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 empiric 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-realted reactions (rash, pruritis), 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 ⅓ 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 (Scedosporim 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 ½ and monitor drug levels
    - Omeprazole - reduce omeprazole dose to ½
    - 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.