As we manage an increasingly complex population of critically ill patients, the burden of fungal infections is continually increasing. Thus, we need to understand antifungal medications and feel comfortable initiating them promptly. Infectious disease consultants will often be involved with these patients, but we shouldn't be calling them at 3 AM for guidance to start an echinocandin for management of candidemia.

Fortunately, this task isn't overly difficult. There are essentially five workhorse antifungal agents commonly used in critically ill patients (table below). Itraconazole and posaconazole are excluded here, due to lack of intravenous formulations and scant evidentiary support in critical illness.
spectrum and use

- Candida species: fluconazole covers most, but not all (missing Candida glabrata and Candida krusei).
  - Fluconazole may be used as initial therapy for mild infection (e.g., candida esophagitis).
  - Fluconazole shouldn’t be used as empiric therapy for invasive Candida infection acquired in the ICU. However, fluconazole may be used as a step-down therapy, following empiric treatment with an echinocandin (if the Candida species is sensitive to fluconazole).
  - Cryptococcus neoformans: Fluconazole is the agent of choice, due to excellent CNS penetration.

pharmacology

- Oral bioavailability is 90-100% (unaffected by gastric pH or food).
- Protein binding in the blood: Fluconazole is only 12% in the blood. Unlike other azoles, fluconazole circulates mostly as free drug.
- Half-life is ~30 hours.
- Elimination is mostly via the kidney, where it is excreted unchanged.
- Penetration
  - Volume of distribution is ~0.7 L/kg.
  - Good penetration of eye and CNS.
  - Excellent urinary concentrations, since fluconazole is primarily excreted unchanged in the urine.
**dose**

- Oropharyngeal or esophageal candidiasis: 200 mg load, followed by 100 mg daily.
- Systemic candidiasis: 800 mg IV load, followed by 400 mg IV daily.
- Renal adjustment:
  - GFR 11-50 ml/min: reduce dose by 50%.
  - Hemodialysis: replace dose after dialysis.
- Hepatic dysfunction: No dose adjustment.
- Obesity: May consider adjusting dose based on actual body weight (Load with 12 mg/kg, then maintenance dose 6 mg/kg daily).

**monitoring, toxicity & contraindications**

- **Contraindications**
  - QTc prolongation.
  - Active hepatitis with deteriorating liver function tests (renders monitoring of liver function tests impossible).
  - Severe drug-drug interaction with an essential medication (see interactions below).
- **Monitoring**
  - Liver function tests are generally followed.
  - Consider following QTc interval, if prolonged at baseline.
- **Toxicity**
  - Fluconazole is generally well tolerated (even when used chronically).
  - Transaminase elevation can occur. Rarely, fluconazole may cause severe hepatic injury.
  - QTc prolongation.
  - Nausea, vomiting, or abdominal discomfort may occur.
- **Drug-drug interactions**
  - CYP inducers (e.g., rifampin, phenytoin) may reduce levels of fluconazole.
  - Fluconazole is a strong inhibitor of CYP2C9 and a moderate inhibitor of CYP3A4 and CYP2C19. This may increase levels of other medications (e.g., warfarin, phenytoin, cyclosporine, tacrolimus). Fluconazole also inhibits uridine diphosphate-glucuronosyltransferase (UGT).
  - Some more common interactions are shown below.
**spectrum and use**

- **Candida**
  - Voriconazole has anti-Candida activity similar to that of fluconazole. ([31789904](https://pubmed.ncbi.nlm.nih.gov/31789904/))
  - It may be used as step-down therapy, for fluconazole-resistant isolates (e.g., Candida glabrata or Candida krusei).

- **Aspergillus**
  - Voriconazole is *front-line therapy for invasive aspergillosis* (with better outcomes than amphotericin in one RCT). ([12167683](https://pubmed.ncbi.nlm.nih.gov/12167683/))
  - Voriconazole doesn’t cover Zygomycetes (e.g., Mucorales spp.) – so it’s not ideal as an *empiric* anti-mold agent in patients with longstanding immunosuppression.

- **Endemic fungi**, including coccidioidomycosis, histoplasmosis and blastomycosis. ([19139290](https://pubmed.ncbi.nlm.nih.gov/19139290/))
  Although voriconazole isn’t traditionally used for these infections, it may be useful in selected cases (e.g., patients with CNS involvement or contraindications to amphotericin).

![Chemical structures](https://emcrit.org/ibcc/antifungal/attachment/fluconazole.png)

**pharmacology**

- **Oral bioavailability**
  - Generally well absorbed (>90%).
  - Fatty foods may decrease absorption by ~30%.

- **Protein binding** in the blood is moderate, at 58%.

- **Half-life** is 6 hours.

- **Elimination** is via hepatic metabolism, largely by CYP2C19 system. Slow metabolizers may accumulate higher levels of voriconazole (more common in patients with Asian or Pacific Islander ancestry).
  - <2% of voriconazole is excreted in the urine.

- **Penetration**
  - Volume of distribution is large, at 4.5 L/kg.
  - Good penetration of CSF and eye.
  - Doesn’t penetrate the urine well (not useful in fungal urinary tract infection).
  - The intravenous form of voriconazole is solubilized with a cyclodextrin vehicle (the same vehicle used to solubilize remdesivir). Cyclodextrin is nephrotoxic and can accumulate in renal dysfunction, so *intravenous* voriconazole is contraindicated if the GFR is <50 ml/min. However, *oral* voriconazole remains safe in renal dysfunction.

**dose**

- **Dosing for invasive aspergillus:**
  - IV: Load with 6 mg/kg q12 hours on day #1, then decrease to maintenance dose of 4 mg/kg q12 hours.
  - PO: Load with 400 mg q12hr on day #1, then maintenance therapy at 200 mg PO q12hr.
- **Hepatic dysfunction** (Child class A & B): Same loading dose, reduce maintenance dose by 50%. Follow liver function tests and voriconazole drug levels.
- **Renal dysfunction**
  - Oral dosing: Same
  - Intravenous dosing: Avoid if GFR <50 ml/min; consider using oral voriconazole instead. Especially avoid prolonged IV use in renal dysfunction.

- **More information:** 📝 [Medscape monograph on voriconazole](https://reference.medscape.com/drug/vfend-voriconazole-342598)
**Contraindications**
- QTc prolongation.
- Renal failure (GFR < 50 ml/min is a contraindication, but only for the intravenous formulation).
- Active hepatitis with deteriorating liver function tests (renders monitoring of liver function tests impossible).
- Severe drug-drug interaction with an essential medication (see below interactions).

**Monitoring**
- Liver function tests are generally followed. ([32000291](https://pubmed.ncbi.nlm.nih.gov/32000291/))
- Consider following QTc interval if prolonged at baseline.

**Toxicity**
- Visual disturbance (transient, infusion-related, rarely requires discontinuation of voriconazole).
- Neurotoxicity may include hallucinations, delirium, agitation, or myoclonus (dose-related, suggests excessive voriconazole levels).
- Liver function test abnormality (mostly reversible, but severe liver injury is possible).
- Hypoglycemia
- Pneumonitis
- QTc prolongation
- Renal failure (IV formulation only, due to cyclodextrin vehicle rather than voriconazole itself).
- Nausea, vomiting, or abdominal discomfort may occur.

**Drug-drug interactions**
- CYP inducers (e.g., rifampin, phenytoin) may reduce levels of voriconazole.
- Voriconazole is metabolized by CYP2C19, so inhibitors of that enzyme may increase voriconazole levels.
- Voriconazole inhibits CYP2C9 weakly, CYP2C19 moderately, and CYP3A4 strongly. This may increase levels of other medications.
- Some more common interactions are shown below.

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**isavuconazole**

*[back to top](https://emcrit.org/ibcc/antifungal/attachment/azoleter/)*

**Spectrum and use**

[https://emcrit.org/ibcc/antifungal/]
Advantages of isavuconazole over voriconazole:

1. Broader spectrum of activity, including Mucorales species (involved in mucormycosis).
2. More favorable safety profile (especially regarding renal dysfunction and QT prolongation). In the SECURE trial, isavuconazole was non-inferior to voriconazole against invasive aspergillus or other filamentous fungi, yet isavuconazole was better tolerated. ([26684607](https://pubmed.ncbi.nlm.nih.gov/26684607/))

3. Isavuconazole causes fewer drug-drug interactions (voriconazole interacts with more hepatic CYP enzymes than isavuconazole does). ([31102782](https://pubmed.ncbi.nlm.nih.gov/31102782/))

Uses of isavuconazole include:

1. Empiric therapy for invasive mold infection: isavuconazole has the advantage of covering for both Aspergillus and Mucorales species, if the causative mold is unknown.
2. Potential use as induction therapy for endemic fungi? This remains unclear, being supported only by a single-arm study. ([27169478](https://pubmed.ncbi.nlm.nih.gov/27169478/)). In vitro, isavuconazole appears to have favorable coverage of endemic fungi compared to other azoles, supporting a potential therapeutic role. ([29534853](https://pubmed.ncbi.nlm.nih.gov/29534853/))

3. Isavuconazole might be used for invasive candidiasis in selected situations. However, one study suggested inferior outcomes compared to echinocandins, so isavuconazole cannot be considered as a front-line agent against Candida spp. ([30289478](https://pubmed.ncbi.nlm.nih.gov/30289478/))

**pharmacology**

- **Oral bioavailability** is ~100%, allowing oral dosing to be used interchangeably with intravenous dosing.
- **Protein binding** is 98-99%. This gives isavuconazole a long half-life and also prevents drug clearance by hemodialysis.
- **Half-life** is ~80-120 hours.
- **Elimination** is via hepatic metabolism (including uridine diphosphate glucuronosyltransferase and CYP3A4).
  - <1% excreted in urine, so isavuconazole may have little use in the treatment of urinary tract infections. ([29725999](https://pubmed.ncbi.nlm.nih.gov/29725999/))
- **Penetration**
  - The volume of distribution is 6.5 L/kg.
  - Isavuconazole penetrates extensively into tissues, including the brain and eye. ([32000291](https://pubmed.ncbi.nlm.nih.gov/32000291/)). However, CSF levels are low. ([29551442](https://pubmed.ncbi.nlm.nih.gov/29551442/))

**dose**

- **Typical dosing scheme**
  - Loading dose: 372 mg isavuconazonium sulfate (a.k.a., 200 mg isavuconazonium base) PO/IV q8 hr x6 doses for two days.
  - Maintenance dose: 372 mg isavuconazonium sulfate (a.k.a., 200 mg isavuconazonium base) PO/IV q24hr.
  - Doses should be infused slowly over one hour to avoid an infusion reaction.
  - Note: The medication itself is given as isavuconazonium sulfate, which is a pro-drug that is metabolized into isavuconazole (the active drug). 372 mg isavuconazonium *sulfate* is equivalent to 200 mg isavuconazonium *base*. This is the same drug, but different countries refer to it differently.
  - No dose adjustment is needed in renal or hepatic impairment (although this hasn’t been studied in severe hepatic dysfunction).

**monitoring, toxicity & contraindications**

- **Contraindications**
  - Congenital short QT syndrome.
- Active hepatitis with deteriorating liver function tests (renders monitoring of liver function tests impossible).
- Severe drug-drug interaction with an essential medication (see below interactions).

**Monitoring**
- Liver function tests are generally followed.

**Toxicity**
- Severe hepatic impairment may rarely occur.
- Short QT interval (!) – clinically this is rarely an issue.
- Most commonly reported adverse events are nausea, vomiting, and diarrhea.
- Hypokalemia.
- Peripheral edema.
- Infusion reactions (chills, dyspnea, and hypotension).

**Drug-drug interactions**
- Isavuconazole levels are affected by medications that affect the CYP3A4 system (e.g., rifampin reduces isavuconazole levels by 90%, and lopinavir/ritonavir doubles isavuconazole levels). [29725999](https://pubmed.ncbi.nlm.nih.gov/29725999/)
- Isavuconazole affects levels of a variety of different agents handled via numerous systems (e.g., CYP3A4 system, P-glycoprotein system, organic anion transport systems, and CYP2C9).
- A table below shows some notable drug interactions. In practice, the best approach is to run an electronic drug interaction check (e.g. using MedScape's [drug interaction checker](https://reference.medscape.com/drug-interactionchecker)).

[echinocandins](https://emcrit.org/ibcc/antifungal/attachment/isainteractions/) (micaFUNGIN, caspoFUNGIN, anidulaFUNGIN)
spectrum and use

- All three agents have similar spectrum and utility. They are generally considered to be clinically interchangeable.
- Clinical efficacy is largely restricted to Candida and Aspergillus.

Candida:
- Echinocandins cover nearly all Candida species. However, some resistance may be found among C. parapsilosis and C. guilliermondii. Resistance rarely may be detected among C. glabrata (especially strains which are resistant to fluconazole).
- Echinocandins are generally the agent of choice for empiric treatment of candidemia in the ICU. Echinocandins may be uniquely effective against Candida embedded in biofilms (e.g., surrounding prosthetic devices), a context where fluconazole or amphotericin-B may be less effective. Echinocandins are fungicidal against Candida (unlike azoles, which are fungistatic). (https://pubmed.ncbi.nlm.nih.gov/32722455/)

Aspergillus
- Echinocandins are not recommended for monotherapy.
- Echinocandins do exert synergistic activity when combined with voriconazole. Combination antifungal therapy isn't usually recommended as front-line therapy, but it can be used in the following situations:
  - Salvage therapy due to clinical failure of an azole.
  - Known azole resistance.
  - High regional rates of azole-resistance.
  - Treating a species with higher rates of resistance (e.g., Aspergillus calidoustus).

pharmacology

- **Protein binding:**
  - Caspofungin: 92-97%
  - Anidulafungin: 99%
  - Micafungin: 99.95%

- **Half-life:**
  - Caspofungin: 8 hours initially, with a terminal half-life of 27-50 hours
  - Anidulafungin: 40-50 hours
  - Micafungin: 13-20 hours

- **Elimination**
  - Caspofungin: Metabolized by N-acetylation in the liver and spontaneous chemical degradation (independent of the CYP system).
  - Anidulafungin: Spontaneous degradation in the plasma.
  - Micafungin: Hepatic metabolism by the CYP system.

- **Penetration**
  - Volume of distribution is low (~0.3-0.6 L/kg) for all.
  - Minimal CSF, urine, or eye penetration.

dose for invasive infection

- **Caspofungin**: 70 mg loading dose, then 50 mg daily (or possibly 70 mg daily if weight >80 kg or simultaneous use of potent inducers of CYP4A4, such as carbamazepine, phenobarbital, phenytoin, and rifampin). (https://pubmed.ncbi.nlm.nih.gov/31617055/)
- **Anidulafungin**: 200 mg loading dose, then 100 mg daily.
- **Micafungin**: 100-150 mg IV q24hr (invasive candidiasis) or 150 mg IV q24hr (invasive aspergillosis).
  - No adjustment for renal or hepatic dysfunction.
  - Other indications (e.g., esophageal candidiasis or antifungal prophylaxis) may involve lower doses.
More information: Medscape monographs on caspofungin, anidulafungin, and micafungin.

**toxicity & contraindications**

- Echinocandins overall have a relatively favorable safety profile (generally superior to either amphotericin or azoles).

  
  ![Contraindications](https://pubmed.ncbi.nlm.nih.gov/29304209/)

- **Contraindications**
  - Consider avoiding in acute hepatic failure with deteriorating liver function tests (renders monitoring of liver function tests impossible).

- **Monitoring**
  - Liver function test monitoring (more frequently with micafungin than with others).

- **Toxicity**
  - Infusion-related reaction may occur with rapid administration.
  - Liver function test abnormality (especially with micafungin)
  - Hypokalemia
  - Phlebitis at the infusion site
  - Neutropenia is rarely reported

- **Drug-drug interactions**
  - Caspofungin: Metabolism of caspofungin may be accelerated, leading to lower caspofungin levels by strong inducers of CYP3A4 (e.g., rifampin, carbamazepine, dexamethasone, phenytoin). This may require using a higher maintenance dose of caspofungin (70 mg instead of 50 mg).
  - Anidulafungin has few drug-drug interactions, due to its physiology of spontaneous degradation (without interacting with any hepatic enzymes).
  - Micafungin has relatively few drug-drug interactions. However, it may increase levels of sirolimus, cyclosporine, itraconazole, or nifedipine.
  - Check for interactions using MedScape's drug interaction checker.

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**spectrum and use**

- Liposomal amphotericin has largely replaced older deoxycholate formulations, as liposomal amphotericin is less toxic but equally effective.

  ![liposomal amphotericin](https://pubmed.ncbi.nlm.nih.gov/29304209/)

- Potential uses:
  - Dimorphic fungi and Cryptococcus neoformans: Traditionally used initially for induction of therapy.
  - Mold: Traditionally amphotericin was used as an empiric anti-mold agent (to cover either Aspergillus or Mucorales species). However, isavuconazole is a safer option here, if it is available.
  - Invasive Candida: Amphotericin had equivalent efficacy compared to micafungin in one study and in meta-analyses, but amphotericin caused greater side effects.

  ![Modern use](https://pubmed.ncbi.nlm.nih.gov/17482982/), 30257597

- Modern use: Amphotericin is increasingly being replaced by newer, safer agents. However, amphotericin continues to have niche roles in situations where other agents cannot be used, such as:
  - Aspergillus species resistant to azoles.
  - Patients with acute hepatic failure or hepatitis (azoles and echinocandins can cause hepatic dysfunction). Note, however, that patients with stable Childs class A-B cirrhosis may be treated with azoles or echinocandins.
  - Induction therapy for patients with dimorphic fungi (although increasing evidence suggests that voriconazole may often be adequate therapy here).
  - Candida species which are resistant to fluconazole and echinocandins (rare).
Pharmacology

- **Protein Binding** in the blood is 95-99%, with a volume of distribution of 0.05-2.2 L/kg. Amphotericin is water insoluble (hence requiring the liposomal formulation).
- **Half-life** is roughly 24 hours.
- **Elimination** is via the reticuloendothelial system. This doesn't appear to be affected by renal or hepatic dysfunction.
- **Penetration**
  - Poor CNS or ocular penetration.
  - Low concentrations detected in the lungs and kidney. (32000291)
  - Volume of distribution is 0.05-2 L/kg.

Dose

- 3-5 mg/kg liposomal formulation IV q24 hours
  - Candidemia without suspicion of CNS involvement: 3 mg/kg daily.
  - Invasive aspergillosis: 5 mg/kg.
- No dose adjustment for renal or hepatic dysfunction.
- In morbid obesity, consider dosing based on ideal body weight (rather than total body weight).

Monitoring, Toxicity & Contraindications

- **Contraindications**
  - Renal failure
  - Hepatic failure
  - QT prolongation
- **Monitoring**
  - Follow renal function and electrolytes, including calcium and magnesium.
  - Consider following QTc interval, if prolonged at baseline
- **Toxicity**
  - Infusion reactions – may include fever, chills, rigors, bronchospasm, nausea/vomiting, hypotension, tachypnea.
  - Acute renal failure – dose-related in terms of cumulative total dose. Usually nonoliguric and reversible.
  - Type IV renal tubular acidosis leading to hypokalemia and hypomagnesemia.
  - Hepatotoxicity (however, this is relatively rare and monitoring of liver function tests isn't generally necessary). (29304209)
- **Drug-drug interactions**: Based on its elimination via the reticuloendothelial system, there aren't any direct drug-drug interactions. However, synergistic toxicity may occur if amphotericin is co-administered with drugs that have the following effects: (32000291)
  - Hypokalemia
  - Torsade de Pointes, QT prolongation
  - Nephrotoxicity
  - Zidovudine use with Amphotericin may lead to synergistic bone marrow toxicity
Amphotericin has a high rate of nephrotoxicity, so reserve this for situations where it is truly necessary.

Azole antifungals are generally well tolerated, but are involved in numerous drug-drug interactions. Look carefully for interactions before initiating these (use a drug-interaction tool such as MedScape's drug interaction checker).

Echinocandins are excellent for candidemia, but they don't penetrate the eye. For patients with ocular involvement, alternative treatment may be needed.

For critically ill patients with a high likelihood of fungal infection, consider empiric initiation of therapy, prior to definitive diagnosis. Relatively nontoxic and broad-spectrum agents exist that can be initiated early, with a positive risk/benefit ratio.

Conflicts of interest: None

references


