Update on Antifungal Treatment in Neutropenic Patients

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Introduction

Fungal infections in neutropenic patients have always posed a great challenge even to the most experienced clinician. Patients are immunocompromised in dismal situations with high mortality (invasive aspergillosis 58-87%, systemic candidiasis 40-60%)\(^1\), and only prompt diagnosis with effective antifungal treatment will salvage these patients. Despite advances in methods of early diagnosis of invasive aspergillosis, such as serial measurement of peripheral blood galactomannan antigen or circulating *Aspergillus* DNA\(^2\), clinical presentations are often late and diagnosis is delayed. With the introduction of the new echinocandins class of antifungal agent and the new triazoles including voriconazole and posaconazole, successful treatment is more likely with less toxic effects. In this article, we will discuss the different classes of antifungal agents and their applications in different clinical scenarios.

Antifungal Agents

**Triazoles**

The triazole antifungals target the fungal cytochrome P-450 dependent 14\(\alpha\) -sterol demethylase\(^3\). This enzyme converts the lanosterol to ergosterol, a vital component of the cellular membrane of fungi. As a result, ergosterol synthesis is disrupted leading to increased cell membrane permeability, cell lysis and death. The triazoles are fungistatic against Candida species and only voriconazole possesses fungicidal activity against *Aspergillus* species\(^4\). The triazoles include fluconazole, itraconazole, voriconazole and posaconazole. Triazoles are associated with abnormal hepatic function, ranging from asymptomatic mild liver function derangement to fulminant hepatic failure. Regular monitoring of the liver function during antifungal treatment with the triazoles is recommended.

**Fluconazole**

Fluconazole is very hydrophilic with an excellent bioavailability of around 90%. It is available in both oral and intravenous preparations. Once it is absorbed in the stomach, it is widely distributed in body fluids and tissues. It also penetrates well into the cerebral spinal fluid (CSF), achieving about 80% of the serum level\(^5\). It has potent activity against most of the *Candida* species; apart from *C. glabrata* that demonstrates significant resistance to fluconazole. It has no activity to *C. norvogenesis*, *C. ciferrii* and *C. krusei*. It is active against *Cryptococcus neoformans*, *Trichosporon*, histoplasmosis and coccidioidomycosis. It has no activity against *Aspergillus*, *Fusarium* and other moulds.

**Itraconazole**

Comparing to fluconazole, the bioavailability of itraconazole is much reduced. It varies with different formulations, ranging from 30% in the solution formulation to 55% in the capsule formulation. It also requires an acidic environment for solubilisation in the capsule form and absorption is increased with food and acidic drinks\(^6\). Proton pump inhibitors that reduce the gastric pH should be avoided. It is lipophilic and cannot penetrate the blood brain barrier. In addition to the *Candida* species, itraconazole is a second-line agent for the treatment of aspergillosis.

**Voriconazole**

It is available in both the oral and intravenous formulations. Similar to fluconazole, it has an excellent bioavailability of over 90%. It is widely distributed in body fluid and tissues including the CSF. It is metabolised by the cytochrome P450 enzyme\(^7\). It is active against the *C. glabrata*, *C. norvogenesis*, *C. ciferrii* and *C. krusei* that fluconazole has no action against. It possesses an enhanced activity against *Aspergillus* and *Fusarium* species.

**Posaconazole**

Currently, it is only available in the oral formulation. Similar to fluconazole and voriconazole, it has an excellent bioavailability. It undergoes hepatic metabolism and is eliminated in the faeces\(^8\). In addition to its activity against *Aspergillus* and *Fusarium*, it is also active against the *Zygomycetes*.

**Polyenes**

The polyenes interact with fungi membrane ergosterols to produce an aggregate that forms a transmembrane channel, allowing the cytoplasmic contents to leak out and subsequent fungal cell death\(^9\).

**Amphotericin B**

This is a polyene originally extracted from *Streptomyces nodosus*. It is insoluble in water and all preparation of amphotericin B must be infused in 5% dextrose. It is fungicidal against all *Candida* and *Aspergillus* species, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans* and *Sporothrix schenckii*. It has no activity against *Fusarium* and *Trichosporon*\(^10\). Synergistic activity of amphotericin B with flucytosine has been demonstrated against...
serious Cryptococcal infection, especially in immunocompromised patients. Nevertheless, serum flucytosine level should be monitored if patients develop amphothericin B related nephrotoxicity.

As previously mentioned, the main side effect of amphothericin B is nephrotoxicity that manifests initially by kaliuresis and hypokalaemia, then fall in serum bicarbonate. Renal injury can be reduced by pre infusion hydration with 500ml saline and avoidance of other nephrotoxins. Infusion related adverse reactions like fever, chills and headache could be minimised by premedication with anti-histamine, corticosteroid or paracetamol. Prolonging the infusion time to 12 hours or continuous intravenous infusion over 24 hours may prevent these reactions.

**Liposomal Amphothericin B**
Liposomal formulation of amphothericin B reduces its nephrotoxicity side effect and improves its tolerance, without reducing its efficacy. Nevertheless, use of liposomal amphothericin B is hindered by its cost.

**Echinocandin**
Echinocandin inhibits synthesis of \( \beta \)-\( (1,3) \)-D-glucan, a critical component of fungal cell walls via noncompetitive inhibition of the enzyme 1,3-\( \beta \) synthetase\(^{14,15} \). It is fungicidal against most *Candida* species and fungistatic against *Aspergillus* species, with minimal activity against the dimorphic fungi. It also demonstrates modest activity against the spore form of *Pneumocystis carinii*. It is not active against *Fusarium* and *Rhizopus*. The echinocandins are embryotoxic (category C) and should not be used in pregnancy. Patients with chronic liver disease need dosage adjustment. Other side effects include nausea, vomiting, diarrhea, headache and hypersensitivity related rash and pruritus.

**Caspofungin**
The first approved echinocandins. It has low oral bioavailability and thus must be given intravenously only. The drug is well tolerated and non-nephrotoxic. It interacts with cyclosporine, causing deranged hepatic parenchymal enzyme. Concomitant use of the two drugs is not recommended. Dosage reduction in patients with moderately deranged liver function is recommended.

**Micafungin**
Another echinocandin, indicated for the treatment of candidaemia, disseminated candidiasis and *Candida* peritonitis. It was recently approved for the prophylaxis of Candida infections in patients undergoing haematopoietic stem cell transplantation.

**Anidulafungin**
The third echinocandin, indicated for invasive *Candida* and *Aspergillus* infection. It differs from other echinocandins in that it undergoes chemical degradation to inactive forms at body pH and temperature. It does not rely on hepatic or renal excretion and thus does not require dosage reduction.

Clinical Scenario Requiring Systemic Antifungal Agents

**Empirical Treatment for Neutropenic Fever**
Neutropenic fever in a patient is defined as a sustained temperature of \( >38^\circ \)C for more than one hour with an absolute neutrophil count (ANC) \( < 500 \text{ cells/mL} \). Threshold for initiation of empirical antifungal treatment for neutropenic fever varies from centre to centre. In general, if fever persists after five days of antibiotics therapy and no microbiological pathogen is isolated, previous guidelines recommended to add amphothericin B to the antibiotics that the patient is already receiving\(^16 \). Recent trials however have demonstrated that caspofungin was associated with a significantly higher survival rate at seven days after the completion of therapy and a superior safety profile than amphothericin B\(^17 \). The primary choice is caspofungin as first-line empirical therapy in patients with suspected fungal infections. Voriconazole and liposomal amphothericin B are effective alternates\(^18 \). It is important to bear in mind that echinocandins are inactive to *Fusarium* and *Cryptococcus neoformans* that were previously mentioned. Besides antifungal treatment, all catheter in-situ should be replaced\(^19 \).

**Invasive Aspergillosis**
The diagnosis of invasive aspergillosis is based on culture and histology, aided by new tests includes galactomannan\(^20 \) and PCR testing\(^21 \). The Infectious Diseases Society of America (IDSA) has recommended voriconazole as the initial treatment of choice for invasive aspergillosis\(^22 \). Trials have shown that voriconazole is superior to standard amphothericin B in the treatment of invasive aspergillosis in terms of both partial and complete response, lower mortality rate, better tolerance and severe adverse reactions\(^23 \). Similar efficacy and safety profile is expected from posaconazole\(^24 \). Itraconazole is considered a second-line treatment when compared to voriconazole, based on its inferior intrinsic activity against aspergillosis. Echinocandins are also active against invasive aspergillosis with a good tolerance\(^25 \). However, due to the lack of data on echinocandins for the treatment of invasive aspergillosis, voriconazole is the treatment of choice. Antifungal combination has great potential to improve outcome based on observational study. In vitro results have shown additive effect with combination therapy with caspofungin and voriconazole\(^26 \), whereas combinations of caspofungin and amphothericin B have a synergistic effect\(^27 \). Most of the in vivo data showed that the use of voriconazole and caspofungin combination therapy for the treatment of invasive aspergillosis showed improved clinical outcomes and reduced mortality. Combination therapy with caspofungin and amphothericin B showed similar results. However, combination therapy with the azoles and amphothericin B is not recommended based on the fact that azole inhibits the ergosterol biosynthetic pathway thereby reducing the amphothericin B binding to the fungal membrane\(^28 \). Nevertheless, spontaneous recovery of bone marrow function with or without the assistance of granulocyte colony-stimulating factor (G-CSF) is the utmost important factor to recovery of invasive aspergillosis.
Candidaemia
Candidaemia is defined as the presence of Candida species in blood. Patients are at risk of developing candidaemia if they are immunocompromised or under intensive care, especially if they have a central venous catheters in-situ, on broad-spectrum antibiotics and on haemodialysis. Diagnosis of candidaemia is based on blood culture with the BACTEC system. Other methods of diagnosis include tissue biopsy and antigen testing with beta-D-glucan assay. All intravenous catheters should be removed and replaced. Amphotericin B deoxycholate was previously the antifungal of choice, with rapid fungicidal action against the Candida species. Unfortunately, its usage is limited by its nephrotoxicity. The less toxic lipid formulation of amphotericin B is often used instead. However, it is more expensive. The azoles are still active against the C albicans. However, C krusei is intrinsically resistant to fluconazole due to an altered cytochrome P-450 isoenzyme but remains susceptible to voriconazole and posaconazole. C glabrata isolates are resistant to the azoles secondary to drug efflux and cross-resistance among the azoles is common. Echinocandins, however, remain a potent antifungal against most Candida species including C krusei and C glabrata with an excellent safety profile. Trials have compared caspofungin against amphotericin B and micafungin against liposomal amphotericin B for the treatment of invasive candidiasis. All trials showed similar efficacy between the two antifungals but the echinocandins are associated with less drug toxicity. In general, echinocandins are the drug of choice for unstable neutropenic patients who have evidence of invasive Candida infection, previously exposed to fluconazole and in institutions where C glabrata or C krusei are a common isolate. Echinocandins are superior to amphotericin B in terms of safety profile and cost-effectiveness when compared to liposomal amphotericin B. Voriconazole and liposomal amphotericin B are second choice. However, cross-resistance with fluconazole may affect voriconazole efficacy.

Hepatosplenic Candidiasis
This occurs in patients with haematological malignancies who have recovered from an episode of neutropenia after chemotherapy. Discrete microabscesses of Candida are found in the liver, spleen and kidneys. The 2004 IDSA guidelines suggested that fluconazole is the first-line drug of choice. Amphotericin B or liposomal amphotericin B may also be used as initial therapy for the first two weeks, followed by long-term therapy with oral fluconazole. Caspofungin is another choice.

Zygomycosis (Mucormycosis)
Combination of surgical debridement and antifungal therapy with lipid formulation of amphotericin B or posaconazole is the treatment of choice for zygomycosis. Underlying diseases including hyperglycaemias, metabolic acidosis and deferoxamine administration should also be treated.

Fusarium Infection
This filamentous fungus has become an important infection in the immunocompromised. Amphotericin B is the most commonly used antifungal for Fusarium, but with the emergence of voriconazole that is fungicidal against filamentous fungi with much fewer adverse effects, it is an alternate to amphotericin B. Posaconazole is also active against Fusarium. In view of the high mortality with disseminated Fusarium infection, a combination therapy of voriconazole and lipid formulation of amphotericin B is a good salvage therapy.

Conclusions
For immunocompromised patients, treatment with antifungal agents not only suppresses the fungal growth but also buys time to allow patients to recover from neutropenia. Clinical suspicion, prompt diagnosis and early treatment are the keys to success in eradication of fungal infection. Supportive therapy with G-CSF may hasten neutrophil recovery and functions. New antifungal agents including echinocandins and the new triazoles will overcome resistant strains with greater efficacy and less toxicity.

References


