point to the importance of thorough cardiac evaluation in patients who may have disseminated candidiasis. Of interest has been the emergence of *Candida* organisms as a cause of pericarditis. A review of purulent pericarditis spanning the years 1960 to 1974 revealed that *Candida* organisms were either the single cause or combined with *Aspergillus* in 15% of the 26 cases.[113] A more recent review is available.[114]

### *Candida* Endocarditis

Fungi are the cause of between 1% and 10% of all forms of endocarditis. In a detailed review of 319 cases of fungal endocarditis, *Candida* accounted for 67% of the cases. In the last several decades, there have been several hundred reported cases. The entity of *Candida* endocarditis has been reviewed extensively.[115–117] Additional cases have been reported in children.[118] *Candida* endocarditis on native or prosthetic valves occurs mainly in association with six clinical factors: (1) underlying valvular heart disease; (2) heroin addiction[119]; (3) cancer chemotherapy; (4) implantation of prosthetic valves[120]; (5) prolonged use of intravenous catheters (endocarditis, right atrial fungal masses, and infection of atrial myxomas have all been described); and (6) preexisting bacterial endocarditis, on which it is superimposed. Of these associations, by far the most frequent is post–cardiac surgery, accounting for approximately 50% of the prosthetic valve infections. Two-thirds of the cases of *Candida* endocarditis are nosocomially acquired.[121] Of interest is the frequency of species other than *C. albicans* that have caused endocarditis; a minimum of 41% of the cases have been due to organisms of non-*albicans* species, some of which have been very rarely recovered species. Newer species continue to be reported regularly. In heroin addicts, *C. parapsilosis* has been the most common causative organism.[122]

The pathogenic mechanisms for fungal endocarditis are not fully understood, but patients who undergo cardiac surgery are at risk for candidemia by being exposed to multiple antibiotics, prolonged intravenous fluid administration, and intravenous plastic catheters. Both the damaged endocardium and prosthetic material apparently serve as foci for the localization of *Candida* organisms. Also, contamination of suture material has been implicated in cases reported with concentration along the suture line. Contamination of homografts and heterografts before insertion has also been documented.

The valves most commonly involved in *Candida* endocarditis have been the aortic and the mitral (Fig. 256.16). In postoperative *Candida*

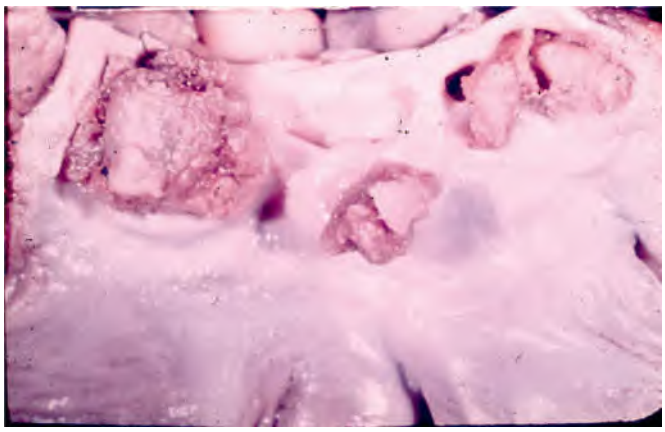

**FIG. 256.16** ***Candida parapsilosis*** **vegetations on an aortic valve.**

endocarditis, the type of surgery has not been as important as the length of the postoperative course and complications during the postoperative period. *Candida* infection has been seen in simple valvulotomies and in prosthetic material placement, heterografts, and homografts. Pacemaker endocarditis has also been described.[123] The physical findings and usual symptoms of *Candida* endocarditis are not significantly different from those of bacterial endocarditis with the exception of the occurrence of large emboli to major vessels. Osler nodes, Janeway lesions, splinter hemorrhages, hepatosplenomegaly, hematuria, proteinuria, pyuria, and urinary casts all can occur. In addition, although the lesions of hematogenous ocular candidiasis have been described much more frequently in the setting of disseminated candidiasis without endocarditis, they may also be seen with endocarditis.

The complications of *Candida* endocarditis are very similar to those of bacterial endocarditis and include valve perforation, myocarditis, congestive heart failure, and major emboli. Although most cases of postoperative prosthetic valve *Candida* endocarditis occur in the first 2 postoperative months, some have occurred later, and some patients who have been treated have had recurrent active disease after 2 years, and perhaps as long as 8 years. Therefore in following patients treated for postoperative endocarditis, careful follow-up must be extended over a prolonged period.

Most patients with *Candida* endocarditis have positive blood cultures. Modern blood culture methods, such as nucleotide detection systems, are likely to provide better sensitivity and specificity. The largest prospective experience with various serum diagnostic tests for *Candida* endocarditis was published in 2012.[124] Detection of serum (1,3)-β-D-glucan and antimannan antibody had a very high negative predictive value. Studies of serodiagnostic tests were inconclusive regarding their impact on treatment. Echocardiography is becoming progressively more helpful, and vegetations may be detected with this technique. False-negative results are common, especially in cases of mural endocarditis without valvular involvement. Transesophageal echocardiography has improved the sensitivity, particularly in the mitral valve.

The therapy for *Candida* endocarditis is discussed in detail in the section on therapy. Before the introduction of surgical procedures for the management of *Candida*-induced endocarditis, the mortality rate from this disease was approximately 90%. With combined surgical and medical therapy, this high mortality rate has dropped to approximately 45%. Because of the introduction of newer antifungals, there has been a greater propensity for their use in chronic suppression for selected patients.

*Candida* endocarditis has been seen in association with bacterial endocarditis as a polymicrobial infection. In general, *Candida* has been a superinfection introduced by prolonged intravenous catheterization for antibiotic administration. Interesting investigations are developing showing how *Candida*-bacteria interactions enhance the pathogenicity of a coinfection.[125,126]

## Urinary Tract Candidiasis

This topic has been reviewed comprehensively and definitively.[127–134] The presence of *Candida* in the urine is common in hospitalized patients and usually does not indicate urinary tract infection. Antibiotics, diabetes mellitus, and Foley catheters have been associated with the acquisition of candiduria, usually asymptomatic. Although the use of colony counting in urine has been attempted to separate colonization from infection, it has not been reliable. Most patients with health care–associated asymptomatic candiduria have spontaneous resolution; however, long-term persistence of candiduria may follow bladder catheter removal, particularly in patients with diabetes mellitus or bladder outlet obstruction with residual urine or urinary diversion structures, such as ileal conduits and orthotopic neobladders. The cystoscopic appearance of *Candida* cystitis is that of a chronic nonspecific mucosal inflammation, though thrushlike patches are occasionally seen. Hematogenous dissemination may occur, usually following an operative procedure on the bladder.

*Candida* infection of the upper urinary tract has been classified into two distinct forms: that developing along an ascending route, and that resulting from hematogenous spread. Ascending infection can arise after a ureteral stent or transcutaneous catheter is placed in the renal pelvis to relieve obstruction. If *Candida* gains access to the renal pelvis through these procedures, subsequent partial or complete obstruction of the urinary drainage predisposes to *Candida* invasion of the renal papillae, followed by papillary necrosis. This can happen when the stent or catheter is removed and the ureter is still partially obstructed. Imaging may show a mass, often called a fungus ball, within the pelvis, composed of a sloughed papilla and inflammatory debris. The mass can obstruct the ureteropelvic junction, catheters, or stents. Relief of obstruction and systemic antifungals are required to prevent progressive kidney destruction and possibly perinephric abscess. If the renal pelvis had been drained percutaneously, *Candida*-infected urine can pass from the pelvis into the perinephric space through the catheter tract.

The hematogenous form of the disease is by far the most common. The pathologic changes are those of multiple microabscesses or renal cortical abscesses large enough to be seen on imaging. Emphysematous pyelonephritis may occur, particularly in insulin-dependent diabetics.

Isolated urethral candidiasis can occur in both men and women. In men, it usually results from sexual contact with women with *Candida* vaginitis. In women, it is generally thought to be acquired from extension of *Candida* vaginitis. *Candida* prostatic infection has also been reported. A history of previous antibiotic use has been frequent.

## *Candida* Arthritis, Osteomyelitis, Costochondritis, and Myositis

Sites of localization for hematogenous *Candida* osteomyelitis include the spine (vertebrae and intervertebral disks [Fig. 256.17]), wrist, femur, cervical spine, and costochondral junctions of the ribs, scapula, and proximal humerus.[135,136] Prosthetic joints may also be infected. Blood cultures have usually been negative, and diagnosis has been made by percutaneous needle aspiration of the involved area. In children the long bones are generally affected, whereas in adults the axial skeleton predominates. Spinal involvement may be accompanied by disk infection. Bone infection may require surgical débridement of bone and drainage of contiguous abscess. Osteomyelitis as a result of contiguous spread from the skin has also been documented but is rare.

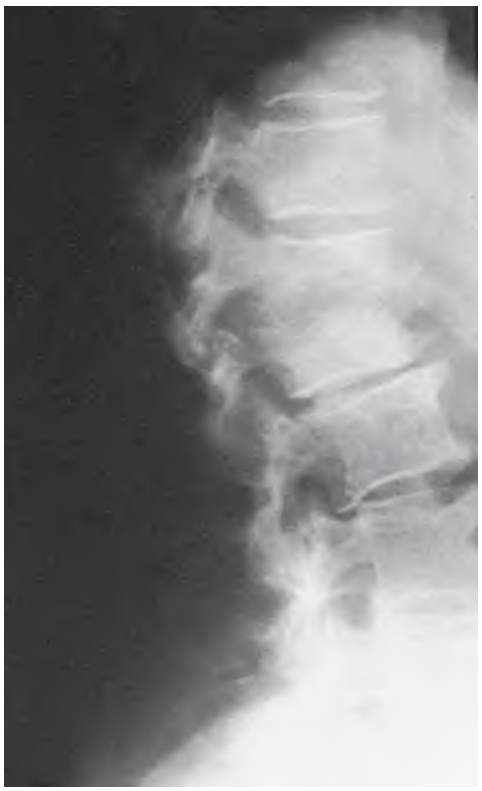

**FIG. 256.17 *Candida* spinal osteomyelitis.** *(From Edwards JE, Turkel SB, Elden HA, et al. Hematogenous candida osteomyelitis.* Am J Med. *1975;59:89–94.)*

*Candida* arthritis of native joints occurs most frequently as a complication of disseminated candidiasis.[135] It can also occur from trauma, surgery, or intraarticular injections of steroids; as a complication of heroin injection; and in patients with rheumatoid arthritis or prosthetic joints, in very-low-birth-weight neonates, or patients with AIDS. Culture of joint fluid may grow only a few colonies, which may be misinterpreted as contamination. In *Candida* arthritis occurring unassociated with disseminated candidiasis, non-*albicans* species have been the most common. Although the majority of cases of *Candida* arthritis have been acute, chronic *Candida* arthritis has been reported, especially in leukemic patients. *Candida* costochondritis can occur from hematogenous seeding, particularly to the sternoclavicular joint cartilage, or as a complication of median sternotomy wound infection.

*Candida* infection of muscle has been described. The majority of patients have been neutropenic, had hematogenously disseminated candidiasis, and had pain in the involved muscle. The organisms may be seen on biopsy of the involved muscle. Cases have also been reported in drug addicts. Generally, the muscle involvement is diffuse. However, a discrete muscle abscess may occur.

## Intraabdominal Candidiasis: *Candida* Infection of Peritoneum, Liver, Spleen, and Gallbladder

*Candida* infection of the peritoneum is a complication of peritoneal dialysis, GI surgery, abdominal trauma, perforation of an abdominal viscus, and organ transplantation.[137–142] Prior antibiotic administration has been an important predisposing factor. The peritoneal process usually remains localized to the abdomen; the incidence of dissemination is approximately 25% in patients acquiring the disease from GI tract perforation or leaking intestinal anastomosis. In patients with peritonitis caused by chronic ambulatory peritoneal dialysis, dissemination is distinctly uncommon.

Other GI organs infected with *Candida* that have been reported include the gallbladder, the liver and spleen, the spleen alone, and the pancreas. Fungus balls may form in the gallbladder and bile ducts.

Hepatosplenic candidiasis has emerged as an important clinical problem in immunocompromised hosts and may require prolonged therapy.[143] Most of these hepatosplenic infections have occurred in severely immunocompromised patients and become manifest during their recovery from neutropenia. Fever may last weeks or months, long after cultures of liver biopsy are culture negative.[143] When the liver and spleen are involved, there is frequently involvement of other organs also, such as the kidney. Computed tomography, ultrasonography, or magnetic resonance imaging may visualize liver, kidney, or spleen abscesses (Fig. 256.18). Shrinkage of lesions on imaging can take weeks or months. Laparoscopic or transcutaneous biopsy can show necrotic lesions with abortive pseudohyphae readily misidentified as *Aspergillus.* The incidence of this entity has diminished in recent years, probably as a function of the increased use of antifungal prophylaxis and empirical therapy.

## Candidemia

Current automated blood culture systems detect *Candida* species after roughly 40 hours of incubation, depending on the system, with *Candida glabrata* taking a day longer. Unlike other *Candida* species, the anaerobic bottle may become positive before the aerobic bottle with *C. glabrata.* Identification of the yeast varies between laboratories but may use MALDI-TOF MS, a multiplex polymerase chain reaction (PCR) panel that includes the five most common *Candida* species (FilmArray Blood Culture Identification; Biofire, Salt Lake City, UT), fluorescence in situ hybridization, or automated or manual biochemical panels or, to identify *C. albicans,* a germ tube test may be used. A PCR-based system that uses magnetic resonance technology to detect the five most common *Candida* species in whole blood within 3 to 5 hours has been marketed (T2Candida Panel; T2 Biosystems, Lexington, MA); susceptibility testing requires culture. Technology in this area is changing rapidly.

Including all species of *Candida* together, they constitute the fourth or fifth most common cause of bloodstream infections in hospitalized patients. Approximately 80% occur in patients with a venous catheter as the likely source. Formation of a biofilm in the lumen and around the catheter tip is thought to contribute to the difficulty in sterilizing the catheter by antibiotic lock therapy or infusion through the catheter or, if there is one, its subcutaneous injection port.[144] Catheter removal is almost always required for cure, but the difficulty in removing implanted catheters in thrombocytopenic patients has prompted delay in selected, hemodynamically stable patients receiving their systemic antifungal through the catheter. Suppurative thrombophlebitis can occur in insertion sites of short peripheral catheters or in arteriovenous fistulae in hemodialysis patients.

## Ocular Candidiasis

*Candida* spp. can enter the eye from the bloodstream (endogenous) or directly into the eye from trauma or surgery (exogenous). Endogenous ocular infection usually begins in the choroid and spreads rapidly to the retina (chorioretinitis) and then may extend into the vitreous humor. Exogenous ocular infection is uncommon but may follow intraocular lens implantation, corneal transplantation, or other procedures that introduce *Candida* into the anterior chamber. The term *endophthalmitis* includes infection in either aqueous or vitreous humor but has been used to include chorioretinitis alone as well (Fig. 256.19).

Through the 1970s there was increased reporting of hematogenous ocular candidiasis and an actual increase in incidence of this complication of candidemia.[145–149] Case reports have described ocular candidiasis as a complication of tattooing, childbirth (in nonimmunocompromised women), abortion, therapy for human immunodeficiency virus (HIV) infection,

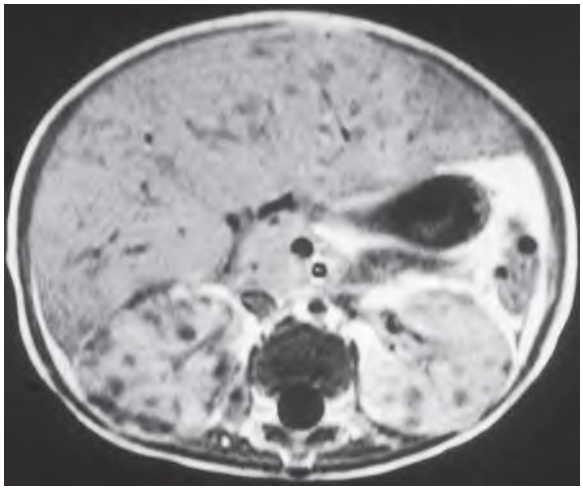

**FIG. 256.18 *Candida* abscess in the liver, kidney, and spleen on magnetic resonance imaging.**

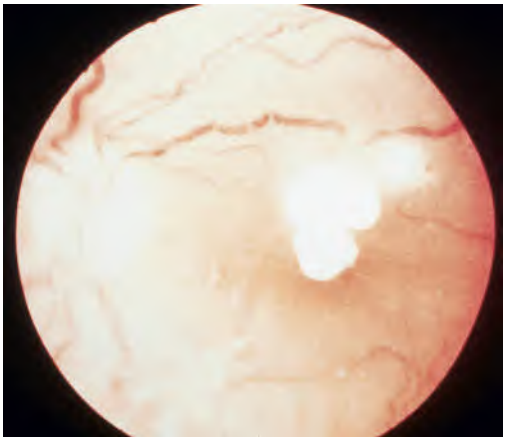

**FIG. 256.19 Advanced hematogenous *Candida* endophthalmitis.** *(From Fishman LS, Griffin JR, Sapico FL, et al. Hematogenous Candida endophthalmitis—a complication of candidemia.* N Engl J Med. *1972;286: 675–681.)*

urinary tract infection, and intravenous administration of contaminated dextrose infusion solution for minor ailments in a rural setting.

### Endogenous Ocular Candidiasis

The bloodstream infection leading to endogenous *Candida* endophthalmitis can be transient or prolonged. Candidemia may result from an intravenous catheter (the most common source), intravenous drug abuse, or a focus in deep tissue. Incidence of ocular lesions in candidemic patients has varied widely, with 2.5%, 8.9%, and 16.2% in three different publications. *C. albicans* is the cause of endogenous ocular candidiasis in 90% or more of patients, with *C. tropicalis* accounting for most of the remainder. *C. glabrata* and *C. parapsilosis,* the second and third most common causes of candidemia after *C. albicans,* seem to have less potential for invading the retina, a feature also observed in experimental ocular candidiasis in rabbits. Early lesions in the retina are not specific and have an appearance similar to lesions from diabetes mellitus, hypertension, HIV, cytoid bodies of systemic lupus erythematosus and chorioretinitis from cryptococcosis, coccidioidomycosis, histoplasmosis, aspergillosis, and other mycoses. The lesions slowly resolve in most patients, if appropriate systemic antifungal therapy is given. Progression into the vitreous begins with vitreous haze, called *vitritis,* and can form masses of neutrophils, lymphocytes, and pseudohyphae floating in the vitreous humor ("fungus balls"). The lesions are not actually "fungus balls," since they are dominantly inflammatory cells surrounding relatively few organisms. A retinal lesion is not always seen, in part because a dense vitritis may obscure the retina, or the lesion may be in the anterior portion of the posterior chamber, such as the ciliary body. Initial symptoms are blurred vision or "floaters," though many patients are too ill or cognitively impaired to relate the symptoms. Deep bulbar pain is a late symptom. The importance of funduscopic examination during the first week of therapy in every candidemic patient, or in patients suspected to have disseminated candidiasis who are not candidemic, is to detect ocular lesions and assure that they do not progress. Early diagnosis depends on dilated funduscopic examination of both eyes, in that about half the patients have lesions in only one eye at the time of diagnosis. Extension of infection into the anterior chamber may be followed by circumlimbal vascular dilation, called a ciliary flush, that may be mistaken for conjunctivitis, particularly in intubated patients with exposure keratitis from inadequate lid closure.

Diagnosis can be confirmed by smear and culture of a vitreous aspirate. When a pars plana vitrectomy is done, the undiluted first specimen, called a "vitreous biopsy," is preferred to the diluted vitrectomy specimen. The latter should be centrifuged and a smear done on the sediment.

### Exogenous Ocular Candidiasis

The indolent appearance of anterior chamber inflammation, with cells and protein in the aqueous humor, may follow intraocular lens implantation, corneal transplantation, other surgery, or trauma. A variety of *Candida* species have been reported. Diagnosis is usually made by smear and culture of fluid aspirated from the aqueous humor.

## "Chronic Candidiasis Syndrome" or "the Yeast Connection"

This entity was popularized by William G. Crooke, MD, in 1979, with the publication of a book written by him entitled, "The Yeast Connection." The entity has been the subject of several lay books describing a multitude of symptoms, generally related to fatigue, GI discomfort, and memory dysfunction (described by some as "brain fog"), thought to be attributable to *Candida* organisms colonizing mainly mucous membrane tissues. Currently, there is considerable information about this disorder on the Internet and a host of different remedies are suggested, as well as support groups for afflicted patients and their families. What would be considered a direct scientific connection between the presence or overgrowth of the organism and these symptoms has not been established to date. Some individuals have claimed amelioration or resolution of their symptoms with various remedies, including special diets; however, the beneficial effects are generally temporary, and the claims of benefit have not been endorsed by the US Food and Drug Administration.[150]

# TREATMENT AND PROPHYLAXIS

## General Comments

Treatment strategies for nearly all forms of *Candida* infections have been reviewed in comprehensive detail in both the United States and Europe for both neutropenic and nonneutropenic patients, pediatric patients, and patients with HIV infection.[151–155] This summary has been formulated from these combined sources and is presented in condensed form in Tables 256.2 to 256.5. Complete dosing recommendations for both adults and pediatric patients will not be discussed herein, but are detailed in the current references.

Granulocyte transfusions have been given for systemic *Candida* infection, but they are not used on a wide-scale basis, and their efficacy has not been clearly established from the limited experience to date. Granulocyte colony-stimulating factor and other cytokines or immunomodulators have not been sufficiently evaluated in clinical settings, but are under investigation, and may be an option in desperate situations.[156]

Antifungal sensitivity testing is being used with significantly increased frequency for directing management of *Candida* infections, especially in refractory cases. The use of susceptibility testing for *Candida* in general has been reviewed[157]; considerable progress has been made by both the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) on developing standardized sensitivity testing. The need for routine sensitivity testing on all isolates has not developed to this point, but work to improve the clinical relevance of specific species and drug breakpoints continues.[158]

For prophylaxis of *Candida* infection in stem cell transplant recipients, fluconazole has remained the drug of choice, with micafungin as an alternative. Prophylaxis in high-risk ICU patients is controversial, with the 2016 Infectious Diseases Society of America (IDSA) guidelines having a weak recommendation for fluconazole with an echinocandin as an alternative[157] (Table 256.2). It should be noted that fluconazole prophylaxis does not provide protection against molds. Table 256.3 summarizes current IDSA recommendations for empirical therapy. Empirical therapy of fever and neutropenia, including the possibility of *Candida* and mold infections, is discussed in Chapter 306.

**TABLE 256.2 *Candida* Prophylaxis**

| POPULATION | RECOMMENDATION |
|---|---|
| Intensive care unit high-risk patients in units with high rates of invasive candidiasis (>5%) | Fluconazole: 400 mg (6 mg/kg) daily |
| Neonates with birth weights <1000 g in neonatal intensive care units with high rates of invasive candidiasis (>10%) | Fluconazole: 3–6 mg/kg twice daily for 6 wk |
| Patients with acute leukemia and remission-induction chemotherapy–induced neutropenia (from induction to end of neutropenia for all regimens) | Fluconazole: 400 mg PO (6 mg/kg) daily<br>*or*<br>Posaconazole tablets: 300 mg PO twice daily for two doses, then 300 mg PO daily<br>*or*<br>Voriconazole: 6 mg/kg PO twice daily for two doses, then 4 mg/kg PO twice daily<br>*or*<br>Caspofungin: 70-mg loading dose, then 50 mg IV daily<br>*or*<br>Micafungin: 100 mg IV daily<br>Itraconazole: 200 mg PO once daily |
| Stem cell transplant recipients | Fluconazole: 400 mg (6 mg/kg) daily<br>*or*<br>Micafungin: 50 mg daily (if concern for molds, or fluconazole side effects)<br>(for all: until engraftment or day 100 and immunosuppressives discontinued) |

An 800-mg (12 mg/kg) loading dose for fluconazole should be given in adults.
*Modified from Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America.* Clin Infect Dis. *2016;62:e1–e50.*

**TABLE 256.3 Empirical Therapy**

| NONNEUTROPENIC PATIENTS | NEUTROPENIC PATIENTS |
|---|---|
| Fluconazole: 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily<br>*or*<br>Caspofungin: 70-mg loading dose, then 50 mg daily<br>*or*<br>Anidulafungin: 200-mg loading dose, then 100 mg daily<br>*or*<br>Micafungin: 100 mg daily<br>(Echinocandins are preferred if there has been previous exposure to azoles or there is a high risk for *Candida glabrata* or *Candida krusei* infection) | LFAMB: 3–5 mg/kg daily<br>*or*<br>Caspofungin: 70-mg loading dose, then 50 mg daily<br>*or*<br>Micafungin: 100 mg daily<br>*or*<br>Voriconazole: 6 mg/kg twice daily for 2 doses, then 4 mg/kg twice daily |
| **Alternatives** | |
| LFAMB, 3–5 mg/kg daily, is an alternative for intolerance or unavailability of other antifungals | Fluconazole: 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily |

*LFAMB,* Lipid formulation of amphotericin B.
*Modified from Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America.* Clin Infect Dis. *2016;62:e1–e50.*

## Systemic Drugs for Candidiasis

### Polyenes

Amphotericin B (AMB) generally remains the cornerstone of therapy for disseminated and deep organ *Candida* infection, especially those infections that may be rapidly fatal or refractory to azoles or to echinocandins. In the overall longitudinal experience of treatment of *Candida* infections, most of the experience has been with amphotericin B deoxycholate (AMB-D). However, lipid formulations of amphotericin B, including liposomal amphotericin B (LAMB) and amphotericin B lipid complex (ABLC), have been approved by regulatory agencies and are used extensively now. While evidence does not exist that LAMB or ABLC is more efficacious than AMB-D for the management of *Candida* infections, their use has become very popular, due mainly to their lower level of renal toxicity.

### Triazoles

The triazoles currently available for the treatment of *Candida* infections include fluconazole, itraconazole, voriconazole, and posaconazole. Isavuconazole is a recently approved, extended-spectrum triazole that has excellent activity against *Candida* species, but is currently undergoing studies in candidemia. All of the triazoles have diminished activity against *C. glabrata, C. auris,* and *C. krusei.* Among the triazoles, fluconazole remains the primary choice, and the majority of experience has been with it. It has excellent oral absorption, which is not affected by food consumption. It is considered the standard of therapy for oropharyngeal candidiasis and esophageal and vaginal infection.[157] It also has high penetration into the cerebrospinal and ocular fluids and the highest level of renal excretion. The aggressiveness for treating patients with candidemia was changed dramatically when fluconazole was found to have equal efficacy to AMB in nonneutropenic patients.[159,160] The considerably less toxicity associated with fluconazole compared to AMB, and the lack of reliable diagnostic criteria for establishing the presence or absence of disseminated candidiasis in candidemic patients, made the risk-benefit ratio of treating highly in favor of treatment rather than watchful waiting. The use of the other triazoles for *Candida* infections is applied mainly to situations in which they may have a specific advantage regarding the susceptibility of an isolate, when fluconazole has failed, or when it is desirable to cover mold infections in addition to treating *Candida.* It does have an indication for prophylaxis of *Candida* infections.

### Echinocandins

Three echinocandins are now approved by regulatory agencies for treatment of *Candida* infections and are the recommended treatment of candidemia in nonneutropenic and neutropenic patients, with fluconazole now indicated as an alternative.[157] The recommended echinocandins are caspofungin, micafungin, and anidulafungin. These drugs have the advantage of lower minimal inhibitory concentrations (MICs) for a broader spectrum of species of *Candida,* including *C. glabrata* and *C. krusei. C. parapsilosis* has a higher MIC, but echinocandins are now considered to be active for this species and the MIC cutoff has been adjusted. The currently marketed echinocandins have the disadvantage of not being available in an oral preparation to date.

The echinocandins have had a favorable toxicity profile. They have highly comparable pharmacodynamics. In patients with moderate to severe hepatic dysfunction, a dose reduction is recommended for caspofungin, but not for the others. In candidemia, the three echinocandins are considered to have equal efficacy. Many clinicians prefer to use these drugs as first-line therapy for patients with candidemia until the species of *Candida* is identified, especially if their recovery of *C. glabrata* is at high rates in their institutions. However, a retrospective analysis of initial treatment of *C. glabrata* sepsis found no difference in mortality whether fluconazole or an echinocandin was used.[161] Catheter removal may be as important as initial choice of antifungal.[150]

With increased echinocandin use in hospitals, *C. albicans* and *C. glabrata* strains with mutations in the *FKS1* and *FKS2* genes and decreased echinocandin susceptibility are being encountered, although this remains a rare event.[142,162,163] Most, but not all, of the patients with these strains have been receiving echinocandins. Whether patients infected with these strains are more likely to fail echinocandin therapy is controversial at present, largely because so many other clinical factors influence the outcome of deep candidiasis.

### Flucytosine

Flucytosine, also known as 5-fluorocytosine (5-FC), is virtually never used alone for management of *Candida* infections. It is sometimes used in combination with AMB-D, ABLC, or LAMB for *Candida* endocarditis, meningitis, hepatosplenic candidiasis, and occasionally progressive endophthalmitis. However, there are no controlled studies demonstrating an advantage with the combination therapy, and it is a toxic agent with respect to bone marrow depression. It is rarely ever used currently. It has broad-spectrum activity against the *Candida* species, except *C. krusei.*

## Candidemia in Nonneutropenic Patients

The decision to administer treatment for candidemia has been discussed previously in this chapter, and the strong consensus that all candidemic patients should be treated with antifungals was described. For nonneutropenic patients, an echinocandin is recommended as initial therapy.[152] If the isolate is susceptible to fluconazole and the patient is clinically stable, the echinocandin should be switched to fluconazole. Although voriconazole is effective for candidemia, it is recommended primarily when additional mold coverage is desired or as step-down oral therapy for candidemia due to *C. krusei* or cases due to voriconazole-susceptible *C. glabrata.* A lipid formulation of AMB is an alternative if the patient is intolerant to other antifungals or has an isolate resistant to other antifungals.[152] Although controversial, removal or at least changing of intravenous lines is recommended.

## Candidemia in Neutropenic Patients

For most neutropenic patients, an echinocandin is recommended for initial therapy.[152] A lipid formulation of AMB is an effective but less well tolerated alternative to echinocandins. For patients less ill, and in whom no fluconazole prophylaxis has been given, fluconazole is an alternative. Fluconazole can be used as a step-down therapy in clinically stable patients who had a fluconazole-susceptible isolate and have cleared their blood cultures.[152] For *C. krusei* infections, an echinocandin is preferred, but LAMB, ABLC, or AMB-D or voriconazole may be used. Continuation of treatment for 2 weeks beyond the documentation of the clearance of the neutropenia is recommended. If possible, intravenous lines should be removed or changed. Granulocyte colony-stimulating factor–mobilized granulocyte transfusions may be used if prolonged neutropenia is expected, although no conclusive benefit has been demonstrated.

## *Candida* Infections of the Cardiovascular System

Once the diagnosis of *Candida*-caused endocarditis is made, the procedure of choice is to initiate LAMB, with or without 5-FC, or an echinocandin.[121,152,164] If an echinocandin is chosen, the 2016 IDSA guidelines recommend using an increased dose, although the evidence was said to be of low quality (Table 256.4).[152] Valve replacement has long been recommended to be performed as soon as possible, although this has not been shown to reduce the high mortality.[121,164] The desirability of waiting for an effect of antifungal therapy before surgery is unknown, and currently it is recommended to perform surgery as soon as it is logistically feasible. After surgery, antifungal therapy should be given for at least 6 to 10 weeks because of the significant incidence of relapse. If there is a perivalvular abscess, or other evidence of residual *Candida,* extended suppressive therapy beyond the 6 to 10 weeks should be administered. Some patients with *Candida* endocarditis have had relapses years after surgery. Patients with *Candida* endocarditis should be monitored carefully for a minimum of 2 years postoperatively. Fluconazole is commonly used as long-term suppressive therapy. Occasional cases of successful nonsurgical therapy are reported in both adults and children.[165,166]

For prosthetic valve endocarditis, the recommendations are the same as for native valve disease. Suppressive therapy should be lifelong if it is not feasible to remove the valve. For other forms of cardiovascular infection, such as pericarditis or myocarditis, in general, prolonged administration of an echinocandin is recommended. For suppurative thrombophlebitis, incision and drainage of the infected vein and removal of the catheter should be done in combination with administration of the antifungal. For pacemaker and defibrillator infections, removal of the device with administration of antifungals for similar durations as those used for endocarditis is recommended. If only the generator or pocket is infected, 4 weeks of therapy following removal of the device is recommended, whereas, if the wire is infected, at least 6 weeks of therapy following the wire removal is recommended. For ventricular assist devices that cannot be removed, treatment is the same as for endocarditis.

## Central Nervous System *Candida* Infection

LAMB, with or without 5-FC therapy, is the recommended treatment for both meningitis and diffuse parenchymal infection.[152] This recommendation is based entirely on observational studies. There is experimental evidence that LAMB may have a higher brain concentration than other formulations.[167] The clinical significance of this evidence remains to be established, but most experts use LAMB in documented CNS infection (authors' observations). In exceptionally severe cases, intrathecal antifungals should be considered. Removal of infected ventricular devices is recommended if feasible. If not, they should be changed if possible. Step-down therapy with fluconazole (400 to 800 mg daily) can be used once infection is controlled.

**TABLE 256.4 *Candida* Treatment Strategies**

| INDICATIONS | PRIMARY TREATMENT | ALTERNATIVE | COMMENTS |
|---|---|---|---|
| Candidemia | | | |
| Nonneutropenic patients | An echinocandin[a] | Fluconazole: 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily<br>*or*<br>LFAMB[b]<br>*or*<br>Voriconazole: 6 mg/kg twice daily for 2 doses, then 4 mg/kg twice daily | Fluconazole for patients who are clinically stable and have no prior azole exposure. Fluconazole can also be step-down therapy for patients who have susceptible isolates and blood cultures converted to negative. |
| Neutropenic patients | An echinocandin[a]<br>*or*<br>LFAMB[b] | Fluconazole: 800-mg (12-mg/kg) loading dose, then 400 (6 mg/kg) daily<br>*or*<br>Voriconazole: 6 mg/kg twice daily for 2 doses, then 4 mg/kg twice daily | An echinocandin is preferred. Fluconazole is step-down therapy for clinically stable patients with susceptible isolates and negative blood cultures.<br>Voriconazole is used when additional coverage for mold is preferred. |
| Cardiovascular endocarditis | LFAMB[b] with or without 5-FC, 25 mg/kg qid<br>*or*<br>An echinocandin[c] | Step-down to fluconazole 400–800 mg (6–12 mg) daily for susceptible organism, patient clinically stable, negative blood cultures | Valve replacement is strongly recommended. |
| Central nervous system | LFAMB[b] with or without 5-FC, 25 mg/kg qid for several weeks | Fluconazole: 400–800 mg (6–12 mg) daily for susceptible organism after clinical improvement | Removal of prosthetic devices is strongly recommended. |
| Urinary tract | | | |
| Asymptomatic candiduria | Not indicated except in neonates and instrumentation of infected urinary tract | | |
| Symptomatic cystitis | Fluconazole: 200 mg (3 mg/kg) daily for 2 wk | AMB-D: 0.3–0.6 mg/kg for 1–7 days<br>*or*<br>5-FC: 25 mg/kg qid | Bladder irrigation with AMB-D, 50 mg/L, can be used for fluconazole-resistant species. |
| Renal parenchymal candidiasis | Fluconazole: 200–400 mg (3–6 mg/kg) daily for 2 wk<br>*or*<br>An echinocandin[a] | LFAMB[b] or AMB-D: 0.5–0.7 mg/kg daily with or without 5-FC 25 mg/kg qid[d]<br>*or*<br>5-FC alone for 2 wk | |
| Ocular: chorioretinitis with or without vitritis | Fluconazole: 400–800 mg (6–12 mg/kg) daily<br>*or*<br>Voriconazole: 6 mg/kg IV q12h for 2 doses, then 4 mg/kg IV q12h | LFAMB: 3–5 mg/kg IV daily, with or without 5-FC, 25 mg/kg qid | Intravitreal AMB-D, 5–10 µg, or voriconazole, 100 µg. Often vitrectomy is used if 3–4+ vitritis or macular involvement is present. |

[a]Once-daily micafungin, 100 mg; caspofungin, 70-mg loading, then 50 mg; or anidulafungin, 200-mg loading, then 100 mg.
[b]Liposomal amphotericin B (AmBisome), 3–5 mg/kg daily, or amphotericin B lipid complex (Ablecet), 5 mg/kg daily.
[c]For initial therapy of *Candida* endocarditis, the 2016 guidelines[157] recommend caspofungin, 150 mg; micafungin, 150 mg; or anidulafungin, 200 mg once daily.
[d]Strength of recommendations for 5-FC is weak.
*AMB-D,* Amphotericin B deoxycholate; *5-FC,* 5-fluorocytosine; *LFAMB,* lipid formulation of amphotericin B.
*Modified from references 150–152, 154, 155, 157, and 162.*

## Intraabdominal Candidiasis, *Candida* Peritonitis, Gallbladder Infection

The topic of when to begin therapy in patients with an abdominal drain that grows *Candida* on culture and the controversy regarding therapy have been discussed and reviewed in detail.[138,168] In general, there has been a lowering in the threshold for treating such patients, but the impact of treatment on their clinical outcome remains to be fully defined. In most instances, recovery of *Candida* from existing drains does not require treatment, while recovery of the organism from "freshly placed" drains does require therapy. Discovery of *Candida* in ascites from an undrained abdomen usually means that therapy is required. Hematogenous dissemination from the peritoneum can occur.

The topic of empirical therapy for nonneutropenic patients in the ICU has been reviewed extensively.[157] For those patients at high risk for intraabdominal infection (probable leaking intestinal anastomosis, fever with no known source, surrogate markers for invasive candidiasis, positive cultures from nonsterile sites), empirical therapy with the same recommendations for candidemia as in nonneutropenic patients should be used. Patients who do not have subsequent evidence of candidiasis and have negative cultures after 4 to 5 days should have the antifungal therapy stopped. Source control, with drainage of potential intraabdominal abscesses, is pivotal.

For chronic disseminated (hepatosplenic) candidiasis, LAMB, ABLC, or an echinocandin is recommended.[152] After several weeks of treatment, step-down therapy with fluconazole can be considered in patients who are stable and no longer neutropenic. Adjuvant corticosteroid therapy has been advocated for patients with prolonged and disabling fever.[56]

*Candida*-caused cholecystitis may respond to an echinocandin, a lipid formulation of AMB, or fluconazole.[169] In candidiasis of the gallbladder or biliary tract, drainage may be necessary[170] in addition to antifungal therapy. *Candida* may complicate necrotizing pancreatitis and has been an increasing cause of pancreatitis. This entity should be treated with an echinocandin until the patient is stable. *Candida* pancreatic abscess has been successfully drained with computed tomography–guided percutaneous aspiration in addition to systemic antifungal therapy.

## Urinary Candidiasis

Postcatheterization asymptomatic candiduria usually resolves without specific antifungal therapy. Current recommendations are to not treat it, unless the patient is symptomatic or in a group at high risk for dissemination. These groups include symptomatic patients, renal transplant patients, very-low-birth-weight infants, patients who are undergoing urinary tract instrumentation, and patients with obstruction of the urinary tract. If the goal is to treat, relief of obstruction and removal of urinary stents and catheters are the primary goals. Fluconazole is the only azole with urine bioactivity and would be reasonable for susceptible *Candida* species. Local amphotericin (a solution of 50 mg of amphotericin B in 1 L of sterile water infused at 40 mL/hr through a Foley catheter) was used extensively in the past but has become unpopular due to the efficacy of oral fluconazole (200–400 mg/day for 7–14 days). However, it may be useful still for patients with resistant *Candida,* especially *C. glabrata.* For fluconazole-resistant isolates, LAMB or AMB-D with or without 5-FC or voriconazole is an alternative.[171] Treatment should be continued until cultures are negative and the patient is asymptomatic. Selected patients may require irrigation with AMB through nephrostomy tubes placed directly in the collecting systems. If fungus balls form in the urinary tract, they require surgical removal. For papillary necrosis or renal abscess, an echinocandin or intravenous LAMB or ABLC is indicated. However, oral fluconazole may be an alternative in patients with mild to moderate infection. 5-FC is another alternative, but is less popular, especially in patients with renal insufficiency, and resistance develops rapidly.

Eradication of candiduria in patients who require a persistent indwelling Foley catheter is unnecessary, with the exception of patients undergoing bladder or prostate surgery. A placebo-controlled trial found that fluconazole at 200 mg/day for 14 days resulted in eradication of the candiduria, but there was a high rate of recurrence, suggesting the futility of antifungal therapy.[172] A large observational study has also verified the futility of antifungal therapy.[173]

## Mucocutaneous Candidiasis

Oral thrush should be treated with topical agents whenever possible (Table 256.5). A 7- to 14-day course of clotrimazole 10-mg oral troches given five times per day or a miconazole mucoadhesive 50-mg tablet applied once daily for 7 to 14 days to the gum on the canine fossa is recommended.[152] For mild disease, nystatin suspension (100,000 U/mL), swish and swallow, 4 to 6 mL four times daily or 1 to 2 nystatin pastilles (200,000 U each) dissolved slowly in the mouth four times daily can be used. For more severe or refractory disease, oral fluconazole at 100 to 200 mg daily is recommended. For cases that are refractory to fluconazole, itraconazole solution and posaconazole suspension or voriconazole are alternatives, although control of HIV with antiretroviral therapy is usually sufficient. Therapy for denture sore mouth is the same as that for thrush, with the addition of meticulous cleaning of the dentures and correction of ill-fitting plates. Angular chelitis, which is frequently associated with denture sore mouth, should be treated with either topical clotrimazole or miconazole cream on the corners of the mouth.

The diagnosis of *Candida* esophagitis is best made on esophagoscopy but less reliably can be made on the basis of the presence of oropharyngeal thrush and symptoms of esophagitis in patients with AIDS or cancer. Topical therapy with clotrimazole troches or nystatin suspension usually fails. Treatment with fluconazole is preferred.

For refractory esophagitis, itraconazole solution is considered the first-choice strategy. Posaconazole suspension and voriconazole are alternatives. If necessary, an intravenous echinocandin may be used. In refractory esophageal infections, low-dose (10–20 mg/day) AMB has been successful. Long-term suppressive therapy may be necessary in patients with AIDS who have not responded to combination antiretroviral therapy.

*Candida* intertrigo is most successfully managed by decreasing the moisture of the involved area and by the application of topical azole cream or lotions, such as miconazole or clotrimazole. Management of *Candida* diaper rash has been successful with nystatin powder or cream in combination with a corticosteroid, such as Mycolog-II cream. The same agents used for diaper rash are generally successful for pruritus ani.

Uncomplicated *Candida* vaginitis responds to short courses of topical or oral therapy in the vast majority of patients. The following regimens used from 1 to 7 days are considered comparable: over-the-counter clotrimazole, butoconazole, miconazole, and tioconazole ointment; and terconazole (prescription only). For uncomplicated cases, oral fluconazole (150 mg once) is effective.[157] Other regimens include nystatin (100,000 units daily for 1–2 weeks) and boric acid (600 mg in a gelatin capsule once daily vaginally for 14 days).[174] For severe acute *Candida* vulvovaginitis, oral fluconazole (150 mg every 72 hr for 2–3 doses) is recommended.[152] Recurrent *Candida* vaginitis requires eradication of causal factors as much as possible. Then treatment for 2 weeks with topical or oral azoles should be used, followed by 6 months of fluconazole; 150 mg orally per week is recommended.[157,175]

*Candida*-caused paronychia is best managed by preventing immersion of the hands in water as much as possible and applying clotrimazole or miconazole cream twice daily. Drainage of any paronychial pus is also important.

## Chronic Mucocutaneous Candidiasis

Topical therapy with azoles or polyenes applied to skin and mucous membranes achieves only slight improvement when used to treat acute infection and is best suited as step-down suppressive treatment in patients already treated successfully with a systemic antifungal. Azole, intravenous AMB, or echinocandin therapy has been effective, but nearly all patients relapse when treatment stops. Oral 5-FC is typically not effective. The most important advance in the therapy of this disease is systemically administered azoles: fluconazole, voriconazole, or posaconazole.[105] Fluconazole is recommended as the primary therapy.[171] Numerous reports illustrate successful treatment, although therapy for months or years may be necessary. Development of azole resistance with long-term therapy is a common problem affecting up to 40% to 50% of patients. In these cases, initial induction treatment with an echinocandin is necessary. Therefore initial induction for at least 4 weeks with fluconazole or an echinocandin (if treating an azole-resistant strain), followed by

**TABLE 256.5 *Candida* Treatment: Other Indications**

| INDICATION | PRIMARY TREATMENT | ALTERNATIVE | COMMENT |
|---|---|---|---|
| Peritonitis | An echinocandin[a]<br>*or*<br>Fluconazole: 400–800 (6–12 mg/kg) daily<br>*or*<br>Voriconazole: 6 mg/kg q12h IV or PO, then 4 mg/kg q12h | LFAMB: 3–5 mg/kg daily | *Candida* recovered from an existing drain does not necessarily indicate peritonitis. Drains may become colonized. *Candida* from "freshly placed" drains usually requires treatment.<br>Infected peritoneal dialysis catheters must be removed. |
| Chronic mucocutaneous candidiasis | Fluconazole<br>*or*<br>Itraconazole<br>*or*<br>Posaconazole | LFAMB: 3–5 mg/kg daily<br>*or*<br>An echinocandin (standard doses) | In severe cases, LFAMB may be necessary. After induction with a systemic antifungal for at least 4 wk, step-down suppressive therapy can be used with topical polyenes. |
| Oral thrush (mucocutaneous candidiasis) | Clotrimazole troches: 10 mg, dissolved slowly in mouth 5 times daily<br>*or*<br>Miconazole mucoadhesive buccal tablet: 50 mg placed on gum near canine tooth once daily for 7–14 d<br>*or*<br>Nystatin suspension: 100,000 U/mL, swish and swallow 4–6 mL 4 times daily; *or* 1–2 nystatin pastilles: 200,000 U each, dissolved slowly in mouth qid for 14 d<br>*or*<br>Fluconazole: 100–200 mg daily | Itraconazole solution: 200 mg daily<br>*or*<br>Posaconazole oral suspension: 100 mg bid on day 1, then 100 mg daily<br>*or*<br>Voriconazole: 200 mg bid<br>*or*<br>IV echinocandin[a]<br>*or*<br>AMB-D: 0.3 mg/kg daily | IV agents are reserved for refractory cases. |
| *Candida* esophagitis | Fluconazole: 200–400 mg IV or PO (3–6 mg/kg) daily for 14–21 days<br>*or*<br>An echinocandin[a] for 14–21 d | Itraconazole oral solution: 200 mg daily for 14–21 d<br>*or*<br>Posaconazole suspension: 400 mg bid for 14–21 d<br>*or*<br>Voriconazole: 200 mg bid<br>*or*<br>AMB-D: 0.3–0.7 mg/kg daily | IV agents are for refractory patients. |
| *Candida* vulvovaginitis | Multiple topical agents are available<br>*or*<br>Fluconazole: 150-mg single dose for mild disease; for severe acute vulvovaginitis, repeat 150 mg q72h for 2–3 doses | *Candida glabrata* unresponsive to azoles; boric acid gel capsule: 600 mg daily for 14 d | Fluconazole, 150-mg single dose weekly, has been used for recurrent disease. |

[a]Once-daily micafungin, 100 mg; caspofungin, 70-mg loading dose, then 50 mg; or anidulafungin, 200-mg loading dose, then 100 mg.
*AMB-D,* Amphotericin B deoxycholate; *LFAMB,* lipid formulation of amphotericin B.
*Modified from references 150–152, 154, 155, 157, and 162.*

chronic suppressive topical polyene administration, offers the best outcomes while decreasing the chances of resistance (authors' experience). Concomitant ringworm infection of the skin or nails is common and may benefit from terbinafine therapy.

## Ocular Candidiasis

Treatment of *Candida* endophthalmitis has been reviewed in detail.[148] *Candida* chorioretinitis usually responds to systemic antifungal drugs in the absence of significant (grade 3–4 of 5) vitritis (see Table 256.4). Vitritis requires both systemic and intravitreal antifungals, a decision always made in consultation with an ophthalmologist. Intravitreal injections of conventional AMB (5 to 10 μg) or intravenous formulations of voriconazole (100 μg) have been used (see Chapter 114). When intravitreal therapy is done intraoperatively at the time of vitrectomy, the antifungal is injected into the vitreous cavity at the end of the procedure. Intravitreal injections may need to be repeated if infection is not controlled, although the antifungal may increase the vitritis transiently.

Exogenous ocular candidiasis in the anterior chamber is treated systemically, though intracameral, subtenon, or subconjunctival antifungal injections or a topical antifungal is sometimes given for refractory cases. Antifungal eyedrops are given every 2 hours initially, to facilitate diffusion into the anterior chamber.

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*The complete reference list is available online at Expert Consult.*


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# 257 *Aspergillus* Species

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## SHORT VIEW SUMMARY

### Definition
- Infection is caused by hyaline mold *Aspergillus*.
- Syndromes range from colonization, such as fungus ball due to *Aspergillus* (aspergilloma); allergic responses to *Aspergillus*, including allergic bronchopulmonary aspergillosis; and semiinvasive or invasive infections, from chronic necrotizing pneumonia to invasive pulmonary aspergillosis and other invasive syndromes.

### Epidemiology
- Highest incidence of infection in patients undergoing hematopoietic stem cell transplant or solid-organ transplantation
- Infection more likely in patients with extensive immunosuppression or those with relapse or recurrence of underlying malignancy
- Improved survival with early diagnosis and newer therapies, but mortality rates in severely or persistently immunosuppressed patients is substantial

### Microbiology
- Culture-based diagnosis useful to establish specific diagnosis
- *Aspergillus* spp. complexes with distinct antifungal susceptibilities so that culture-based diagnosis is clinically relevant
- Molecular analysis required to establish species-level identity
- Increasing rates of antifungal resistance are reported in some settings.

### Diagnosis
- Proven infection is established by culture of the organism.
- Assay of biomarkers, such as galactomannan (GM) and β-D-glucan, and polymerase chain reaction are useful as criteria for establishing a probable diagnosis but are not diagnostic alone
- Serial assessment of biomarkers may be useful for measuring response to therapy.

### Therapy
- Voriconazole or isavuconazole is recommended for primary therapy in most patients (see Table 257.4).
- Liposomal amphotericin B can be used as primary therapy in patients in whom voriconazole or isavuconazole is not tolerated or contraindicated because of drug interactions or other reasons.
- Alternative agents for salvage therapy include amphotericin B lipid complex, the echinocandins (caspofungin, micafungin, or anidulafungin), posaconazole, or itraconazole.
- Combination therapy of voriconazole plus an echinocandin is not recommended for routine use, but there may be some subgroups of patients, such as those with early diagnosis of infection based on detection of GM or those with failure or primary therapy with a single agent, who may benefit from such an approach.

### Prevention
- Antifungal prophylaxis with posaconazole or possibly voriconazole is used for high-risk patients
- Risk-benefit ratio of prophylaxis in individual patients should be considered.
- Infection control is important to reduce risk in hospitalized patients, but long duration of risk (>180 days) in high-risk hematopoietic stem cell transplant (HSCT) or solid-organ transplantation patients makes community-acquired infection likely.

Invasive aspergillosis (IA) remains a major cause of morbidity and mortality in the immunosuppressed population. This infection is caused by *Aspergillus*, a hyaline mold, and is responsible for a variety of noninvasive or semiinvasive conditions. These syndromes range from colonization, such as a fungus ball due to aspergillosis (also known as aspergilloma); allergic responses to *Aspergillus*, including allergic bronchopulmonary aspergillosis (ABPA); and semi-invasive or invasive infections, from chronic necrotizing pneumonia to invasive pulmonary aspergillosis and other invasive syndromes.

Aspergillosis syndromes are a major focus in clinical mycology due to the dramatic increase in the number of patients affected and the associated morbidity and mortality of this infection.[1] The increased number of *Aspergillus* infections has coincided with the growing immunosuppressed population. Patients with established IA have poor outcomes.[2-5] Successful therapy depends not only on an early diagnosis but also on reversal of underlying immune defects. Even when therapy is begun promptly, outcomes are often poor, particularly in patients with disseminated or central nervous system (CNS) disease and in those who remain profoundly immunosuppressed.[1] New diagnostic approaches and new management strategies have been established. In this chapter clinical mycology, epidemiology, pathogenesis, clinical presentation, diagnosis, treatment, and prevention of aspergillosis are described.

## MYCOLOGY

The genus *Aspergillus* was first recognized in 1729 by Micheli, in Florence, who noted the resemblance between the sporulating head of an *Aspergillus* sp. and an aspergillum used to sprinkle holy water.[6] In 1856 Virchow published the first complete microscopic descriptions of the organism.[7] *Aspergillus flavus* was formally named by Link in 1809.[8] Thom and Church first classified the genus in 1926 with 69 *Aspergillus* spp. in 11 groups. The term "group" is now more correctly referred to as "section," but this reporting is not commonplace in clinical mycology laboratories.[9] Because phenotypic methods and internal transcribed spacer sequencing identify *Aspergillus* isolates within a section and not individual species, it has been recommended that isolates should be reported as members of a "species complex."[10] With the recent use of molecular techniques to characterize pathogenic fungi, aspergilli have now increased dramatically to include more than 250 species in 8 subgenera (*Aspergillus*, *Fumigati*, *Circumdati*, *Candidi*, *Terrei*, *Nidulante*, *Warcupi*, and *Ornati*) that are subdivided into multiple sections and species complexes.[10,11]

Most species of *Aspergillus* reproduce asexually, but a teleomorph (or sexual form) has been identified for a number of species, including pathogenic species such as *Aspergillus nidulans* (teleomorph, *Emericella nidulans*); *A. flavus (Petromyces flavus); A. udagawae (Neosartorya udagawae);* and the most common pathogen, *A. fumigatus (Neosartorya fumigata);* and many others.[12–14] Even though the correct taxonomic nomenclature would rename these organisms using the sexual form, generally the generic name *Aspergillus* has been retained to simplify nomenclature regardless of their teleomorphs, rather than separating the organisms into unfamiliar species based on discovery of a sexual state.[15] As with other pathogenic fungi, the taxonomy of *Aspergillus* has undergone extensive reclassification with use of molecular studies,