Antifungals

Definitions:
- **Definite**: invasive aspergillosis is established by positive culture or histopathology for aspergillosis from tissue obtained during an invasive procedure. Washings, brushings, or suctioning of secretions do NOT represent invasive procedures.
- **Probable**: aspergillosis is indicated by a positive galactomannan assay from serum or BAL or positive culture for aspergillus species AND clinical evidence suggestive of aspergillosis.
- **Possible**: aspergillosis is indicated by a positive galactomannan assay from serum or BAL or radiographic findings highly suggestive of aspergillosis in a compatible host (follow-up diagnostic studies are highly recommended).
- **Refractory**: means disease progression or failure to improve despite at least 96 hours of treatment with Voriconazole or an IV Amphotericin B product (deoxycholate or lipid-based product).

Caspofungin

Aspergillosis

**Acceptable uses**
- Infusional toxicity or acute renal failure on ABLC and intolerance to voriconazole defined as serious hepatotoxicity, persistent visual disturbance, or allergic reaction.
- Refractory disease for use in combination with voriconazole or ABLC for **definite** or **probable** invasive pulmonary aspergillosis in patients who are refractory to voriconazole or ABLC alone (ID consult advised)

**Unacceptable uses**
- Caspofungin alone or in combination with other antifungal agents is not recommended for empirical therapy in patients with CT findings suggestive of aspergillosis (e.g., possible aspergillosis) without plans for diagnostic studies
- Caspofungin does not have good **in vitro** activity against zygomycoses (Mucor, Rhizopus, Cunninghamella, etc.)

Candidiasis

**Acceptable uses**
- Treatment of invasive candidiasis due to *C. glabrata* or *C. krusei*
- Treatment of invasive candidiasis in patients who are NOT clinically stable due to candidemia or have received prior long-term azole therapy.
- Alternative treatment of recurrent esophageal candidiasis
- Alternative treatment of endocarditis

**Unacceptable uses**
- Caspofungin has poor penetration into the CNS and urinary tract. It should be avoided for infections involving those sites. Positive urine cultures for resistant *Candida* in catheterized patients usually represent colonization and should not be treated with caspofungin.
- Monotherapy for zygomycoses (Mucor, Rhizopus, etc.)
Neutropenic Fever
● Caspofungin can be used for neutropenic fever in patients who are not suspected to have aspergillosis or zygomycosis

Dose
● 70 mg IV once, then 50 mg IV daily

Toxicity
● Infusion-related reactions (rash, pruritus), phlebitis, headache, nausea and vomiting, elevations in hepatic enzymes
● Monitoring: AST/ALT/bilirubin at baseline and every 1-2 weeks

Posaconazole
Posaconazole is a broad spectrum azole anti-fungal agent. It has in vitro activity against Candida, Aspergillus, Zygomycosis and Fusarium spp.

Acceptable uses
● Treatment of invasive zygomycosis in combination with Amphotericin B
● Monotherapy for zygomycosis after 7 days of combination therapy with Amphotericin B
● Note: posaconazole requires up to 7 days to achieve steady state concentrations. ID consult is advised.

Unacceptable uses
● Candidiasis/neutropenic fever
● Primary treatment of aspergillosis

Dose
Note: each dose should be given with a full meal or with liquid nutritional supplements if patients cannot tolerate full meals.
● Loading dose: 200 mg PO q6h for 7 days
● Maintenance dose: 400 mg PO q8-12h

Drug Interactions
● Posaconazole is an inhibitor and is metabolized by cytochrome P4503A4; therefore, co-administration with other agents that are cytochrome P450 substrates, inducers, or inhibitors will result in significant drug interactions.
● You must check for potential drug interactions when initiating Posaconazole therapy or starting a new medication in patients already receiving Posaconazole therapy.
● Administration of the following agents with Posaconazole is contraindicated:
  ○ Terfenadine, Astemizole, Pimozide, Cisapride, Quinidine, Sirolimus, Halofantrine and ergot alkaloids
● Posaconazole inhibits metabolism of the following agents. Dose reductions and close monitoring are recommended when Posaconazole is used with agents concomitantly:
  ○ Tacrolimus – reduce Tacrolimus dose to ½ and monitor levels
  ○ Cyclosporine – reduce Cyclosporine dose to ¾ and monitor drug level
  ○ Midazolam – consider dose reducing
○ Cimetidine, Rifabutin, Efavirenz and Phenytoin – unless the benefit outweighs the risk, AVOID concomitant use. If used together, monitor effect of the drugs and consider decreasing dose when Posaconazole is added
○ Statins (avoid Lovastatin and Simvastatin), vinca alkaloids, calcium channel blockers, Digoxin, Atazanavir, Ritanovir, QTc prolonging drugs (e.g. Amiodarone and Erythromycin) – monitor effect of the drugs and consider decreasing dose when Posaconazole is added
○ Cimetidine, Rifabutin, Phenytoin, Efavirenz, Esomeprazole, Metoclopramide may decrease Posaconazole blood levels.

Toxicity
- GI upset (~40%), headaches, elevation in hepatic enzymes. Rare but serious effects include QTc prolongation
- Monitoring: Hepatic enzymes at baseline and every 1-2 weeks after

Voriconazole

Note: Voriconazole does not cover zygomycoses (Mucor, Rhizopus, Cunninghamella, etc)

Acceptable uses (ID consult advised):
- Aspergillosis (please refer to prior definitions)
- Oncologic neutropenic and BMT populations:
  - Definite (biopsy-proven) invasive non-zygomycete filamentous fungal infections
  - Probable invasive non-zygomycete filamentous fungal infections
  - Empiric therapy in patients with possible aspergillosis (follow-up diagnostic studied are highly recommended
- Other patient populations:
  - Definite infections or as otherwise deemed appropriate after consultation with the Infectious Diseases service or the ASP
  - Pseudallescheria boydii (Scedosporium spp), Fusarium spp. Voriconazole is recommended as first-line therapy
  - Alternative therapy for C. krusei if susceptible and oral therapy is desired in stable patient.

Unacceptable uses:
- Candidiasis / Neutropenic fever: Voriconazole should not be used as first-line therapy for the treatment of candidiasis or for empiric therapy in patients with neutropenic fever.
- Treatment of positive urine cultures due to resistant Candida spp.

Dose
- Loading dose: 6 mg/kg IV/PO q12h x 2 doses
- Maintenance dose: 4 mg/kg IV/PO q12h
- Patients receiving concomitant phenytoin or efavirenz should receive following maintenance doses of voriconazole due to induced hepatic clearance by phenytoin and efavirenz.
  - Intravenous: 5 mg/kg q12h
  - Oral: 400 mg q12h (wt >40 kg) or 200 mg Q12h (wt <40kg)
  - Efavirenz dose should be decreased to 300 mg PO daily
  - Monitor phenytoin levels and adverse events
Dose escalation may be necessary for some patients due to subtherapeutic levels.

- Voriconazole IV is packaged with a cyclodextrin vehicle which can accumulate in patients with renal dysfunction. The clinical significance of risk vs benefit of using IV voriconazole in patients with renal dysfunction is unknown.

**Therapeutic monitoring**

- Obtaining voriconazole trough levels should be considered in patients who are:
  - Not responding to therapy after at least 5 days of therapy using a mg/kg dosing strategy
  - Receiving concomitant drugs that may increase or decrease voriconazole levels
  - Experiencing adverse events due to voriconazole
  - Experiencing GI dysfunction

- Voriconazole trough levels should be obtained 5-7 days after start of therapy
- Goal trough: 1-5.5 mcg/mL. Levels < 1 mcg/mL have been associated with clinical failures and levels >5.5 mcg m/mL with toxicity

**Drug interactions**

- Voriconazole is an inhibitor and is metabolized by cytochrome P450; therefore co-administration with other agents that are cytochrome P450 substrates, inducers, or inhibitors will result in significant drug interactions.
- **You must check for potential drug interactions when initiating voriconazole therapy or starting a new medication in patients already receiving voriconazole therapy.**

- Administration of the following agents with voriconazole is contraindicated:
  - Sirolimus, Rifampin, Rifabutin, Carbamazepine, Terfenadine, Astemizole, Cisapride, Pimozide, Quinidine, long-acting barbiturates, Ritonavir (400 mg BID), St. John’s Wort, and ergot alkaloids

- Voriconazole inhibits metabolism of the following agents: dose reductions and close monitoring are recommended when voriconazole is used with agents concomitantly:
  - Tacrolimus - reduce tacrolimus dose to ⅓ and monitor levels
  - Cyclosporine - reduce cyclosporine dose to ⅓ and monitor drug levels
  - Omeprazole - reduce omeprazole dose to ⅓
  - Warfarin - monitor INR
  - Ritonavir low dose (100 mg q12h) - avoid this combination unless benefit outweighs risk
  - Sulfonylureas, statins (avoid Lovastatin and Simvastatin), vinca alkaloids, calcium channel blockers, benzodiazepines (avoid midazolam and triazolam), oral contraceptives, Alfentanil, and Methadone – monitor effect of the drugs and consider decreasing dose when Voriconazole is added.

**Toxicity**

- Visual disturbances (~30%) usually self-limited, rash, fever, elevations in hepatic enzymes.
- Monitoring: hepatic panel at baseline and every 1-2 weeks after.