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Opportunistic Fungal Infections

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INTRODUCTION

Opportunistic fungal infections constitute an increasing proportion of infections seen in immunocompromised patients; these infections are associated with a very high mortality rate. On the other hand, the endemic mycoses affect tens of thousands of persons. These infections are often asymptomatic, but endemic fungi can cause severe and even fatal infection in the appropriate host. New antifungal agents have changed the treatment of many fungal infections in the past few years. One can now choose from multiple effective drugs for many of the invasive mycoses. The following clinical syndromes will aid in the diagnosis and management of fungal infections :

DIAGNOSIS

1. Fever, a pulmonary infiltrate, and erythema nodosum in a young adult could be either coccidioidomycosis or histoplasmosis. Both of these mycoses are endemic to North America but also occur in many countries. More travelers are participating in ecotours or working vacations and are exposed to Coccidioides or Histoplasma in the course of these activities. Outbreaks are typically related to activities that disturb the soil or create a cloud of dust, such as construction sites.

The usual manifestation of acute infection with endemic fungi that are inhaled from the environment is pneumonia which is generally accompanied by fever, myalgias, and fatigue. Erythema nodosum is seen mostly in young adults who have acute coccidiodomycosis or histoplasmosis; the rash appears to reflect a good host response to the infection.

Growth of Coccidioides immitis or *Histoplasma capsulatum* in cultures of sputum or bronchoalveolar fluid is diagnostic for acute infection; however, this test is not very sensitive. Testing for antibodies to *C. immitis* or *H. capsulatum* is most useful for making the diagnosis of acute pulmonary infection with these fungi, but it may take weeks for seroconversion to occur. The urine assay is positive for Histoplasma antigen in as many as 75% of patients with severe acute pulmonary histoplasmosis.

2. A mass-like lesion on a chest radiograph in a former smoker is not necessarily lung cancer, it might be blastomycosis.

Blastomyces dermatitidis is endemic in the north central, south central, and southeastern United States. Middle-aged to older men are the usual hosts. In patients with blastomycosis, there is a propensity for mass-like lesions to form; these lesions are frequently mistaken for lung cancer on chest radiographs. Cytologic examination of bronchoalveolar lavage fluid or lung tissue stained with periodic acid-Schiff or silver stain often shows the classic thick-walled yeast with a single, broad-based bud that is characteristic of *B. dermatitidis.* Definitive diagnosis is made by growth of *B. dermatitidis* in cultures of sputum, bronchoalveolar lavage fluid, or lung tissue. Serologic testing currently plays no role in the diagnosis of blastomycosis.

1. Chest radiographs show a right lower lobe mass-like lesion in a middle-aged man who was thought to have lung cancer. Biospy of the lesion revealed granulomatous inflammation, and special stains revealed yeast-like organisms.
2. Periodic acid-shiff stain of tissue obtained from the patient whose chest radiograph is shown in large,

thick-walled, broad-based budding yeasts typical of blastomyces dermatitidis can be seen.

3. An ulcerated skin lesion with extension to local lymph nodes in a person who cared for a cat with a draining skin lesion may not be caused by Bartonella.

   Although Bartonella infection might be the first diagnosis entertained in this scenario, these is a high likelihood that this could be sporotrichosis. Zoonotic transmission from squirrels, armadillos, and birds is well described, but most cases of animal-associated sporotrichosis are in persons caring for cats with the disease. In cats, ulcerated lesions tend to develop on the head and face: these lesions frequently are teeming with the yeast-like tissue form of Sporothrix schenckil.

4. A positive result on a serum Cryptococcus antigen test from a patient with neutropenia who has fever, multiple nodular skin lesions, and pneumonia does not always signify infection with *Cryptococcus neoformans*.

   Tricosporon asahil (formerly known as *Trichosporon beigelii*) is a yeast-like fungus that is found in water and soil. In normal hosts, several species of Trichosporon cause superficial cutaneous lesions and onychomycosis. Disseminated trichosporonosis most often occurs in a patient with leukemia who has profound neutropenia. In this type of patient, pneumonia, multiple nodular cutaneous lesions, and widespread visceral abscesses are found. Mortality rates approach 80 to 90%.

   The organism is able to grow in blood cultures, and on initial Gram stain of the fluid from the blood culture bottle it may look like a Candida species; further studies reveal Trichosporon species. Antigens in the cell wall of *T. asahil* cross-react with the capsular polysaccharide of *C. neoformans* and may lead to a positive result in the serum latex agglutination test for Cryptococcus antigen. Biopsy specimens of skin lesions usually reveal a characteristic mixture of blastoconidia, arthroconidia, and hyphae typical of Trichosporon species.

5. Zygomycosis is the most likely diagnosis in a patient with myelodysplastic syndrome who is being treated with desferrioxamine for iron overload and who exhibits a pulmonary mass-like lesion. Rhinocerebral, pulmonary, and disseminated forms of zygomycosis have been described in patients receiving desferrioxamine, and the infection tends to be very aggressive.

   The diagnosis of infection caused by a fungus of the Zygomycetes class must be made quickly so that appropriate therapy can be initiated as soon as possible. Initial diagnosis is usually made by a tissue biopsy specimen that shows broad nonseptate hyphae invading blood vessels. It is some what ironic that it is often difficult to grow Zygomycetes *in vitro* from tissue samples, in spite of their aggressive *in vivo* growth; this is likely related to damage to the hyphae during the processing of tissue for culture in the laboratory. The clinician must treat the patient based on results from histopathologic examination; positive culture results provide confirmatory evidence of the specific fungus involved. There are no rapid antigen or antibody tests for the Zygomycetes.

6. Infective fungi with acutely branching septate hyphae: Not always Aspergillus.

   Aspergillus is the most common nonpigmented acutely branching septate filamentous fungus that causes infections in immunocompromised hosts. However, other opportunistic fungi are increasingly seen in immunocompromised hosts, often can not be distinguished from Aspergillus on histopathologic examination of tissues, are frequently resistant to amphotericin B, and are often associated with dismal outcomes.

7. A patient with leukemia and neutropenia in whom fever, a pulmonary infiltrate, and painful nodular skin lesions develop and whose blood cultures are positive for a mold most likely is infected with Fusarium.

   The genus Fusarium includes non-pigmented septate filamentous fungi that commonly cause disease in plants. Fusarium species cause onychomycosis and locally invasive infections, usually after traumatic inoculation. In non-immunocompromised hosts. Disseminated infection is the rule in patients with hematologic malignancies, especially when they have neutropenia or have received a stem cell transplant. The source of the infection can be either aerosolization into the lung from an environmental source or inoculation through the skin, often beginning as a paronychia.

   Widespread hematogenous dissemination is frequent, and multiple painful nodular cutaneous lesions are characteristic. The diagnosis can be made by biospy and culture of skin lesion. The histologic picture is similar to that of Aspergillus, showing acutely branching, non-pigmented hyphae that

invade through blood vessel walls. Fusarium grows in routine blood culture media, a phenomenon that is rarely encountered with other molds. Fusarium species are often resistant to amphotericin B, and the mortality rates are as 100% in infected patients who remain neutropenic. Voriconazole has shown success in the treatment of Fusarium infection.

8. Infection with angioinvasive fungi leads to characteristic findings on high-resolution CT scan of the lung.

   The most common angioinvasive fungal infections are those caused by the genera Aspergillus, Fusarium, and Scedosporium (Pseudallescheria) and the class Zygomycetes (mostly Rhizopus and Mucor). Hyphae of these fungi have the propensity to invade through blood vessel walls, leading to local tissue infarction and necrosis. With early infection, the chest radiograph may appear normal or show only a small nodule or infiltrate. High-resolution CT scans have become invaluable in the diagnosis of infection with angioinvasive fungi. They often reveal multiple nodules when only 1 was seen on the chest radiograph.

   A "halo sign" is an extremely helpful on the CT scan. This sign is seen in approximately 90% of cases at the onset of symptoms and consists of an area of ground-glass infiltrate surrounding a nodule, reflecting parenchymal hemorrhage secondary to blood vessel invasion by the fungus. A "crescent sign" demonstrates cavitation and is also indicative of infection with an angioinvasive fungus. This occurs in as many as 63% of cases, but it appears late (usually in the second week) and thus is not helpul for early diagnosis. This sign occurs with tissue necrosis and often appears when the patient's neutropenia has begun to resolve.

9. Fever, right upper quadrant abdominal discomfort, nausea, and an elevated alkaline phosphatase level in a patient with leukemia who has just recovered from neutropenia is likely caused by chronic disseminated (hepatosplenic) candidiasis.

   Candida disseminates widely in patients with neutropenia. In many of them, the extent of visceral dissemination if not clear until the patient experiences a return of circulating neutrophils. At that time, fevers (often high and spiking), right upper quadrant or abdominal pain and tenderness, and nausea and vomiting occur. Generally, patients do not appear terribly ill except when their temperature is elevated. Values of serum liver enzymes, predominantly alkaline phosphatase, are modestly elevated in most patients; white blood cell counts are normal limits; and blood cultures show no growth.

   A CT scan of the abdomen reveals multiple lucencies, some of which can become quite large, in liver, spleen, and less often in kidneys. Ultrasonography is less sensitive than CT for defining the lesions. A liver biopsy specimen shows multiple well-circumsribed micro abscesses containing neutrophils and organisms that suggest Candida species. Culture often yields no growth even though organisms are clearly seen on the biopsy specimen. The clinical, laboratory, and radiologic findings are so characteristic that liver biopsy does not need to be performed in all patients before starting antifungal therapy. However, if a patient does not respond to therapy, a biopsy should be done because other organisms, including Trichosporon and Aspergillus, uncommonly can cause a similar syndrome.

10. Acute onset of face pain in an immunocompromised patient: suspect invasive fungal sinusitis.

    Pain out of proportion to initial physical findings is often the presenting manifestation of an invasive mold infection. Most often the pathogen is aspergillus; Fusarium;Scedosporium one of the Zygomycetes; or less commonly, a pigmented dematiaceous fungus, such as Alternaria or Bipolars. All pf organisms are commonly found in air, water, and soil. The usual host is a patient who has a hematologic malignancy and neutropenia and has been receiving broad spectrum antimicrobial agents.

    Findings from the initial examination may be within normal limits or there may be only slight swelling of the face over the maxillary or frontal sinuses. Plain radiographs of the sinuses may show an air-fluid level, but radiography is generally insensitive. CT scans of the sinuses are needed to assess the extent of mucosal involvement and whether the infection has spread into bone. An otolaryngologist should be consulted immediately, and endoscopic evaluation of all sinuses should be undertaken. Culture of purulent material usually reveals the organism, and biopsy, if it can safely be performed, will reveal the extent of invasion into the walls of the sinuses. Drainage of the involved sinuses is carried out at the time of endoscopy, and surgical debridement of adjacent infected structures is often

necessary. Follow-up endoscopy is essential to assess response to therapy and to ensure that drainage is adequate.

Therapeutic Decisions

11. Coccidioidal meningitis requires life-long antifungal treatment.

    The treatment of choice for isolated coccidioidal meningitis is oral fluconazole, 800 mg/d most patients will respond to this therapy within several weeks. If the patient does not respond to fluconazole, itraconazole can be tried, but most physicians would go directly to intrathecal administration of amphotericin B. This can be accomplished through lumbar injection initially, but almost always will require a lumbar, cisternal, or ventricular reservoir for long-term therapy. If the patient has severe disseminated coccidioidomycosis as well as meningitis, intravenous amphotericin B should be used long with fluconazole initially. Experience clearly shows that this infection is rarely, if ever, cured and thus therapy should be given for life.

12. Cryptococcal meningitis: Combination antifungal therapy and aggressive control of intra-cranial pressure is required.

    Several randomized controlled trials in patients with AIDS have shown excellent results when induction therapy is given with amphotericin B combined with flucytosine, followed by consolidation therapy with fluconazole. It should be noted that the dosage of flucytosine should be never exceed 100 mg/kg/d, which is less than the dosage listed in the package insert (150 mg/kg/d). Flucytosine exibits dose-related marrow toxicity, which can be decreased by using the lower dosage noted above. Fluconazole is not as effective as amphotericin B when used for initial therapy. Therapy is the same for patients who do not have HIV infection, even though no controlled trials have been performed to compare azoles with amphotericin B in the population. Fluconazole alone can be used for isolated pulmonary and other forms of cryptococcal infection unless the patient is severely ill.

    An important finding that emerged from treatment trials in patients with AIDS was that increased intracranial pressure was common in cryptococcal meningitis and was associated with increased mortality. It is postulated that there is increased brain edema because of the osmotic effect from the large polysaccharide capsule surrounding each organism and the huge burden of cryptococci found in patients with AIDS; an alternative postulate is that the arachnoid villi are plugged by the large amount of capsular polysaccharide.

    A patient in whom the intracranial pressure is elevated should have repeated lumbar punctures over the succeeding few days to be certain that the pressure remains low. If repeated taps are required to keep the pressure low, a temporary shunting device, either lumbar or ventricular, should be placed lower the pressure. Most patients will respond to antifungal therapy and will not require a permanent shunting device.

13. Infection with Zygomycetes: Use amphotericin B combined with aggressive surgical debridement.

    Despite recent advances in antifungal therapy, infections with the Zygomycetes remain quite difficult to treat. These organisms are relatively resistant to amphotericin B, and current azoles have no activity against these fungi. Invasion through blood vessels with tissue infraction and necrosis is characteristic. Aggressive early and repeated surgical debridement to remove all necrotic tissue is essential for cure of the infection, and it should be combined with treatment with high doses of amphotericin B.

    It is appropriate to use a lipid-based formulation of amphotericin B so that a higher daily dose can be administered. The initial dosage of lipid formulation amphotericin B should be no lower than 5 mg/kg/d, and increasing the dosage to 10 mg/kg/d or higher has proved helpful in individual cases. Therapy must be continued until all foci of infection are eradicated. Decreasing immunosuppression, reversing diabetic ketoacidosis, and stopping any iron chelators that the patient may have been taking are also essential.

14. Candidemia: Treat all patients with an antifungal agent.

    Candidemia has become the most common serious fungal infection in hospitalised patients. Candida species now rank as the fourth most common cause of nosocomial bloodstream infections and are associated with the highest crude mortality rate. Currently, patients at greatest risk for candidemia are not those with neutropenia, but those who are in an ICU. These patients usually have multiple medical problems, including renal failure that

requires dialysis; have been treated with broad-spectrum antibiotics; and have uninary, endotracheal, and central venous catheters in place.

The source of candidemia is most often the GI tract or a central venous catheter. Some patients will clear the organism from the blood following removal of the intravenous catheter if that is the source, but many will not. Unfortunately, it is impossible for a clinician to know which patients will and which will not clear the infection without antifungal therapy.

The risks of persistent candidemia include seeding of the infection to the eye, osteoarticular structures (especially the vertebrae), the endocardium, and multiple other organs. The recommendations from a selected consensus panel and from the Infectious Disease Society of America guidelines are that all patients with candidemia should be treated with an antifungal agent, therapy most often is continued of 2 weeks after blood cultures have been shown to no longer yield Candida.

15. Options for the treatment of invasive aspergillosis.

    Amphotericin B has been the treatment of choice for invasive aspergillosis for the past 4 decades. Lipid formulations of amphotericin B are all approved only for refractory invasive aspergillosis, but many clinicians caring for patients who already have renal disease or are at risk for nephrotoxicity use a lipid formulation as primary therapy for aspergillosis. Although few comparison studies are available, the lipid formulations appear to have the same efficacy as standard amphotericin B. The dosage used is usually 5 mg/kg/d, but higher dosages have been used for severe disease.

    Voriconazole is approved for the primary treatment of invasive aspergillosis, basesd on the results of a randomized, controlled multicenter trial that included 277 patient with proven or probable invasive disease. Outcomes with voriconazole were superior to those noted with amphotericin B; voriconazole will likely assume a more prominent role in the primary treatment of aspergillosis.

    Caspofungin is approved for the treatment of patients who have refractory aspergillosis or those who cannot tolerate other agents.

16. In pregnant women, amphotericin B is the antifungal agent of choice.

    Although associated with more serious side effects than any other antifungal agent, amphotericin B is the only agent that has been given to pregnant women with no serious consequences for the fetus. The azoles are teratogenic in animals and have caused birth defects in humans receiving long-term therapy with fluconazole. All azoles should be considered contraindicated in pregnancy. The echinocandins are teratogenic in animals and are contraindicated in pregnancy.

17. Be aware of the individual absorption characteristics of oral azole formulations.

    Fluconazole has the best absorption characteristic of all the azoles. The drug is essentially 100% bioavailable, and absorption is not influenced by the presence of food in the stomach or by gastric acidity.

    The original capsule formulation of itraconazole requires both gastric acid and the presence of food in the stomach for adequate absorption. Administering H2 blockers, antacids, or proton pump inhibitors will markedly reduce serum levels of itraconazole. The oral suspension of itraconazole was developed to obviate this issue. The suspension should be given on an empty stomach.

    Voriconazole is approximately 95% bioavailable when given without food in the stomach 1 to 2 hours before or after eating); however, the presence of food reduces bioavailability to 80 to 85%. Gastric acid is not required for absorption.

18. Although relatively nontoxic, each of the azoles has certain side effects that should be monitored.

    All azoles have the potential to cause hepatitis; measurement of liver enzymes should be done at baseline and after several weeks of therapy. During long-term treatment with an azole, liver enzyme tests should be done every month.

    Itraconazole can cause a syndrome of hypertension, hypokalemia, and edema; this occurs mostly in older patients and often requires stopping the drug. Itraconazole is also uniquely associated with ventricular dysfunction.

    Fluconazole causes alopecia in many patients who receive the drug for several months. This may involve only thinning of scalp hair, but it can involve loss of all body hair. The effect is reversible when the drug is stopped. Dry, chapped lips are also noted frequently with fluconazole use.

    Although rashes are an uncommon side effect of all azoles, voriconazole has been noted to cause a rash in up to 80% of patients. The rash has been related to photosensitivity in some patient; these patients experience severe blistering of sun-exposed

skin. A side-effect noted only with voriconazole is photopsia, in which the patient perceives bright lights, wavy lines, or enhanced colors within 30 to 60 minutes after administration of either the oral or the intravenous formulation of the drug. This side effect occurs in as many as 30% of patients receiving the drug, lasts about 30 to 60 minutes, and eventually fades after several weeks despite continuation of therapy. It is not associated with any long-term visual consequences.

19. The echinocandins will assume an increasing role in the treatment of Candida infections.

    Caspofungin is the only echinocandin currently available; 2 other agents will likely be available soon. The echinocandins are fungicidal for all Candida species. Results from a multicenter, randomised, blinded trial comparing caspofungin with amphotericin B for serious Candida infections showed equivalent efficacy of the 2 agents. Approximately 80% of the patients had candidemia, and the others had peritonitis or deep-seated abscesses. There were fewer side-effects noted with caspofungin than with amphotericin B. The relative lack of toxicity of the echinocadins makes them attractive for use in ICU patients who have multiple underlying disease. These agents are available only as intravenous formulations that are given once daily.

20. For patients in renal failure, antifungal therapy must be individualized.

    Amphotericin B should be avoided if at all possible, and lipid formulation should be substituted if amphotericin B must be used. Obviously, if the patient is already on dialysis, there is no need to use a lipid formulation to avoid nephrotoxicity.

    Flucytosine is renally excreted; in renal failure, this agent accumulates to toxic levels, causing severe bone marrow suppression and hepatotoxicity. If serum flucytosine levels cannot be obtained, it is safer to not use this agent in patients with renal failure.

    Fluconazole is also renally excreted, and the dosage should be reduced when renal failure is present. However, fluconazole is relatively nontoxic; following suggested dosage reduction. Recommendations in the package insert allows safe use of intravenous or oral fluconazole in patients with renal failure.

    The intravenous formulations of both voriconazole and intraconazole are solubilized in cyclodextrins. Because of concerns over the nephrotoxic potential of these cyclodextrin components, which are cleared through glomerular filtration, it is recommended that neither drug be used in patients who have creatinine clearances below 30 to 50 mL/min. The oral formulations of these 2 azoles can be used safely in patients with renal failure. Because caspofungin is not nephrotoxic or excreted through the kidneys, it is a good choice for treating patients with renal failure.

SUGGESTED READING

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