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Identifying Patients With Leukemia Who Are at Risk for Fungal Infections

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H&O Approximately how many patients with leukemia will develop fungal infections?

VB The risk of fungal infection varies according to several factors, such as the type of leukemia, the status of remission, and comorbidities. Studies have demonstrated a wide range of 5% to 40%. The incidence, on average, is approximately 10% to 15%. Patients with acute lymphocytic leukemia have a lower risk of approximately 5% to 7%. The risk is almost double among patients with acute myeloid leukemia.

> Studies have demonstrated that as many as two-thirds of fungal infections are related to mold, and the rest are from *Candida*.

H&O Why are these patients at risk for fungal infections?

VB There are several reasons why patients with leukemia are at risk of developing a fungal infection. One of the most important risk factors is neutropenia. Many patients with leukemia have severe, prolonged neutropenia caused by either the disease itself or chemotherapy. Mucositis, a complication of chemotherapy, may lead to fungal infections. Another risk factor is immunosuppressive therapy, a common treatment among these patients. For example, graft-vs-host disease after allogeneic stem cell transplant is managed with corticosteroids. Many patients have comorbid conditions, including diabetes, cytomegalovirus, and other infections, that can increase the risk of fungal infections.

H&O Which types of fungal infections are likely to occur in these patients?

VB These patients are at risk for fungal infections with both *Candida* and mold. The epidemiology has changed owing to fungal prophylaxis and also because of the type of therapy, such as immunotherapy, transplant, and immunosuppressive medication. Studies have demonstrated that as many as two-thirds of fungal infections are related to mold, and the rest are from *Candida*. The prevalence of mold infection has increased in the past several years because of antifungal prophylaxis with therapies such as fluconazole. Among patients who receive antifungal prophylaxis, the *Candida* infections are frequently caused by resistant *Candida* species, such as *Candida glabrata*. Breakthrough infections in patients receiving antifungal prophylaxis with posaconazole (Noxafil, Merck) and voriconazole (Vfend, Pfizer) may also be caused by mucormycosis or zygomycosis.

H&O What are the risk factors for fungal infection?

VB One of the most important risk factors for fungal infection is neutropenia, both the degree and the duration. Patients with more severe neutropenia—a neutrophil count of less than 100/μL for more than 3 weeks—are at higher risk than those with moderate neutropenia lasting for a week.

Risk factors for *Candida* infection and aspergillosis may differ slightly. Total parenteral nutrition, renal failure, colonization of *Candida* in the gastrointestinal mucosa, the use of broad-spectrum antibiotics, and mucositis from chemotherapy are other important risk factors for infection with *Candida*. Invasive aspergillosis is associated with the use of corticosteroids for a long duration, as in patients who develop graft-vs-host disease after allogeneic transplant.

There are likely some genetic predispositions for many fungal infections. Factors that can increase the risk of fungal infection include polymorphisms in genes that encode toll-like receptors. Prior use of prophylactic antifungal therapy could alter the epidemiology of zygomycosis. For example, when patients who have been previously treated with voriconazole develop a breakthrough infection, the chances of zygomycosis are much higher.

H&O How do these fungal infections manifest?

VB The most common manifestations include bloodstream infection; infection of the lungs, such as pulmonary aspergillosis; and involvement of the sinuses.

H&O What signs and symptoms are associated with invasive fungal infections?

VB A fungal infection of the sinuses may lead to symptoms of sinusitis, such as headache and fevers. Infection of the lungs can cause fever, cough, and hemoptysis. Patients may have difficulty breathing, and imaging studies may demonstrate changes in the sinuses and lungs. Patients with a bloodstream infection or a disseminated infection may have fevers. Other specific changes depend on the organ involved. For example, in patients with disseminated liver involvement, the results of liver function tests may be abnormally high.

H&O How is the diagnosis made?

VB Diagnosis can be challenging because the tests are not always sensitive and specific. It is necessary to integrate clinical features, imaging findings, serologic biomarkers, and microbiologic evidence of fungal infection. Clinical factors include the patient's risk level. Patients with prolonged neutropenia have a much higher risk of infection than patients without prolonged neutropenia. Another clinical feature is a fever that does not respond to appropriate initial antibacterial therapy. Diagnosis also relies on imaging, such as computed tomography (CT) scans. For example, a CT scan showing nodules, a cavity, or a halo sign is suggestive of a fungal infection. In clinical practice, antimicrobial agents may be altered based on these findings.

Other important diagnostic tools include serologic biomarkers, such as the β-D-glucan assay or the galactomannan assay. In certain situations, bronchoalveolar lavage with a positive galactomannan assay can help in the diagnosis. It should be noted that these serum biomarkers can have both false-positive and false-negative results, so it is important to integrate other findings in the diagnosis.

Patients with prolonged neutropenia have a much higher risk of infection than patients without prolonged neutropenia.

The definitive diagnostic test is histopathologic examination of a biopsy specimen that demonstrates *Candida* or mold. Identifying a fungal element in a biopsy can confirm the suspicion of infection. This method, however, can be challenging to use in certain settings. Thrombocytopenia and coagulopathy, both sequelae of leukemia, can increase the risk of bleeding during a lung biopsy. A lung biopsy can also be difficult in a patient who is doing poorly and receiving a high amount of oxygen supplementation. Lung biopsies are associated with pneumothorax, which is a practical consideration.

H&O What are some ways to minimize a patient's risk of contracting a fungal infection?

VB The most important preventive approach is to utilize fungal prophylaxis, which is supported by high-quality, randomized trials. Two of the many studies that have provided important insight are randomized, multicenter trials that evaluated the outcome of patients treated with various antifungal drugs. A study by Cornely and colleagues of patients with acute myeloid leukemia and myelodysplastic syndrome initiated this prophylaxis regimen at the time of diagnosis and continued it

until patients recovered from neutropenia and were in remission. This study demonstrated that posaconazole significantly improved the risk of contracting invasive fungal infection and reduced overall mortality compared with fluconazole and itraconazole.

A study by Ullmann and coworkers demonstrated that posaconazole prophylaxis was superior to fluconazole in patients with severe graft-vs-host disease requiring immunosuppressive therapy. Most other patients who undergo allogeneic transplant and patients with acute lymphocytic leukemia do just as well with fluconazole prophylaxis. The most important way to reduce the risk of fungal infection is to utilize appropriate fungal prophylaxis.

H&O When should antifungal therapy be stopped?

VB In patients with leukemia, antifungal prophylaxis is continued until they have recovered their neutrophil count and achieved remission. We continue antifungal prophylaxis until the end of chemotherapy and until remission is achieved.

Disclosure

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Suggested Readings

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