In the management of invasive fungal infections...

...Candida and Aspergillus can be menace
Epidemiology

Incidence of invasive fungal infections is increasing rapidly in clinical practice. Long-term use of broad spectrum antibiotics, cancer chemotherapy, transplant immunosuppression and overall increase in the population of immune-compromised hosts has increased the risk of fungal infections. There is a need of high degree of suspicion of fungal infections for early diagnosis and later treatment of fungal infections.¹ Fungi are commonly present in our environment. About 70000 species of fungi are found to be present in the environment. However, only about 300 species of fungi are present in human beings. Aspergillus and Candida species of fungi are most common in human body.²

The incidence of invasive fungal infections is on the rise, and also the morbidity and mortality associated with it. According to a study, 91/110 patients (82.7%) had critical care patients have fungal infection.³ It is difficult to gain exact picture of epidemiology of invasive fungal infections owing to different definitions used, the different risk groups studied, and variation from institution to institution.⁴

The studies show an overall invasive fungal infection prevalence of 8.2%. Studies also suggest an increase in prevalence of invasive fungal infections over the years: 1993–1996 (6.6%), 1997–2000 (8.6%), and 2001–2005 (10.4%). Invasive fungal infections were most common in hematologic malignancy (33%), followed by transplant (22.9%), acquired immunodeficiency syndrome (19.7%), solid tumours (4.8%) and other diagnoses (3.5%). Among the fungi, Candida species were most frequent (18%), followed by invasive fungal infections caused by Aspergillus species (1.4%).²

Management of IFI and associated challenges

Various approaches have been used in the management of fungal infections. The approaches used are as follows:⁴

- Empiric approach
- Pre-emptive approach
- Prophylactic approach
- Pathogen-specific approach

Empiric approach is often initial approach, when the pathogen associated is not clear and patient has persistent unexplained fever. Pre-emptive approach is followed when there is high suspicion of IFIs such as in case of mold infection, radiological evidence, high risk patients and positivity for immunoglobulins GM. Prophylaxis against IFIs is followed in patients such as haematopoietic cell transplant recipients. Pathogen-specific approach is an ideal approach. However, in most of the cases identity of the specific pathogen is not known and thus practically directed empirical approach is employed.⁴
Management of IFIs is challenging. Some of the challenges in the management of IFIs are as follows:

<table>
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<th>Challenge</th>
<th>Description</th>
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<tr>
<td>Challenge 1</td>
<td>Early and accurate diagnosis</td>
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<td>Challenge 2</td>
<td>Subsequent use of appropriate antifungal therapy</td>
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<td>Challenge 3</td>
<td>Unchanged epidemiology of invasive fungal infections in spite of wide use of antifungal prophylaxis</td>
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<td>Challenge 4</td>
<td>Resistance rates</td>
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<td>Challenge 5</td>
<td>More resistance among emerging fungi vs. earlier fungi</td>
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<tr>
<td>Challenge 6</td>
<td>Toxicity and low potency of antifungal agents</td>
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Advances in more potent and less toxic antifungal agents, such as second-generation triazoles and echinocandins (e.g. micafungin), may potentially improve the outcomes of these invasive fungal infections.

**Place of micafungin in the management of invasive fungal infections**

Micafungin is an echinocandin, which is approved for use in oesophageal candidiasis and prophylaxis of invasive Candida infections in patients undergoing haematopoietic stem cell transplantation in the year 2005. It was later approved for additional uses in candidaemia, acute disseminated candidiasis, Candida abscesses and peritonitis. The drug is also useful as fungistatic against Aspergillus species. Core evidence clinical impact summary for micafungin is elicited in Table 1.

**Table 1: Core evidence clinical impact summary for micafungin**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Evidence</th>
<th>Implications</th>
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<tr>
<td>Disease-oriented evidence</td>
<td>Demonstrates excellent efficacy for the treatment of candidemia/invasive candidiasis.</td>
<td>May be used as front-line therapy in treating candidemia/invasive candidiasis, except for meningitis.</td>
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<tr>
<td>Disease-oriented evidence</td>
<td>Demonstrates good efficacy as primary or salvage therapy in high-risk patients with invasive aspergillosis</td>
<td>The major role remains as salvage therapy.</td>
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<tr>
<td>Disease-oriented evidence</td>
<td>Demonstrates very good efficacy as antifungal prophylaxis in neutropenic patients.</td>
<td>May be used as a first-line prophylactic agent in neutropenic patients.</td>
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<tr>
<td>Disease-oriented evidence</td>
<td>Demonstrates good efficacy in the treatment of Candida esophagitis.</td>
<td>May be used in patients, refractory to or unable to tolerate, oral therapy.</td>
</tr>
<tr>
<td>Disease-oriented evidence</td>
<td>Multiple randomized clinical trials show very good outcome data for prophylaxis in neutropenic patients and treatment of candidemia/invasive candidiasis.</td>
<td>Monitoring for potential adverse effects, especially hepatotoxicity is necessary while on therapy.</td>
</tr>
<tr>
<td>Economic evidence</td>
<td>Acquisition costs are high compared to oral azoles and conversion to less expensive oral alternatives should be accomplished as soon as possible</td>
<td>Cost-effective for hospitalized patients with serious infections, primarily because of efficacy and decreased length of hospital stay.</td>
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Mechanism of action
Micafungin is a member of the echinocandin class of antifungal agents. Micafungin inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls, which is not present in mammalian cells.7 Micafungin acts in a concentration-dependent manner as a non-competitive inhibitor of the formation of the enzyme 1,3-β-D-glucan synthase. Micafungin demonstrates a prolonged concentration-dependent anti-fungal effect.8

Pharmacokinetics

Distribution: The mean ± standard deviation volume of distribution of micafungin at terminal phase was 0.39 ± 0.11 L/kg body weight when determined in adult patients with esophageal candidiasis at the dose range of 50 mg to 150 mg. Micafungin is highly (>99%) protein bound in vitro, independent of plasma concentrations over the range of 10 to 100 mcg/mL. The primary binding protein is albumin; however, micafungin, at therapeutically relevant concentrations, does not competitively displace bilirubin binding to albumin. Micafungin also binds to a lesser extent to α1-acid-glycoprotein.7

Distribution: Metabolism Micafungin is metabolized to M-1 (catechol form) by arylsulfatase, with further metabolism to M-2 (methoxy form) by catechol-O-methyltransferase. M-5 is formed by hydroxylation at the side chain (ω-1 position) of micafungin catalyzed by cytochrome P450 (CYP) isozymes. Even though micafungin is a substrate for and a weak inhibitor of CYP3A in vitro, hydroxylation by CYP3A is not a major pathway for micafungin metabolism in vivo. Micafungin is neither a P-glycoprotein substrate nor inhibitor in vitro. In four healthy volunteer studies, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 6% for M-1, 1% for M-2, and 6% for M-5. In patients with esophageal candidiasis, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 11% for M-1, 2% for M-2, and 12% for M-5.

Excretion: The excretion of radioactivity following a single intravenous dose of 14C-micafungin sodium for injection (25 mg) was evaluated in healthy volunteers. At 28 days after administration, mean urinary and fecal recovery of total radioactivity accounted for 82.5% (76.4% to 87.9%) of the administered dose. Fecal excretion is the major route of elimination (total radioactivity at 28 days was 71% of the administered dose).

Dosage and administration

Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses: 100 mg daily IV infused over 1 hr

Treatment of Esophageal Candidiasis: 150 mg daily IV infused over 1 hr

Prophylaxis of Candida Infections: 50 mg daily IV infused over 1 hr adults

Micafungin should not be mixed with other drugs in same vial or infusion. Loading dose of micafungin is not required. Please see the prescribing information for information on reconstitution and dilution.

Contraindications
Micafungin is contraindicated in persons with known hypersensitivity to micafungin, any component of Mycamine, or other echinocandins.7

Warning and precautions
Warning and precautions include hypersensitivity reactions, hematological effects like acute intravascular hemolysis and hemoglobinuria, hepatic effects and isolated cases of significant renal impairment.7

Adverse drug reactions
General adverse drug reactions include: Histamine-mediated symptoms like rash, pruritus, facial swelling, and vasodilatation. Injection site reactions including phlebitis and thrombophlebitis are also observed. Most common adverse reactions include diarrhea, nausea, vomiting, pyrexia, hypokalemia, thrombocytopenia, and headache.7
Drug interactions
A total of 14 clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between micafungin and amphotericin B, mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, itraconazole, voriconazole, ritonavir, and rifampin.

Use in special populations
Some of the key benefits of micafungin in the management of IFIs are as follows:
- Micafungin is pregnancy Category C drug
- It is not known whether micafungin is excreted in human milk
- Safety and effectiveness in pediatric patients have not been established
- No overall differences in safety and effectiveness were observed between elderly subjects and younger subjects

Part 3: Clinical studies

Micafungin in Candida infections
Several studies have examined the efficacy of micafungin in the management of invasive Candida infections.

A study by Van Burik et al. showed that the overall efficacy of micafungin was superior to that of fluconazole as antifungal prophylaxis during the neutropenic phase after haematopoietic stem cell transplantation (HSCT) (see Fig. 2).

A study by Goto et al. reported an overall success rate of 70% for micafungin as an empirical treatment in suspected fungal infection in patients with febrile neutropenia in haematological malignancies. Micafungin was administered at a dose of 150 mg/day.


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Fig. 1: Overall success rate: Micafungin vs. fluconazole

Study design: Randomised, double-blind, multi-institutional, comparative phase III trial, involving 882 adult and paediatric patients. Treated with 50 mg of micafungin (1 mg/kg for patients weighing <50 kg) and 400 mg of fluconazole (8 mg/kg for patients weighing <50 kg) once per day. Outcome measures: absence of suspected, proven or probable invasive fungal infection (IFI) through the end of therapy and 4 weeks thereafter.

Overall success rate of 70% for micafungin as an empirical treatment in suspected fungal infection

Study design: Safety and efficacy of micafungin was evaluated in febrile neutropenia with suspected fungal infection in 53 patients who had undergone chemotherapy. The patients were evaluated for fever resolution, and with chest imaging and serum fungal tests.

A study by Kuse et al. compared micafungin with liposomal amphotericin B. Both the drugs were equally effective in terms of clinical success rate (micafungin: 89.6% and amphotericin B: 89.5%). Efficacy was independent of the Candida spp. and primary site of infection, as well as neutropenic status, APACHE II score, and whether a catheter was removed or replaced during the study. Micafungin had higher mycological and clinical response rate vs. amphotericin B. In addition, fewer adverse events were reported with micafungin.

Micafungin is as effective but safer than liposomal amphotericin B


In a study by Viscoli et al., 67% favourable response rate was observed at the end of micafungin treatment (EOMT). In the study, survival at EOMT was 90% (97/108 patients), with rates of 97% (35/36) and 86% (62/72) among children and adults, respectively (see Fig. 4).


Six years of global surveillance study by Pfaller et al. showed higher success rates with micafungin vs. caspofungin and anidulafungin against various invasive Candida species (see Fig. 5). Micafungin had 100% efficacy rates against all invasive Candida species.

A study by de Wet et al. showed that micafungin is more effective than fluconazole in the management of oesophageal candidiasis. Mycological eradication of 78.3%.

Clinical efficacy in Aspergillosis


A study by Koho et al. showed that micafungin is as effective as caspofungin in terms of overall response in chronic pulmonary aspergillosis (both caspofungin and micafungin: 100.0%) including aspergilloma (caspofungin: 46.7% and micafungin: 42.4%) (see Fig. 8).

Study design: A post hoc analysis of a phase 3 trial assessing micafungin (100 mg/day for subjects >40 kg; 2 mg/kg/day for subjects ≤40 kg) versus liposomal amphotericin B (3 mg/kg/day).


A study by Kobayashi et al. showed that micafungin is an effective option for paediatric patients suffering from aspergillosis. Results of the study showed an overall clinical response rate of 86.6% in children and 90% in neonates suffering from Aspergillus infection (see Fig. 9).

Study design: This was a prospective, randomised, double-blind study conducted among Japanese patients.
Study design: This was a prospective multicentre, post-marketing, observational study. Micafungin at a dose of 1 mg/kg for candidiasis and 1 to 3 mg/kg for aspergillosis, with the option of increasing the dose if required to 6 mg/kg once daily. All adverse events were recorded. A total of 201 paediatric patients were enrolled.


Micafungin in vitro studies

The results of micafungin in vitro studies are elicited in Table 2.

Table 2: Micafungin in vitro studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Laverdiere et al.</td>
<td>Potent but slow fungicidal activity has been shown by micafungin against clinical isolates of Candida albicans, Candida dubliniensis, Candida tropicalis, Candida glabrata, and Candida krusei, with somewhat higher MIC90s for Candida parapsilosis, Candida lusitaniae, and Candida guillermondii</td>
</tr>
<tr>
<td>Ostrosky-Zeichner et al.</td>
<td>Fluconazole-resistant clinical isolates of Candida demonstrated no cross-resistance to micafungin. A 5–10-fold increase in the inhibitory activity of micafungin, compared with that of caspofungin, against C. albicans, C. glabrata, C. tropicalis, and C. dubliniensis was observed</td>
</tr>
<tr>
<td>Uchida et al.</td>
<td>Overall, micafungin was more active than amphotericin B, fluconazole, or itraconazole, with MICs against most Candida species generally 0.25 mg/mL.</td>
</tr>
<tr>
<td>Kuhn et al.</td>
<td>Micafungin blocked adherence of C. albicans to epithelial cells and demonstrated activity against C. albicans biofilms, which indicates a potential role in the prevention and treatment of catheter-related Candida infections</td>
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<tr>
<td>Gil-Lamaignere et al.t</td>
<td>Micafungin also enhances in vitro neutrophil fungicidal activity against Candida pseudohyphae</td>
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</table>
Conclusion

- Invasive fungal infection incidence is growing over past few decades
- There are several challenges associated with diagnosis and treatment of IFIs
- Various treatments are available but there are shortcomings with respect to clinical efficacy and resistance rates
- Micafungin is an effective antifungal with favourable pharmacological profile
- Micafungin is found to be as effective and in some cases better than other antifungal agents in the management of *Candida* and *Aspergillus* infections
- Micafungin is well tolerated as well

References


