

Fungal Infections in PIDD Patients

PIDD patients are more prone to certain types of infections. Knowing which ones they are most susceptible to and how they are most commonly treated can help to minimize the risk.

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Individuals with primary immune deficiencies (PIDDs) are at greater risk for recurrent infections compared with those with normal immune systems. PIDD patients frequently have a genetic defect that causes an abnormality in the number and/or function of one or more components of the immune system that fights infections. These infections can be predominantly viral, bacterial or fungal, depending on the type of white blood cells affected by the specific immune deficiency. For instance, neutrophil abnormalities lead to recurrent bacterial and mold infections; B lymphocytes typically lead to bacterial infections, more specifically those that antibodies prevent such as *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*; and T lymphocytes frequently lead to recurrent viral infections and yeast infections such as *Candida*. Other types of immune system abnormalities lead to other specific recurrent infections.

Individuals with PIDDs often require recurrent courses of antibiotics, which can lead to an imbalance in the normal bacteria and fungi (normal flora) that inhabit all of our protective barriers such as the skin, gastrointestinal tract and oral mucosa. This imbalance, in turn, increases vulnerability to other types of infections such as yeast infections and *Clostridium difficile* (C. diff) infections.

What Are Fungi, and What Diseases Do They Cause?

Fungi are categorized as eukaryotes, organisms whose cells are larger and more complex in their makeup compared with bacteria, which lack nuclei inside the cells, and viruses, which require assistance from host cells (the cells it infects) to replicate. For medical purposes, fungi are divided into three groups: yeasts, molds and those that can exist as both yeasts and molds (dimorphic fungi).

Yeasts commonly include *Candida* species and *Cryptococcus* species, with *Candida* being the more common. *Candida* are a part of human normal flora and mostly reside in the mouth, gastrointestinal tract and vagina. Problems arise when their numbers multiply in these areas due to the eradication of normal bacteria from antibiotic use, medications like corticosteroids that weaken the immune system, or when the improper function of the immune system allows them to replicate unchecked. *Candida* can cause infections in the mouth, known as thrush, which appear as white plaques on the inside of the cheeks and tongue. It can also cause vaginal yeast infections and diaper rash in infants and young children. And, it can cause infections on the skin surrounding the fingernails

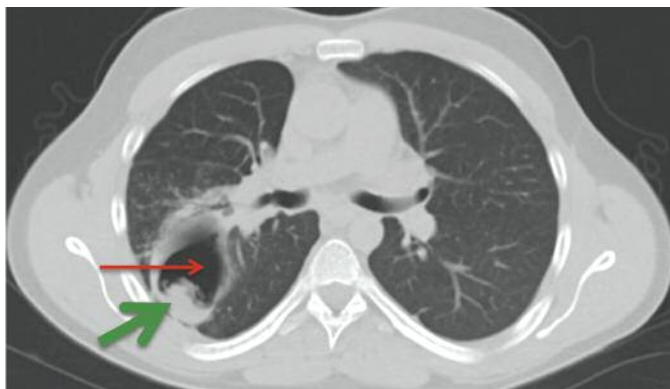
(paronychia) or the fingernails and toenails themselves (onychomycosis). *Candida* can enter the bloodstream and cause more severe infections when the normal skin barriers are compromised such as with central venous access lines (long-term IV access) that are sometimes needed for various treatments. These invasive infections usually cause fever and more acute illness compared with the more mild infections such as thrush and vaginal yeast infections. Ringworm is also caused by yeasts, including *Trichophyton* and *Microsporum* species, that cause rashes on the skin or scalp. *Tinea versicolor* is caused by the yeast *Malassezia furfur* and causes a rash usually on the trunk.

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Cryptococcus is a yeast that can be found in the soil, in wild bird droppings and around certain plants. In healthy individuals, it rarely causes problems. However, in immune deficiencies with T lymphocyte abnormalities, it can usually cause lung infections when it is inhaled. The lung infection can look like a mass on chest imaging scans but rarely causes many symptoms. However, *Cryptococcus* can spread to the brain and cause meningitis. The meningitis symptoms may evolve over weeks to months, which is different from bacterial meningitis, which rapidly causes significant illness. This may present with symptoms such as headaches, personality changes or vision changes.

Molds are fungi that grow as multicellular organisms that usually have branches called hyphae. The most common mold responsible for causing infections is *Aspergillus*. *Aspergillus* species grow in almost all oxygen-rich environments. It is rare for people with normal immune systems to have infection from mold, although breathing in high quantities of molds can make asthma and other lung diseases worse. Problems with the neutrophil white blood cells, either due to a PIDD (e.g., chronic granulomatous disease,

Figure 1.



This chest CT scan of a 23-year-old man with Hyper IgE syndrome shows a cavity in the right lung (thin red arrow) in which there is an aspergilloma (thick green arrow). Aspergillomas can cause hemoptysis (coughing up blood).

Figure 2.



*This individual has a primary immunodeficiency (Hyper IgE syndrome) that leads to recurrent *Candida* infections. The arrow points to a nail that was infected with *Candida*.*

or CGD) or to chemotherapy, can cause severe mold infections that require long-term antifungals and possibly surgery to cure. In CGD, pneumonias from molds can cause chest pain, cough and fever and may worsen slowly over weeks compared with bacterial infections that usually cause more symptoms rapidly. Molds can cause less severe, but still problematic, chronic pulmonary infections in individuals with bronchiectasis (irreversible dilation of part[s] of the bronchial tubes) or other structural lung problems. People with asthma or cystic fibrosis can develop an allergy to molds and have allergic sinus or lung disease, known as allergic bronchopulmonary aspergillosis (ABPA) or allergic fungal sinusitis. ABPA normally causes wheezing and productive cough with usually brown-colored mucous

plugs. Allergic fungal sinusitis causes thick mucous that often requires sinus surgery to clear. Both ABPA and allergic fungal sinusitis improve typically with steroids such as prednisone.

Dimorphic fungi that are mainly responsible for causing infections include Histoplasmosis, Blastomycosis and Coccidioidomycosis. Histoplasmosis is found in the soil mostly in the Ohio River Valley and lower Mississippi River area and usually causes a self-limited lung infection with a dry cough. Blastomycosis grows in moist or wet environments and vegetation and is found most frequently around the Great Lakes. Coccidioides is found in the soil of primarily the Southwestern United States and causes valley fever, which is a flu-like illness with cough. All three can cause infections in individuals with normal immune systems, but the infections are not usually severe and frequently clear without any medications. Those with PIDDs can develop significant infection affecting the respiratory, neurologic and dermatologic systems from these organisms.

What PIDDs Lead to Fungal Infections?

As mentioned earlier, individuals with PIDDs have increased risk for certain fungal infections, and the type of PIDD determines the susceptibility to the infection and the severity of illness.

CGD is caused by a problem in the neutrophil oxidative burst, which is the chemical end product of neutrophil activity that kills certain bacteria and fungi. This abnormal killing ability of neutrophils leads to susceptibility to infections with molds, most commonly with the *Aspergillus* species. These mold infections are usually of the lung, skin or bone and can cause fever and sometimes localizing symptoms to the site of infection. Diagnosis is best made by taking a biopsy and sending the sample for fungal and bacterial cultures so that specific treatment can be given.

Severe combined immune deficiency (SCID) is caused by severe abnormalities in T lymphocytes along with B and/or NK lymphocytes. Affected individuals present early in life as infants with recurrent, severe bacterial and viral infections, as well as failure to grow normally. Lymphocytes are also important for the control of yeasts, and infants with SCID frequently have yeast infections causing thrush and diaper rash.

Hyper IgE (Job's) syndrome is caused by mutations in a gene called STAT3, which is needed for T lymphocytes to mature into a special type of T lymphocyte called a Th17

cell. Th17 cells are involved in the control of yeast on the skin and mucous membranes, and individuals with abnormal Th17 cells can have trouble with Candida in the mouth (thrush), as well as fingernail Candida infections and recurrent vaginal yeast infections. Less frequently, there can be more severe infections from Cryptococcus, Histoplasmosis, and Coccidioides. These can cause gastrointestinal infections and, in the case of Cryptococcus and Coccidioides, can cause meningitis.

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STAT1 immune deficiency is caused by gain of function mutations in a gene called STAT1, which also leads to abnormal Th17 function. Therefore, yeast infections occur affecting the mouth, skin, fingernails and vagina. Severe Coccidioides infections also can occur in patients with gain of function STAT1 mutations.

APECED (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy) is an autoimmune disorder in which autoantibodies (antibodies that the body makes against some of its own proteins) can cause a deficiency in the inflammatory proteins made by Th17 cells leading to mucosal and skin yeast infections.

What Are Treatments for Fungi?

Several antifungal medications exist for fungal infections. Following are the most frequently used medications. The use of any of these medications, with their potential side effects and interactions with other medications/herbals, should always be discussed with one's medical team beforehand.

Polyene Antifungals:

- Nystatin is used topically to treat thrush or skin infections with Candida. With thrush, it is usually administered as a swish and spit. Side effects are rare.
- Amphotericin has activity against many fungi and is used frequently for severe infections. Amphotericin use is limited due to its intravenous administration and risk for kidney toxicity.

Azole Antifungals:

- Miconazole/clotrimazole are topical medications primarily used for Candida infections.
- Fluconazole is a medication taken by mouth used most frequently to treat Candida infections but can be used for Cryptococcal or Coccidioides infections if mild or after an initial course of amphotericin. Main side effects include abnormal elevations in liver enzymes, which are usually reversible. At high doses, hair may thin.
- Itraconazole has activity against both yeasts and molds. For molds, it is usually used for prophylaxis or treatment of mold infections. It can be used for some infections with Histoplasmosis as well. Similar to fluconazole, it can affect the liver.
- Voriconazole has excellent activity against many yeasts and molds. In addition to liver enzyme abnormalities, it can also increase risk for sun sensitivity and sunburn.
- Posaconazole is very similar to voriconazole in its activity against yeasts and molds. It does not increase risk for sun sensitivity, but is only dispensed in a liquid formulation.

Echinocandin Antifungals:

- Caspofungin, micafungin and anidulafungin have excellent activity against yeasts, and are sometimes used for molds, usually along with other antifungals such as voriconazole. Unfortunately, they are only available as intravenous medications at this time.

Allylamine Antifungal:

- Terbinafine is used frequently for skin or nail fungal infections either as a pill or in a cream.

What Are Ways to Prevent Fungal Infections?

Fungi are found in abundance throughout the environment, and exposure cannot be totally avoided. But, there are ways to avoid high-risk exposures. Molds are common outdoors in shady, damp spots, as well as in areas of decomposing vegetation. Mulch and hay can have increased amounts of mold, and avoiding exposure to it through activities such as gardening and hayrides or barns if one is susceptible to infection is often advised. Buildings with ongoing renovations may often have high amounts

of mold. Histoplasmosis can be found in caves frequently as it is present in bat droppings. Bird droppings can have Histoplasmosis and Cryptococcus. Coccidioides is found in the desert areas of the Southwestern United States.

Candida frequently becomes problematic when the normal flora is disrupted such as with antibiotics. Taking an antibiotic directed against a specific bacteria, when a broad spectrum is not necessary, can be helpful. Candida infections of the mouth (thrush) can also occur when using inhaled corticosteroids, which are frequently used in asthma and in other chronic lung diseases. Rinsing the mouth after using the inhaler can really diminish the risk of thrush in this setting.

Probiotics are good bacteria or yeast that can be ingested in attempts to restore the normal flora. The digestive system has greater than 500 different types of bacteria that keep the intestines healthy and assist in food digestion and are believed to help the immune system. Probiotics are available as dietary supplements, often as capsules, or in certain foods, typically yogurts. Probiotics are frequently used, especially in the setting of antibiotic use, to replenish the balance of friendly bacteria/yeast, but data showing consistent benefit is limited. There is some suggestion that they may be used to diminish Candida overgrowth in the setting of antibiotics, as well as decreasing diarrhea caused by antibiotics. However, the true benefit and proper dosages need further investigation. Probiotics are generally well-tolerated, although long-term safety has not been well studied. PIDD patients should discuss the use of probiotics with their healthcare team to minimize any risks.

Several antifungal medications exist for fungal infections.

Prophylactic antifungals are used in the setting of certain PIDDs to try to prevent fungal infections. CGD is one example of this, as it is recommended that prophylactic antifungals such as itraconazole be administered daily to prevent mold infections. Fluconazole is used sometimes as prophylaxis for PIDDs characterized by mucocutaneous candidiasis.

Future Directions

There has been an increased amount of research regarding the human normal microbiome (normal flora) in recent years, focusing on areas such as the skin, intestines and vagina, where there are lots of normal bacteria and yeasts. It is hoped that this research will help us understand more about how antibiotics and other treatments disrupt the normal flora and how we can then prevent overgrowth of certain microbes leading to infection. Improving this disruption will hopefully diminish some of the Candida infections.

An increasing number of medications are being evaluated as well to combat fungal infections, especially since molds and yeast can cause very severe infections and death in severely immunocompromised patients such as those undergoing bone marrow transplants. In addition, vaccines are being studied for the prevention of fungal infections. ■

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