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Fungal Infections of the Immunocompromised Host: Clinical and Laboratory Aspects

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INTRODUCTION

Previously, opportunistic fungal infections were most often seen in patients with hematological disorders, in those who had undergone extensive surgical procedures, and in those receiving high doses of corticosteroid, cytotoxic, or immunosuppressive therapy. Currently, a dramatic increase in fungal infections, particularly candidiasis and cryptococcosis, is being seen in patients with the acquired immunodeficiency syndrome (AIDS). When one considers these increasing groups of patients who are likely to acquire an opportunistic fungal infection, the situation presents a unique challenge to the clinician and laboratorian.

The clinician must be familiar with the variety of clinical manifestations that may occur with opportunistic fungal infections in the immunocompromised patient. Fever is often the first indication of infection; this may be followed by signs and symptoms which suggest involvement of a specific organ system. Pulmonary disease occurs in many patients; cough (may be nonproductive in patients with granulocytopenia), shortness of breath and chest pain along with physical signs of tachypnea and auscultatory findings (rhonchi or decreased breath signs), and abnormal laboratory findings (arterial hypoxemia, decreased diffusion capacity with pulmonary function tests) may be observed.

Opportunistic fungal infections of the skin or musculoskeletal system are usually associated with disseminated disease. Head and neck infections may be self-limited (i.e., oral candidiasis or thrush) or rapidly fatal (i.e., ocular or sinus infections which may spread to involve the brain). Gastrointestinal infections most often involve the esophagus and rarely the small bowel and colon. Cardiovascular disease is usually the result of disseminated infection. Genitourinary disease may result from disseminated disease (renal parenchymal disease) or chronic indwelling urinary catheters (cystitis and pyelonephritis). Central nervous system infections may occur as a result of dissemination or direct extension from infected facial sinuses.

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TABLE 1. Common clinical specimens from which opportunistic fungal pathogens can be recovered

Suspected pathogens	Clinical specimen source							
	Blood	Bone marrow	Central nervous system	Eye	Respiratory tract	Skin and mucous membranes	Multiple systemic sites	Urine
Candida spp.	X		X	X	X	X	X	X
Cryptococcus neoformans	X	X	X	X	X	X	X	X
Aspergillus spp.			X	X	X		X	
Zygomycetes (*Mucor, Rhizopus* spp.)			X	X	X	X	X	
Trichosporon beigelii	X				X	X	X	X
Penicillium spp.				X	X	X		X
Fusarium spp.	X			X	X	X	X	X
Pseudallescheria boydii	X		X	X	X	X	X	
Drechslera, Bipolaris, and *Exserohilum* spp.			X	X	X	X	X	

Specific fungal pathogens are known to be associated with specific case scenarios. Granulocytopenia has a significant association with many fungi, especially *Aspergillus* species. Sinus infections caused by the zygomycetes are often associated with diabetic ketoacidosis. Certain dimorphic fungi are associated with opportunistic infections, particularly in those patients who have resided or visited in areas where the organisms, i.e., *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*, are ubiquitous. In addition, patients having granulocytopenia and those having lymphoproliferative disorders or lymphocyte dysfunction or quantitative depletion (AIDS) are subject to the acquisition of opportunistic fungal infections. Patients who present with opportunistic fungal infections and who are not known to be immunocompromised might have an immunologic investigation to include testing for antibodies to human immunodeficiency virus (HIV), the causative agent of AIDS.

The clinician must submit appropriate specimens to the laboratory to confirm and, in many instances, make the diagnosis of opportunistic fungal infection. Most often stains and cultures of tissue biopsies are necessary to establish a primary diagnosis. Blood cultures should be performed on all patients since this source may most rapidly detect the etiologic agent(s) of disseminated disease. Other body fluids including urine, cerebrospinal fluid, pleural fluid, peritoneal fluid, and synovial fluid, should be submitted for culture if the clinical signs and symptoms suggest infection of these sources (Table 1). In addition, appropriate fungal serologic tests may be helpful in making the diagnosis.

The clinical microbiology laboratory should provide and have experience with methods used for the rapid detection and identification of the fungi associated with infections of the immunocompromised patient. In addition, good communication between the laboratorian and clinician must exist to ensure prompt reporting and interpretation of results.

General Discussion of Laboratory Methods

Measures useful for the rapid detection and identification of fungi include microscopic demonstration of fungal elements in a clinical specimen, detection of fungal (cryptococcal) antigens, when appropriate, and recovery of the etiologic agent by using suitable culture media, along with rapid screening and confirmatory testing for the identification of an etiologic agent.

Perhaps the most rapid and useful of the methods available is the microscopic detection of fungal elements in clinical specimens. It is of interest to note that this may be accomplished in laboratories other than microbiology, such as the hematology or cytology laboratory (Table 2). Therefore, it is necessary that laboratories involved with the microscopic screening of specimens be familiar with the characteristic microscopic morphologic features of the fungi as related to their own unique laboratory setting.

The potassium hydroxide (KOH) preparation is the most widely used method for the detection of fungal elements. Basically, samples of a clinical specimen, usually body fluid, and 10% KOH are placed on a microscope slide and gently heated. Background debris and artifact sometimes make interpretation of the slide difficult and may decrease the sensitivity of detection; however, when positive, this method may provide the earliest evidence of a fungal infection for the clinician. Currently, a fluorescent brightener, Calcofluor white, is recommended for use with the KOH preparation (51). This reagent fluoresces upon excitation with ultraviolet light and stains fungi, causing them to exhibit fluorescence which can be detected microscopically. Tissue can also be stained with Calcofluor white, and results are immediately available. This method exhibits the same sensitivity as the KOH preparation, but allows for easier and faster detection of fungal elements (C. D. Horstmeier and G. D. Roberts, Abstr. Annu. Meet. Am. Soc. Microbiol. 1985, F82, p. 378). Slides stained with Calcofluor white can also be examined by bright-field or phase-contrast microscopy.

The Gram stain used in the bacteriology laboratory is useful for the detection of yeasts such as *Candida* spp. and *Cryptococcus neoformans* and hyphal elements of fungi such as *Aspergillus fumigatus* and others. The Wright or Giemsa stain performed in the hematology laboratory will allow one to detect *H. capsulatum* in bone marrow or peripheral blood smears. The Papanicolaou stain used in the cytology laboratory for the detection of malignant cells in respiratory tract secretions also detects fungi such as *B. dermatitidis*, *Cryptococcus neoformans*, *Coccidioides immitis*, and the hyphae of *Aspergillus* and the zygomycetes, including *Rhizopus* and *Mucor* spp. A brief discussion of methods is presented in Table 2.

Specific histologic stains including the methenamine silver and periodic acid-Schiff stains are used for the detection of fungi in tissues, body fluids, and exudates. Both can be processed within 0.5 h, and slides can be observed by the pathologist, technologist, microbiologist, and, in some instances, the infectious disease specialist.

Most methods used for the rapid detection of fungal antigens are available in research laboratories; however, the latex test for cryptococcal antigen is commercially available

TABLE 2. Characteristics of methods available for direct detection of fungi in clinical specimens[a]

Method	Use	Time required	Advantages	Disadvantages
Calcofluor white	Detection of fungi	1 min	Can be mixed with potassium hydroxide; detects fungi rapidly due to bright fluorescence	Requires use of a fluorescence microscope; background fluorescence prominent, but fungi exhibit more intense fluorescence; vaginal secretions difficult to interpret
Gram stain	Detection of bacteria	3 min	Commonly performed on most clinical specimens submitted for bacteriology and will detect most fungi, if present	Some fungi stain well; however, others, e.g., *Cryptococcus* sp., stain weakly in some instances
India ink	Detection of *Cryptococcus neoformans* in CSF	1 min	When positive in CSF, it is diagnostic for meningitis	Positive in <50% of cases of meningitis; not reliable
Cryptococcal antigen	Detection of *C. neoformans* antigens in CSF or serum	40 min	Extremely sensitive method for detection of meningeal cryptococcosis; titers may have prognostic value	False-positive results can occur in patients with rheumatoid factor; interference can be removed with pronase treatment; positive results also found in the presence of *T. beigelii* antigenemia and may be helpful in the diagnosis of *T. beigelii* infection
Potassium hydroxide	Clearing of specimen to make fungi more readily visible	5 min; if clearing is not complete, an additional 5–10 min is necessary	Rapid detection of fungal elements	Experience required since background artifacts are often confusing; clearing of some specimens may require an extended time
Methenamine silver stain	Detection of fungi in histologic section	1 h	Best stain to detect fungal elements	Requires specialized staining method not usually readily available to microbiology laboratories
Papanicolaou stain	Examination of secretions for presence of malignant cells	30 min	Cytotechnologist can detect fungal elements	
Periodic acid-Schiff stain	Detection of fungi	20 min; 5 min additional if counterstain is used	Stains fungal elements well; hyphae of molds and yeasts can be readily distinguished	*Nocardia* spp. do not stain well; *B. dermatitidis* appears pleomorphic
Wright stain	Examination of bone marrow or peripheral blood smears	Detects *H. capsulatum*	Detection limited to *H. capsulatum*	

[a] Modified from *Manual of Clinical Microbiology*, 4th ed., p. 501 (see reference 66). CSF, Cerebrospinal fluid.

and detects >95% of the cases of cryptococcal meningitis and approximately 67% of the cases of disseminated cryptococcal infection. This method is inexpensive, sensitive, and highly specific when used with appropriate controls or methods to eliminate interference factors. Fungal serologic tests to detect antibodies are available but, in general, are not helpful in the immunocompromised patient.

It is recommended that laboratories of all sizes make use of the previously mentioned methods so that a presumptive and/or a final identification of the fungal etiologic agent can be reported to the physician in a timely manner.

The recovery of fungi on culture media is the most definitive manner to detect and identify an etiologic agent as a cause of infection. A battery of fungal culture media should be used since no single medium alone is adequate for the recovery of all fungi found in clinical specimens. General guidelines are that at least one medium should contain cycloheximide to inhibit the rapidly growing molds which may overgrow the slower-growing dimorphic fungi and others. However, it is necessary to use at least one medium lacking this ingredient since cycloheximide inhibits such pathogens as *Cryptococcus neoformans*, *A. fumigatus*, and others. In addition, a blood-containing medium, i.e., brain heart infusion agar supplemented with 5 to 10% sheep blood, is helpful for the recovery of fastidious fungi. Since most specimens submitted for fungal culture are contaminated with bacteria, antimicrobial agents are necessary to reduce or inhibit the growth of these organisms and to enhance fungal recovery.

Fungemia is often associated with an opportunistic infection, and in many instances blood cultures provide the earliest suggestion of etiology. The detection time is dependent on the inoculum density and growth rate. The use of the Isolator System (E. I. du Pont de Nemours & Co., Inc.,

Wilmington, Del.), a lysis-centrifugation system, has not only shortened the time to detection but also improved the overall rate of detection. Two studies have shown this method to be superior to a biphasic brain heart infusion medium (14) and the Roche SeptiChek System (Roche Diagnostics, Div. Hoffmann-La Roche Inc., Nutley, N.J.) (49). The Isolator is the method of choice for the detection of fungemia and should be considered for use by all laboratories.

After fungal growth occurs, whether in blood cultures or others, the identification of the etiologic agent is primarily obtained by observing the characteristic microscopic morphologic features. Commonly, a subculture (usually from a blood-containing medium) onto appropriate medium is necessary to induce conidiogenesis (70). Dimorphic pathogens may be identified by specific exoantigens produced; some may be identified by mold to yeast conversion.

A number of screening or confirmatory tests are available for the identification of fungi commonly associated with the immunocompromised patient, and more specific information is presented later in this report.

Many different fungi have been associated with infections of the immunocompromised host and the list continues to grow. However, certain of the fungi, the subject of this report, are seen with greater frequency than others and include the following: *Candida* species; *A. fumigatus* and other *Aspergillus* species; the zygomycetes, including *Mucor* and *Rhizopus* spp.; *Cryptococcus neoformans*; *Trichosporon* (*beigelii*) *cutaneum*; *Pseudallescheria boydii*; and *Fusarium* species. Additional fungi, including the dimorphic pathogens, are briefly reviewed.

A brief discussion of the clinical manifestations of each infection is presented, as well as information regarding the selection of appropriate clinical specimens for culture (Table 1) and direct microscopic examination (see Table 3) and appropriate therapy. Pertinent diagnostic methods and laboratory tests are presented in brief within the text and in tabular form to allow the clinical microbiologist to select useful and rapid means to detect and identify the fungal etiologic agents in a timely fashion.

CANDIDIASIS

Candida species are the most frequent cause of fungal infections in the immunocompromised host. Species most commonly recovered include *Candida albicans*, *Candida tropicalis*, *Candida* (*Torulopsis*) *glabrata*, and *Candida parapsilosis*. Others such as *Candida lusitaniae* (8, 78, 125), *Candida rugosa* (119), and *Candida pseudotropicalis* (89) have more recently been reported to be associated with disseminated infection. Some are considered part of the usual flora, which makes the clinical significance of an isolate difficult to determine. Recovery of an organism from a normally sterile site or recovery of the same species from several different body sites is an indicator of disseminated infection with probable fungemia.

Onychomycosis

Species of *Candida* may produce infection in the fingernails and toenails which may be an early manifestation of immunoincompetence. The condition may, however, also occur in immunocompetent patients. Paronychia may coexist. Cultures of scrapings from the nail beds will identify *Candida* species or other fungi. When the former are incriminated, ketoconazole therapy is useful. Onychomycosis along with oral candidiasis may be the initial manifestation of immune deficiency in patients with HIV infection (30).

Chronic Mucocutaneous Candidiasis

A specific complex presentation of *Candida* infection of the skin, mucous membranes, hair, and nails occurring in patients with an acquired T-lymphocyte deficit has been described. Specifically, T lymphocytes (thymus derived) do not respond with lymphocyte transformation or synthesis of macrophage inhibition factor after presentation with *Candida* antigen in vitro (116). The clinical manifestations occur in infancy. Mucocutaneous candidiasis (onychomycosis and oral candidiasis) may also occur in other lymphocyte-deficient states, including HIV infection and endocrine disorders such as hypoparathyroidism and adrenal insufficiency. Cultures of scrapings from mucosa or skin lesions will result in the recovery of *Candida* species. The condition responds well to long-term ketoconazole therapy (100).

Oral Candidiasis

In oral candidiasis or thrush, a white pseudomembranous patch forms on the tongue and other oral mucosal surfaces. Oral candidiasis occurs with HIV infection and other T-lymphocyte deficiency states, as well as with use of broad-spectrum antimicrobial agents or inhaled steroid use by asthmatics. In patients with HIV infection, the presence of unexplained oral candidiasis predicts the development of serious opportunistic infections more than 50% of the time (68, 123). The condition may be treated with oral nystatin, oral ketoconazole, or clotrimazole troches. The infection may be particularly recalcitrant in patients with HIV infection. Oral candidiasis may be associated with esophageal candidiasis, especially in patients with AIDS. Scrapings of the lesions will show pseudohyphae or yeast forms or both on KOH or Gram stain examination. Cultures of the lesion will also recover the etiologic agent.

Epiglottitis

Recently, several reports implicated *Candida* spp. as a cause of epiglottitis in immunocompromised patients. *Candida* epiglottitis may be underdiagnosed and should be considered in immunocompromised patients with pharyngeal complaints, including severe pain and odynophagia. *Candida* epiglottitis may occur as a localized infection, as a source of *Candida* bronchopneumonia, or as a manifestation of disseminated candidiasis. Diagnosis is achieved via cultures and microscopic examination of infected material collected by biopsy or scraping via direct visualization of the epiglottis. Treatment is with intravenous amphotericin B, and prompt endotracheal intubation may be necessary if the airway patency cannot be maintained (21, 23, 135).

Esophagitis

Candida infection of the esophagus often presents with odynophagia or dysphagia. This condition occurs in patients with lympho- or myeloproliferative disorders, HIV infection, and other T-lymphocyte deficiency states and with the use of cytotoxic drugs or corticosteroids. The diagnosis is supported by an X ray of the upper gastrointestinal tract which may show ulcerations. The definitive diagnosis is achieved by endoscopic biopsy; lesions often appear as multiple plaques or ulcerations. In patients with AIDS,

localized involvement of the esophagus may be present (35). Histopathologic examination will reveal the yeast or pseudohyphal form or both, and culture of the lesion will recover *Candida* spp. Treatment consists of either oral ketoconazole or oral clotrimazole, intravenous miconazole, or intravenous amphotericin B alone or in combination with oral flucytosine (5FC). The latter therapy is recommended in particularly severe cases. In patients with AIDS, the infection may be recurrent; moreover, instances of *Candida* esophagitis not responding to ketoconazole therapy have been reported in this population (124).

Other Gastrointestinal Infections

Species of *Candida* may also produce lesions in the remainder of the gastrointestinal tract. As with esophageal infection, *Candida* spp. can produce plaques or ulcerations in the stomach, small bowel, or colon. Endoscopic biopsy is the method of diagnosis, and treatment is often amphotericin B alone or in combination with 5FC. Recently, focal granulomatous hepatitis due to *Candida albicans* has been observed in immunosuppressed patients, especially those with acute leukemia. Prominent gastrointestinal symptoms and signs along with elevated levels of alkaline phosphatase have been noted. In addition, computerized axial tomographic scans have shown hepatic defects with or without accompanying splenic defects. Often the infection is localized to the liver without evidence of dissemination. Microscopic preparations of liver biopsy material will reveal small numbers of yeast or pseudohyphal forms or both; however, cultures may be negative (52, 60, 122). Species of *Candida* may also cause focal abscesses in the liver and spleen as well as in the abdominal peritoneal cavity.

Genitourinary Infection

Candida infections in both immunocompetent and immunocompromised patients may involve the genitourinary tract (*Candida* cystitis and pyelonephritis particularly in patients with chronic indwelling urinary catheters), the vagina (vaginitis), and the extragenital areas (cutaneous candidiasis). *Candida* vaginitis may be particularly difficult to treat due to frequent recurrences in women infected with HIV (95).

Candida cystitis is diagnosed by histopathologic examination and culture of the biopsied bladder tissue. Cystoscopy with retrograde ureteral studies may demonstrate fungus balls if present. The diagnosis of *Candida* pyelonephritis is more difficult; however, in the presence of recurrent funguria and azotemia, the diagnosis should be considered. Renal parenchymal abscesses may occur with disseminated infection.

The treatment for *Candida* cystitis is amphotericin B (by instillation into the bladder or systemically or both) and/or oral 5FC. The use of 5FC alone, however, may result in the emergence of resistant organisms. Treatment of upper urinary tract disease, including fungus balls in the ureters, pyelonephritis, and renal abscesses, requires the use of intravenous amphotericin B alone or in combination with 5FC. Fungus balls may require surgical removal, especially when mechanical obstruction occurs. Neither ketoconazole nor miconazole is excreted in the urine as a biologically active agent, and theoretically neither is useful for treating genitourinary disease. Vaginitis may be treated with miconazole, clotrimazole, or nystatin vaginal suppositories; ketoconazole may be useful in recalcitrant cases (113). Cutaneous infections of the perineum should respond to topical antifungal therapy, using either amphotericin B lotion or nystatin cream or powders.

Disseminated Infection

Candida fungemia and deep-seated *Candida* visceral infections occur as a result of dissemination of the organism. The source of the fungemia may be secondary to colonization or infection of the alimentary tract or intravascular or intraurinary catheters. Disseminated *Candida* infection in immunosuppressed patients is most frequently associated with leukemia and the use of cytotoxic drugs or corticosteroid therapy. Disseminated candidiasis can also occur in patients who are not immunosuppressed but have indwelling intravascular catheters ("barrier" or anatomical immune disruption), especially central venous catheters. Patients requiring long-term parenteral nutrition via central venous catheters have a significant incidence of *Candida* endophthalmitis (29). Patients with peripheral venous catheters may experience septic thrombophlebitis (126). Other organ systems involved with disseminated candidiasis include the heart (myocarditis [37], endocarditis [22], and pericarditis [43]), the lungs (often not a true pneumonitis but septic pulmonary emboli with microabscess formation [84]), integument (macronodular erythematous or pink lesions and occasionally necrotic lesions resembling ecthyma gangrenosum), central nervous system tissue (meningitis and cerebral abscess [36, 110]), and musculoskeletal system (arthritis [34], osteomyelitis [107], costochondritis [31], and myositis [6]). Disseminated disease may also result in infection of the peritoneum, liver, spleen, and gallbladder.

Diagnosis is achieved by blood cultures, biopsy, and cultures of other clinical specimens. Treatment is with amphotericin B with or without 5FC. Some species of *Candida* exhibit in vitro resistance to 5FC and susceptibility testing should be performed whenever this drug is used (67).

Laboratory Diagnosis

Candida albicans and other species of *Candida* are easily recognized by their characteristic microscopic morphologic features whether in culture, a clinical specimen, or tissue. Blastoconidia (budding yeast cells) 2 to 4 μm in diameter or pseudohyphae with regular points of constriction or both can be seen by direct microscopic examination of clinical specimens, using phase-contrast microscopy or Calcofluor white staining (Table 2). The organism is strongly gram positive and is easily recognized in specimens such as urine, vaginal secretions, and respiratory tract secretions. After growth appears in culture, *Candida albicans* may be identified by its ability to produce germ tubes or chlamydospores (Table 3). The germ tube test can be completed within 3 h of incubation. Other species of *Candida* must be identified by their specific biochemical profiles. In general, the germ tube test, cornmeal agar morphology, and carbohydrate utilization tests are adequate to make a final identification. Commercially available systems such as the API-20C (Analytab Products, Plainview, N.Y.) and Uni-Yeast Tek (Flow Laboratories, Inc., McLean, Va.) require 48 to 72 h and up to 7 days, respectively, and are recommended methods. Systems involving instrumentation such as the Automicrobic System (Vitek Systems, Inc., Hazelwood, Mo.) and Abbott Quantum II (Abbott Laboratories, Abbott Park, Ill.) are also available for the rapid identification of yeasts; these are usually used by laboratories having the automation available in their bacteriology section.

TABLE 3. Summary of characteristic features of fungi commonly recovered from the immunocompromised host

Fungus	Growth rate (days)	Cultural chracteristics, 30°C	Microscopic morphologic features	Screening tests	Microscopic morphologic features of tissue form	Confirmatory tests for identification	Serology tests available[a]
Candida spp.	2–4	Colonies vary in morphology, but are usually white to tan, shiny to dull, flat to heaped, smooth to wrinkled, and moist to dry; some colonies produce pseudohyphal fringes at the periphery; colonies growing on blood-enriched media are somewhat smaller and drier than those grown on non-blood-containing media	Most species produce either blastoconidia, pseudohyphae, or true hyphae; chlamydospores are produced by *C. albicans* and certain isolates of *C. tropicalis*	Germ tube production by *C. albicans*	Blastoconidia 2–5 μm in diameter and pseudohyphae or hyphae are present	Germ tube production for C. *albicans* Carbohydrate utilization	Latex agglutination tests for *Candida* mannan and protein antigens (40, 63) Other (research): GLC for arabinitol, (metabolite) (47), EIA and RIA (25)
Cryptococcus neoformans	3–10	Colonies are dry to mucoid and shiny, dome shaped, smooth, and cream to tan in color; some isolates appear golden to orange on certain media, i.e., inhibitory mold agar; on a blood-enriched medium, colonies are usually dome-shaped, dry, cream to tan, and smaller	Cells are usually spherical, vary in size, and may be encapsulated; cells may have more than one "pinched off" bud present on parent cell	Urease production Phenol oxidase production Nitrate reductase production	2–15 μm, single or multiply budding (pinched off) spherical cells that vary in size are seen; evidence of encapsulation may be present	Carbohydrate utilization Pigment on niger seed agar	Latex agglutination test to detect cryptococcal polysaccharide antigen (117)
Aspergillus spp.	3–5	Colonies of *A. fumigatus* are usually blue-green to gray-green, while those of *A. flavus* and *A. niger* are yellow-green and black, respectively; other species of *Aspergillus* exhibit a wide range of colors, including *A. terreus* which produces a tan cinnamonlike color; blood-enriched media usually have little effect on colonial morphologic features	*A. fumigatus*: uniserate heads with phialides covering the upper half to two-thirds of the vesicle *A. flavus*: uniserate or biserate or both with phialides covering the entire surface of a spherical vesicle	Not available	Septate hyaline hyphae 3–12 μm in diameter that exhibit dichotomous branching at 45° angle; rounded swollen cells are commonly seen; cannot be distinguished from other filamentous fungi in tissue; larger hyphae may resemble zygomycosis	Identification based on microscopic morphologic features and colonial morphology	Research methods: RIA, EIA for *Aspergillus* antigens (25, 27, 103, 121)

			A. niger: biserate with phialides covering the entire surface of a spherical vesicle; conidia are black *A. terreus*: biserate with phialides covering surface of a hemispherical vesicle; aleuriospores often seen on submerged hyphae				
Zygomycetes (*Rhizopus, Mucor,* others)	1–3	Colonies are extremely fastgrowing, woolly, and gray to brown to gray-black in color	*Rhizopus* species: rhizoids produced at the base of a sporangiophore *Mucor* species: no rhizoids produced	Not available	Large, ribbonlike (10–30 μm), twisted; often distorted pieces of aseptate hyphae may be present; septae may occasionally be seen; smaller hyphae may resemble *Aspergillus* sp.	Identification based on characteristic morphologic features	Research method: EIA for antibody to zygomycetes (75)
Trichosporon beigelii	2–5	Colonies are smooth, shiny to membranous, dry, and cerebriform	Hyphae and pseudohyphae; blastoconidia and arthroconidia; no chlamydospores or sexual spores	False-positive cryptococcal latex agglutination test; hyaline septate hyphae	Arthroconidia and blastoconidia 2–4 by 8 μm	Carbohydrate utilization	Cross-reaction with cryptococcal latex agglutination test for antigen (87, 88)
Penicillium spp.	2–6	Colonies are green or yellow; yellow and brown also; velvety to powdery	Brushlike branching of conidiophores resemble fingers on a hand; phialides with blunt ends give rise to long chains of small spherical conidia	None available	Hyaline, septate hyphae 2–7 μm in diameter; angioinvasion common	Identification based on characteristic morphologic features	None available
Fusarium spp.	2–6	Colonies are lavender, purple, or rose-red; yellow variants occasionally seen; cottony or woolly	Both macroconidia and microconidia are present in some isolates; macronidia are cylindrical, multicelled, and sickle shaped; microconidia are arranged in clusters on top of short delicate phialides	None available	Hyaline, septate hyphae 2–7 μm in diameter; angioinvasion common	Identification based on characteristic morphologic features	None available
Pseudallescheria boydii	2–6	Colonies are mousey gray with dark brown or brown-black reverse; woolly	Single-celled brownish conidia are produced singly or in small groups at the tips of simple single conidiophores (*Scedosporium apiospermum*); some cultures produce cleistothecia containing ascospores (*P. boydii*)	None available	Hyaline, septate hyphae 2–7 μm in diameter; angioinvasion common	Identification based on characteristic morphologic features	None available

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TABLE 3—*Continued*

Fungus	Growth rate (days)	Cultural characteristics, 30°C	Microscopic morphologic features	Screening tests	Microscopic morphologic features of tissue form	Confirmatory tests for identification	Serology tests available[a]
Drechslera, *Bipolaris*, and *Exserohilum* spp.	2–6	Colonies are gray to blackish brown; woolly	Conidiophores are twisted and dematiaceous; conidia are cylindrical and smooth walled with transverse septa containing 4 or more cells; produced sympodially (refer to reference 1 for more detail to separate genera)	None available	Dematiaceous, septate hyphae 2–5 μm in diameter	Identification based on characteristic morphologic features	None available

[a] GLC, Gas-liquid chromatography; EIA, enzyme immunoassay; RIA, radioimmunoassay.

Since yeasts are the most common etiologic agents of fungemia, it is necessary that laboratories have the capability to detect their presence in blood. The Isolator (E. I. du Pont de Nemours), a lysis-centrifugation method, is considered by many to be the optimal fungal blood culture system. It has been shown to be more sensitive and rapid for the detection of yeasts and filamentous fungi than other systems, particularly a biphasic brain heart infusion medium (14). Most yeasts are detected within 24 to 48 h of incubation. Some laboratories prefer to use the BACTEC radiometric system (Johnston Laboratories, Inc., Towson, Md.) since it is in common usage for the detection of bacteremia. Regardless of which system is used, fungal blood cultures should be offered to facilitate a diagnosis of fungemia in the immunocompromised patient.

Methods used for the detection of antibodies to *Candida* species include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, counterimmunoelectrophoresis, immunoelectrophoresis, double immunodiffusion in gel, and immunofluorescence. However, since immunocompromised patients are often unable to produce antibodies, there is a lower sensitivity of detection in this patient group than in the immunocompetent patient. These tests also lack specificity in distinguishing between colonization and deep-seated invasion (25, 65). Because of this insensitivity, tests for the detection of circulating *Candida* antigen and metabolites have been developed. The Candida Detection System, CAND-TEC (Ramco Laboratories, Inc., Houston, Tex.), is a latex agglutination test for the detection of circulating *Candida* protein antigens. In one study the system was evaluated for its ability to distinguish between patients with deep-seated candidiasis and those colonized with *Candida albicans* (40). Results showed that the test may be useful in differentiating the two groups of patients, even among those who are immunocompromised. Another study of latex agglutination tests for circulating *Candida* antigens showed that they may be useful for diagnosing invasive candidiasis, but the transient nature of antigenemia requires frequent testing of patients' sera, which limits their usefulness (63). Finally, metabolites of *Candida* spp. such as mannose and arabinitol have been detected in serum by gas-liquid chromatography. One study showed that patients with proven invasive candidiasis have elevated serum arabinitol levels and arabinitol/creatinine ratios compared with control patients without invasive candidiasis (47). Commercially available kits for the detection of *Candida* antigens include the LA-Candida Antigen Detection System (Immuno-Mycologics, Inc., Washington, Okla.) for detection of circulating mannan antigen and the Candida Detection System (CAND-TEC).

Currently, the serologic diagnosis of candidiasis is complicated by the presence of a large, ever-growing number of reports of new tests that are proposed to be useful. Most have not been compared with already existing methods, and many are impractical to use or are generally unavailable except to the developer. We think that the serologic diagnosis of candidiasis is generally unhelpful at this time but predict that this will change in the near future.

ASPERGILLOSIS

Species of *Aspergillus* are among the most frequently recovered fungi in the clinical laboratory; some are known to be pathogenic, whereas others rarely cause infection. They are ubiquitous in the environment and their conidia are easily dislodged and dispersed, allowing susceptible hosts to

become infected by inhalation. Nosocomial outbreaks have occurred especially during renovation or construction of buildings or when air-conditioning ducts become heavily contaminated with *Aspergillus* spp. (74, 105). *A. fumigatus* is the most common species seen in respiratory tract secretions and is responsible for most cases of aspergillosis. Others, including *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* are being seen with greater frequency as a cause of infection in the immunocompromised host.

The aspergilli are frequently recovered in cultures of respiratory tract secretions, skin scrapings, and other specimens, which makes an assessment of their significance difficult. Repeated recovery of an organism from the same site or its recovery from several different sites may serve as evidence for infection, especially in the neutropenic patient (2, 128).

Clinical Manifestations

In the immunocompromised host, *Aspergillus* spp. commonly produce an acute pneumonia which is usually fatal. Patients with acute leukemia, those receiving high-dose corticosteroid or cytotoxic drug therapy or both, or those who have recently undergone bone marrow transplantation with functional or absolute neutropenia are most often afflicted. Local invasive disease may occur in immunocompromised patients and has been reported rarely in immunocompetent hosts (18).

Typically, a patient develops fever followed by pulmonary infiltrates with areas of consolidation on chest X ray. With time the lungs become more extensively involved, with an increase in infiltrates, even while the patient may be receiving amphotericin B therapy. Several authors have observed a "halo sign" (a halo of low attenuation appearing around masslike infiltrates). While this sign may not be pathognomonic for aspergillosis, its presence on tomograms or computerized axial tomographic scans of the lungs in the appropriate host may suggest early invasive aspergillosis (39, 73, 109).

Often *Aspergillus* spp. disseminate from the lungs (114) to the brain (143), liver, kidneys, heart (55, 134), skin (48), and rarely to the gastrointestinal tract (50, 90, 138). Localized infection may also occur in the immunocompromised host, especially in the facial sinuses (131), often with contiguous spread to the brain to produce rhinocerebral aspergillosis (143). Disseminated aspergillosis most often occurs in patients with granulocytopenia (44).

Treatment for local disease is extensive surgical debridement and amphotericin B therapy; in pulmonary and disseminated disease, early treatment with amphotericin B is essential (2). There is debate as to whether the use of rifampin or 5FC in combination with amphotericin B is beneficial. Nevertheless, despite therapy, the prognosis is poor and the infection is usually fatal.

Laboratory Diagnosis

The diagnosis of aspergillosis is achieved by microscopic examination and culture of infected tissue. Tissue invasion is prominent, with obvious vascular invasion and subsequent tissue infarction. Aspergilli appear as hyaline, septate hyphae that exhibit dichotomous branching at 45° angles (Table 3). *A. flavus* may be confused with zygomycetes (*Rhizopus* and *Mucor* spp.) since some isolates have large, sparsely septate hyphae.

Cultures of respiratory tract secretions commonly reveal *Aspergillus* spp., and their significance must be determined based on the clinical correlation. Venous blood cultures are not useful; however, it has been suggested that arterial blood cultures may be used to recover the organism. Most species of *Aspergillus* are partially or totally susceptible to cycloheximide; therefore, the battery of fungal culture media used should include at least one medium lacking this ingredient. However, when recovered, species of *Aspergillus* grow rapidly and produce mature colonies within 7 days. Identification of distinct species is based on the colonial and microscopic morphologic features (Table 3).

An early diagnosis of aspergillosis is difficult to make. Serologic methods to detect antibodies are usually not helpful since the humoral response in the immunocompromised patient may be variable or absent (103). Therefore, attempts have been made to develop methods to detect soluble antigens of *Aspergillus* spp. in the serum, urine, or other body fluids to provide a rapid and specific diagnosis (27). Tests that have been developed include radioimmunoassay (121) and ELISA (103). However, none are commercially available for routine use in a clinical laboratory.

An inhibition ELISA capable of detecting 10 ng of *Aspergillus* carbohydrate antigen per ml in serum was developed which, in a retrospective study, detected antigen in the sera of 11 of 19 patients with invasive aspergillosis (103). None of 14 healthy controls or 28 patients with a variety of other infections had antigen in their serum. Purified galactomannan from *A. fumigatus* has been used in both a radioimmunoassay and an ELISA for the detection of antigen in serum and urine (27). The detection of galactomannan in the urine appeared to be a more sensitive test than serum antigen detection. Urinary antigen excretion roughly paralleled extent of disease. Other investigators (121) used radioimmunoassay retrospectively and detected *A. fumigatus* antigen in the sera of 30% of a group of patients with hematologic malignancies before invasive aspergillosis was suspected and in 46% before there was pathological or preliminary evidence of disease. Overall, the test would have been clinically useful for diagnosis and management in 80% of 16 patients with fatal pulmonary invasive aspergillosis. More recently, the development of an ELISA method that uses monoclonal antibodies for the detection of *Aspergillus* antigenemia and its use in the diagnosis of invasive aspergillosis was reported (R. Harrington, Jr., and M. Weiner, Abstr. Annu. Meet. Am. Soc. Microbiol. 1987, C344, p. 380). Patients with leukemia were tested retrospectively, and results were positive in three of four patients with infection. Antigenemia was detected 11 and 10 days prior to onset of pneumonia in two patients and in the first serum sample of a third patient admitted to the hospital for pneumonia. The data include such a small number of patients that definite conclusions cannot be drawn; however, the method appears promising.

Currently, the diagnosis of aspergillosis remains a problem to the clinician and to the laboratory. Prompt reporting of smear or culture results can lead to making the diagnosis in a clinically relevant period of time.

ZYGOMYCOSIS

Fungi in the class *Zygomycotina* produce serious infection of the immunocompromised host, but cause infection less often than *Candida* or *Aspergillus* species. Members of this group are ubiquitous in nature, often found growing on bread, fruit, silage, and leaves and other vegetation, in addition to soil.

Infection is usually a result of inhalation or, sometimes, traumatic inoculation of the organism into the skin. Zy-

gomycosis is most often seen in patients having diabetes mellitus, hematologic malignancies, neutropenia, extensive burns, or organ transplants, in those receiving cytotoxic drugs and corticosteroid therapy, and sometimes in drug addicts. Infections may be nosocomial and may be associated with construction or renovation of sites adjacent to or near areas where patients are hospitalized (137). Ventilation ducts may become contaminated and then act as a means for the spread of fungal spores.

Pulmonary Infection

The clinical presentation of zygomycosis resembles, in many instances, that of aspergillosis. Pulmonary zygomycosis occurs frequently enough that it must be considered and, if highly suspected, treated immediately. Pulmonary infection occurs in patients with uncontrolled leukemia and other hematologic malignancies, and dissemination is common. The infection begins with fever and pulmonary infiltrates which persist despite antimicrobial therapy. In patients with diabetes mellitus, the infection may be slower to develop; however, in other immunocompromised patients, it rapidly disseminates by vascular invasion. Infarction occurs and necrosis of surrounding tissue follows. Dissemination to the liver, heart (10, 58), alimentary tract (93), kidneys, brain, and integument is common.

Rhinocerebral Infection

Rhinocerebral zygomycosis occurs most commonly in patients with uncontrolled diabetes and ketoacidosis. It may also be associated with leukemia or the use of corticosteroid or cytotoxic drug therapy (9, 99). Patients complain of headache, orbital edema, and nasal congestion, and many develop orbital cellulitis. Examination of the nose and palate commonly reveals black eschar exuding from the nares or black necrotic areas of the hard palate. Patients often complain of diplopia due to extraocular muscle paresis, and proptosis may also occur. Treatment includes extensive debridement and prompt antifungal therapy with amphotericin B. Despite aggressive measures, the mortality rate is high.

Laboratory Diagnosis

Several genera have been implicated as causes of zygomycosis, but most cases of infection in immunocompromised patients are produced by *Mucor* and *Rhizopus*. Other genera including *Absidia*, *Rhizomucor*, *Cunninghamella*, *Saksenaea*, *Basidiobolus*, and *Conidiobolus* are known to produce infection, primarily in immunocompromised patients.

Zygomycosis is known to be a rapidly progressing infection. For this reason, it is imperative that the laboratory diagnosis be made as quickly as possible.

Direct microscopic examination of respiratory tract secretions, eschar, and tissue taken at biopsy can provide a diagnosis within minutes if a zygomycete is present. Large, sparsely septate hyphae or fractured hyphal fragments are easily recognized by using the KOH preparation with or without Calcofluor white (Table 3). Some confusion has been noted in trying to distinguish *A. flavus* from a zygomycete; however, the former usually appears to be somewhat more septate. Histopathologic examination of tissue, using hematoxylin-eosin stain, reveals the same morphologic features previously discussed. Methenamine silver usually fails to stain the hyphal elements well and is of little help in detecting the organism in many cases. However, an organism that stains well with hematoxylin-eosin but fails to stain with methenamine silver is suggestive of a zygomycete.

Cultures of respiratory tract secretions commonly contain zygomycetes; therefore, careful review of the clinical picture of the patient must be made to assess the significance of a positive culture. Specimen sources useful for the recovery of the etiologic agent of zygomycosis are presented in Table 1.

In culture, the zygomycetes grow rapidly, within 1 to 2 days, and produce fluffy, white to grey to brown hyphal growth. Species of *Mucor* and *Rhizopus* grow as rapidly in vivo as in culture. Genera cannot be separated by their colonial morphologic features but must be distinguished by their microscopic morphologic characteristics (Table 3). All have large ribbonlike hyphae that are irregular in diameter and are sparsely or occasionally septate. Specific identification is confirmed by observing characteristic sporangia at the tips of sporangiophores, presence or absence of rhizoids, and the position of the rhizoids in relation to the sporangiophores.

Diagnostic serologic tests are not available for use in the clinical laboratory. One report, however, describes a case of systemic zygomycosis diagnosed by percutaneous needle aspiration of a perinephric abscess and confirmed with an enzyme immunoassay that detected humoral antibodies (75). The rapid detection of an organism in a clinical specimen by direct microscopic examination or culture is currently the most important means of making a diagnosis of this important infection.

CRYPTOCOCCOSIS

Cryptococcosis, primarily an infection of the immunocompromised host, is produced by *Cryptococcus neoformans*, a member of the class *Basidiomycotina*, the group to which the mushrooms belong. The organism is widely distributed in nature and is most often found in association with the excreta of pigeons. It is thought that exposure to *Cryptococcus neoformans* is common and that the primary route of entry is by inhalation. However, a history of exposure is difficult to obtain from patients, and activities associated with aerosol production are most often lacking. In addition, the number of recognized cases of pulmonary cryptococcosis are few when compared with cases of disseminated infection or meningitis; perhaps many are self-resolving.

Since cryptococcosis most often occurs in the immunocompromised host, its presence in any specimen should be considered significant until proven otherwise. However, a recent review of our patient records at Mayo Clinic from 1975 to 1984 showed >100 cases of colonization of the respiratory tract without subsequent development of infection within 6 years of patient follow-up. However, none of the patients were immunocompromised. Therefore, it is necessary to rule out infection in patients from whom *Cryptococcus neoformans* is recovered to ensure a proper diagnosis.

Central Nervous System Infection—Meningitis

A frequent presentation of cryptococcosis involves the central nervous system in the form of meningitis. The onset is insidious, with decreasing hearing, impaired cognitive function, headache, fatigue, drowsiness, irritability, and clumsiness often preceding overt clinical signs involving cranial nerve dysfunction and meningismus. The gradual

onset of the illness and lack of specific signs and symptoms in early disease are likely a result of a minimal inflammatory reaction in tissues. In AIDS patients, large numbers of organisms may be present in tissue, with a striking paucity of an inflammatory response (41, 101).

Remarkably, some patients with cryptococcal meningitis have no specific immune deficit preceding their illness. Others may be receiving high-dose corticosteroid therapy or have lymphoproliferative disorders, especially lymphoma, sarcoidosis, or HIV infection (32, 72, 147) or diabetes mellitus. Interestingly, in many patients receiving high doses of corticosteroids, the signs and symptoms of meningitis are often suppressed. Cryptococcal central nervous system infection should be suspected in patients receiving corticosteroid therapy since this association has been well documented.

Treatment may be with amphotericin B alone or in combination with 5FC. In non-AIDS patients, the latter treatment regimens result in a cure rate similar to that with amphotericin B alone, but toxicity is less (11). In AIDS patients, continuation of suppressive antifungal therapy is usually necessary. Recently, fluconazole, a triazole compound, has been shown to be of use in the treatment of cryptococcal infection in AIDS patients who have not responded to amphotericin B and 5FC therapy (19).

Infection of the Respiratory Tract and Other Sites

As previously mentioned, *Cryptococcus neoformans* may be recovered from patients having only pulmonary colonization. This, in conjunction with the relatively few reported cases of pulmonary cryptococcosis, makes the clinical diagnosis of this entity somewhat difficult in patients with or without chest roentgenogram abnormalities. Pulmonary cryptococcosis may occur in both immunocompromised and immunocompetent hosts. Many cases of pulmonary infection resolve without treatment in the latter, but disseminated infection commonly occurs in the abnormal host unless antifungal therapy is administered.

Other sites that may be involved include the skin and bone and, rarely, the kidneys, liver, and genitourinary tract. Blood cultures may be positive for *Cryptococcus neoformans* in afebrile patients who are immunosuppressed, without an identifiable source of infection. In many of these patients the organism can be found in respiratory tract secretions or cerebrospinal fluid. Cryptococcosis is the most common disseminated fungal infection seen in patients with AIDS. Unusual cases of myocarditis (76), cutaneous infection resembling molluscum contagiosum (97), arthritis (96), and prostatitis (79) have been reported.

Treatment of extraneural cryptococcosis is as described for cryptococcal meningitis.

Laboratory Diagnosis

The laboratory diagnosis of cryptococcosis may be made by direct microscopic detection of *Cryptococcus neoformans* in clinical specimens including respiratory tract secretions, body fluids, and tissue; by the serologic detection of cryptococcal antigen in serum or cerebrospinal fluid; or by recovery of the organism in culture.

The direct microscopic examination of cerebrospinal fluid for the detection of *Cryptococcus neoformans* has been traditionally associated with the India ink preparation. It is commonly used in clinical laboratories, but has a low sensitivity and detects <40% of culture-proven cases of cryptococcal meningitis (Table 2). We recommend that it not be used in the clinical laboratory but rather be replaced by the cryptococcal latex test for antigen. The latex test detects the presence of solubilized capsular polysaccharide antigen in serum and cerebrospinal fluid. The test is sensitive and detects as many as 99% of patients having meningitis (66). A small number of false-positive tests occur due to rheumatoid factor or other interference factors, but a simple method to eliminate these factors has been developed (117). A portion of the serum or cerebrospinal fluid is treated with a protease (pronase), heat inactivated, and tested. False-positive results are eliminated, and in many instances titers are higher after treatment due to the disassociation of antigen-antibody complexes. This treatment appears to enhance the sensitivity of the test by detecting antigen previously bound by antibody. Cryptococcal antigen may be detected in the serum of approximately 66% of patients having disseminated infection and only a few (<10%) with pulmonary infection (28).

Direct microscopic detection of *Cryptococcus neoformans* in specimens other than cerebrospinal fluid is also easily accomplished. *Cryptococcus neoformans* appears as a spherical, single, or multiply budding yeast. Extreme variation in the size of cells (2 to 15 μm) is apparent, and although the organism is described as being encapsulated, not all isolates produce the polysaccharide capsule (Table 3). Calcofluor white staining or phase-contrast microscopy makes it easier to detect this organism in clinical specimens. The methenamine silver stain is optimal for detection of *Cryptococcus neoformans* in tissue.

Recovery of *Cryptococcus neoformans* in culture is easily accomplished by using most routine fungal culture media without cycloheximide. Yeastlike colonies (dry or mucoid) appear within 1 to 5 days, and pigmentation varies depending on the medium used for culture. After growth appears, a presumptive identification may be made based on urease production, lack of nitrate reductase, and presence of phenol oxidase. The definitive identification is based on carbohydrate utilization profiles and pigment production on niger seed agar (Table 3).

TRICHOSPORONOSIS

Species of *Trichosporon* are widely distributed in nature and may also be found in respiratory secretions, stool, and urine (53) and on the skin of healthy persons. *Trichosporon beigelii* (*T. cutaneum*), the most common cause of trichosporonosis, has long been recognized as the etiologic agent of white piedra, an infection of the hair of persons living in tropical and temperate parts of the world.

Trichosporonosis, as an infection of the immunocompromised host, has been recognized only during the past 17 years. Of the 42 cases of disseminated infection recognized, 27 (64%) were reported during 1986 to 1987.

Disseminated infection is seen primarily in patients with hematologic malignancy and profound neutropenia (57). However, infection has been found in patients undergoing renal (53) and bone marrow (57) transplantation, prosthetic valve surgery (94), or hepatitis (71).

Clinical Manifestations

The clinical manifestations of trichosporonosis are diverse and the diagnosis is usually not suspected. Many patients present with signs and symptoms that suggest disseminated candidiasis (6). Purpuric skin lesions are common, and most

progress to produce large areas of necrosis (46, 144) and deep-tissue involvement (5, 7, 77, 82, 133). In some instances an oral infection resembling thrush may be seen (92), pneumonia is common (69, 106), and hepatitis (71) may occur. Significant mortality has been associated with disseminated infection.

In vitro studies have shown the organism to be susceptible to amphotericin B, ketoconazole, and miconazole. Large clinical studies are lacking regarding the appropriate treatment, although case reports have suggested that amphotericin B alone or in combination with 5FC may be useful (12, 136).

Laboratory Diagnosis

The diagnosis of trichosporonosis is made most often by the recovery of *T. beigelii* from blood, skin lesions, or other tissue obtained at autopsy. The organism grows well on all commonly used fungal culture media and forms smooth, shiny colonies within 1 week of incubation which later become membranous, dry, and cerebriform (Table 3). Identification is based on the presence of hyphae with arthroconidia and blastoconidia produced on cornmeal agar. Biochemically, *T. beigelii* does not ferment carbohydrates and produces urease and a characteristic carbohydrate utilization profile.

The diagnosis may also be made based on recognition of the organism in tissue by observing hyphae with numerous arthroconidia and a few blastoconidia (Table 3). Lesions are typically composed of radially arranged hyphae with or without central necrosis (77). In some instances, blastoconidia are absent, and the differential diagnosis will include trichosporonosis or geotrichosis since the etiologic agents of both produce arthroconidia.

T. beigelii produces a heat-stable antigen which shares antigenic determinants with the capsular polysaccharide of *Cryptococcus neoformans*. The latex test for cryptococcal antigen has been reported to be positive when serum of patients having disseminated trichosporonosis has been tested (87, 88). Detection of antigenemia may correlate with invasive disease in patients whose surveillance cultures of skin, sputum, stool, or urine become positive with *T. beigelii*. In this situation, the cryptococcal latex test for antigen might suggest infection with *Trichosporon* spp. before identification of the culture is made.

PSEUDALLESCHERIASIS

P. boydii, the organism most commonly recognized as the major etiologic agent of mycetoma in North America, is being seen with greater frequency as the cause of a number of different clinical entities. The organism is widely distributed in nature and has been recovered from soil, poultry, cattle manure, polluted streams, brackish water, and coastal waters. It is common to recover *P. boydii* from respiratory tract secretions and gastric washings of healthy persons; however, its presence deserves serious consideration as a potential pathogen.

Clinical Manifestations

Recognition of *P. boydii* as a cause of infection in the immunocompromised host is becoming increasingly important. Pulmonary disease with massive intra-alveolar hemorrhages, congestion, mycotic thrombi, and multiple fungal lesions has been noted. Local disease may occur in the paranasal sinuses which may then extend into the orbit and meninges (45, 54). In addition, disseminated infection with involvement of deep viscera including the thyroid, kidneys, brain, and heart has been described (33, 108, 111). Cases of brain abscess are being reported more often (127, 142). Tricuspid valve endocarditis reported in a patient receiving corticosteroid therapy apparently evolved as a result of an implanted pacemaker which became infected with *P. boydii* (24). Fungal sinusitis in both immunocompetent and immunocompromised patients is becoming more prevalent.

Pseudallescheriasis presents a serious threat to the immunocompromised patient by its potentially pathogenic nature, but more importantly, from a therapeutic standpoint: little success has been achieved in the treatment of this infection. Surgical debridement, when appropriate, in combination with intravenous amphotericin B has been used with varying degrees of success. Miconazole now appears to be the recommended treatment of choice; however, ketoconazole has been used in a limited number of cases (42, 81). Early diagnosis and rapid treatment appear to increase the chances of a favorable outcome.

Laboratory Diagnosis

The definitive laboratory diagnosis of pseudallescheriasis depends on the recovery and identification of *P. boydii* from clinical specimens. The organism is easily recovered from tissue, blood, and other sources within 5 days of incubation. Colonies are initially white and fluffy but soon become mousey grey with a dark black to brown reverse. The asexual form of *P. boydii* (*Scedosporium apiospermum*) produces elliptical to elongated, single-celled conidia borne singly from the tips of long or short conidiophores (annellophores). Some cultures produce the *Graphium* state in which clusters of conidiophores producing conidia at their tips appear to be cemented together (synnemata). The sexual form exhibits cleistothecia (50 to 200 μm) which contain asci and ascospores (Table 3). According to taxonomists, one should report the organism as *S. apiospermum* when the asexual form is seen and *P. boydii* when the sexual form is found. Clinical laboratories can make their own decision as to what name should be used for reporting the results to clinicians.

P. boydii may be seen in tissue as small hyphae which may or may not exhibit dichotomous branching. Microscopically, this organism cannot be distinguished from *Aspergillus* spp. or other fungi (Table 3).

FUSARIUM INFECTION

The genus *Fusarium* contains nine species, all of which are plant pathogens and widely distributed in nature. Only a few species have been incriminated as causes of human infection, keratomycosis being the most common. However, during the past few years, an increasing number of different infections have been reported in the immunocompromised host. *Fusarium solani* has been shown to cause disseminated infection with fungemia (3, 4, 20, 85, 91, 129). *Fusarium moniliforme* and *Fusarium proliferatum* have been associated with pneumonia and disseminated infection in patients with leukemia (61, 120, 145). Infection with *Fusarium* spp. has also been seen in patients undergoing bone marrow transplantation (15, 91).

Most infections have been fatal, but amphotericin B therapy has been of benefit in a few cases.

Laboratory Diagnosis

The definitive diagnosis of *Fusarium* infection is made by recovering and identifying the organism from a patient who has a compatible clinical history or histopathologic evidence of infection or both. *Fusarium* spp. cannot be distinguished from *Aspergillus* spp., *P. boydii*, or other fungi by microscopic examination of tissue sections. The definitive diagnosis depends on identification of the genus and species involved. The genus is easily recognized by observing hyphae having single phialides which produce either single-celled oval microconidia or, more commonly, gelatinous heads of large sickle-shaped septate macroconidia. Some cultures produce chlamydospores which aid in their identification (Table 3).

Colonies of *Fusarium* spp. may appear in many colors, including pink, purple, yellow, and green, and are fluffy to cottony in texture. Colonial morphology, however, plays little role in the final identification of the organism.

OTHER UNCOMMON FUNGAL INFECTIONS

The immunocompromised host is susceptible to any microorganism if host responses are diminished and other factors are impaired. This is evident by the number of infections reported that have been caused by organisms not usually known to be pathogenic under ordinary circumstances.

A variety of fungi other than those discussed in this review have been recognized as causing infection in the immunocompromised host; only a few examples are included in this discussion. *Paecilomyces lilacinum* has been associated with cellulitis in an immunosuppressed patient (59). Cutaneous infections have also been reported to be caused by *Exophiala jeanselmei* (cutaneous nodules) (146), *Malassezia furfur* (folliculitis) (141), *Alternaria* species (cutaneous nodular lesions) (132), and *Penicillium* species (generalized subcutaneous abscesses) (112). Other infections reported include *Aureobasidium pullulans* (splenic and disseminated infection) (62, 104), *Rhodotorula* species (disseminated infection) (102), *Chaetomium* species (empyema) (56), *Torulopsis candida* (fungemia) (115), *Curvularia* species (nasopharnygeal infection) (80), *Cunninghamella* species (pneumonia) (130), *Geotrichum candidum* (disseminated infection) (64), and members of the dematiaceous fungi including *Drechslera*, *Bipolaris*, and *Exserohilum* (1, 26, 38, 86, 98).

To this partial list can be added the dimorphic pathogens *H. capsulatum*, *B. dermatitidis*, *Coccidioides immitis*, *Sporothrix schenckii*, and *Paracoccidioides brasiliensis*. In the past these infections have been associated with the immunocompetent host, but now they are being increasingly recognized in the immunocompromised hosts, including those with leukemia and AIDS and patients receiving long-term corticosteroid therapy (13, 16, 17, 83, 118, 139, 140).

The intent of this review is to make the reader aware that fungal infections of the immunocompromised patient are becoming much more common and that any organism should be considered a potential etiologic agent. This requires that the clinical microbiology laboratory thoroughly identify and report all fungi found in clinical specimens from such patients. By doing this, the clinician may assess the clinical significance of a fungal isolate. It is reasonable to expect that opportunistic fungal infections will be seen with increasing frequency, and the clinical laboratory should be prepared to identify fungi that are infrequently encountered on a daily basis.

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