In Brief: Antifungal Drugs

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Fungi cause both superficial and serious systemic infections in children. Eradication of fungal infections typically involves the use of agents that inhibit cell membrane function, leading to cell death. Selection of the appropriate medication for fungal infections depends on the susceptibility of the organism and the adverse effects of the drug. The major classes of systemic antifungal agents are polyenes, azoles, and echinocandins.

The most commonly used polyene is amphotericin B. Since 1960, this product of the actinomycete *Streptomyces nodosus* has been widely used for systemic infections against a broad array of fungal species. Amphotericin B deoxycholate, the conventional formulation of this drug, remains the preferred treatment for newborns with systemic candidiasis because of its better penetration into the central nervous system, urinary tract, and eye. However, potential adverse reactions, particularly renal toxicity, necessitate close monitoring. Lipid-associated and liposomal formulations of amphoterin B are less toxic, but their penetration into some tissues, such as the kidney, does not reach therapeutic concentrations.

Amphotericin B is only available parenterally. It must be mixed in a dextrose and water solution because saline causes it to precipitate. Because of infusion reactions such as fever and chills, some patients must be premedicated with acetaminophen and diphenhydramine. Less common reactions include nausea, vomiting, headache, malaise, hypotension, and arrhythmias, which require the addition of hydrocortisone, although these reactions are less common in children than in adults.

Amphotericin B may cause nephrotoxicity, hepatoxicity, anemia, and neurotoxicity. Nephrotoxicity may be increased by concurrent administration of aminoglycosides, cyclosporine, tacrolimus, cisplatin, nitrogen mustard compounds, and acetazolamide. Early signs of nephrotoxicity include increasing blood urea nitrogen (BUN) and creatinine values, hypokalemia, and hyponatremia. Permanent nephrotoxicity is related to the cumulative dose that is administered. BUN and creatinine should be assessed every other day while adjusting the amphotericin B dose and followed weekly thereafter along with electrolytes. Hydration and sodium repletion before administration of amphotericin B may decrease the risk of developing nephrotoxicity.

Two subclasses of azoles are used to treat fungal infections: imidazoles and the newer triazoles. Imidazoles include clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, and sulconazole. Ketoconazole was the first oral antifungal used to treat systemic infections and has a broad spectrum of coverage. Although newer triazole antifungals are available, oral ketoconazole can be used as a second-line therapy for certain *Candida* species and invasive histoplasmosis, blastomycosis, and coccidiomycosis.

Because absorption of oral ketoconazole depends on gastric pH, antacids and histamine-2 blockers may decrease its activity. Ketoconazole can mount therapeutic

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concentrations in the skin, synovial fluid, lung, saliva, and vaginal secretions. It does not penetrate the cerebrospinal fluid (CSF); therefore, it cannot be used to treat fungal meningitis. Adverse effects include gastrointestinal (GI) upset and anorexia. In addition, due to its interference with steroid biosynthesis of fungal cell membranes, menstrual irregularities, gynecomastia, impotence, and decreased adrenocorticotropic hormone-stimulated adrenal cortisol production may occur.

Of the triazoles, which include fluconazole, itraconazole, voriconazole, and posaconazole, both fluconazole and itraconazole are oral agents most commonly used to treat systemic fungal infections. Fluconazole is readily absorbed by the GI tract. Oral concentrations closely match intravenous concentrations, making it effective against candidiasis, superficial tinea infections, histoplasmosis, mucormycosis, cryptococcosis, and coccidiomycosis. In fact, its penetration into the CSF is excellent and useful in the treatment of fungal meningitis, usually in conjunction with amphotericin B in immunocompromised patients. GI upset is the most common adverse effect, along with reversible alopecia and hepatotoxicity. Itraconazole is available both orally and intravenously but has a broader spectrum of coverage than fluconazole. Itraconazole penetrates the CSF poorly, making fluconazole the optimal choice in this class for fungal meningitis. Voriconazole, a newer agent, has broader coverage than other triazoles, including non-albicans *Candida* species and invasive *Aspergillus*.

Echinocandins are a new class of antifungal medications that are administered only parenterally. Caspofungin can be used for empiric therapy for presumed fungal infection in febrile neutropenic patients and for candidiasis and aspergillosis in patients who are intolerant or resistant to other antifungal agents. Micafungin is approved for use in patients for candidemia, acute disseminated candidiasis, and prophylaxis of invasive candidal infections in patients undergoing hemopoietic stem cell transplantation. Although a major adverse effect of echinocandins is hepatoxicity, these agents have fewer adverse effects than amphotericin B and are often preferred for parenteral use.

The emergence of newer systemic antifungal agents over the last 2 decades has expanded the options to treat invasive fungal infections beyond amphotericin B. Use of amphotericin B is now limited to neonatal systemic fungal infections due to its significant adverse effects. Newer antifungals have fewer adverse effects and oral agents provide more flexibility and treatment options.

COMMENT: I find it fascinating that fungus can cause both relatively common superficial infections in healthy children and systemic, life-threatening infections in immunocompromised patients. This In Brief provides a great review of antifungal agents and their appropriate uses. The recent development of new antifungal agents is impressive, with fewer adverse effects yet improved effectiveness. Another example of the wonder of pediatric medicine and translational research!

– Janet Serwint, MD
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