Invasive Aspergillosis

CONSULT ID

Aspergillus species are ubiquitous environmental molds and are the most common cause of invasive mold infection among immunocompromised patients. While benign inhalation of *Aspergillus* conidia commonly occurs among non-immunocompromised patients, invasive aspergillosis (IA) is associated with high mortality among immunocompromised patients. Pulmonary disease is the most common manifestation of IA. Patients with pulmonary IA present with cough, prolonged fever, chest pain and dyspnea.

Risk factors for invasive aspergillosis
Recent neutropenia (<0.5x 10^9 neutrophils/ L) for > 10 days
Active hematologic malignancy
Receipt of allogenic hematopoietic cell transplantation
Receipt of solid organ transplantation
Treatment with T-cell immunosuppressants (eg: calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues) during the past 90 days
Prolonged corticosteroids (>0.3 mg/kg prednisone over 3 weeks in the past 60 days)
Treatment with B-cell immunosuppressants (eg: Bruton's tyrosine kinase inhibitors)
Inherited severe immunodeficiencies (eg: chronic granulomatous disease, STAT 3 deficiency, severe combined immunodeficiency)
Acute graft-versus-host disease grade III or IV involving gut, lungs, or liver refractory to steroids

DEFINITIONS:

Aspergillus colonization: Absence of typical clinical disease and tissue invasion but presence of *Aspergillus* by fungal culture (eg: from a broncho-alveolar lavage specimen), *Aspergillus* antigen (eg: galactomannan), or PCR testing. *Aspergillus* colonization is increased among patients with chronic obstructive pulmonary disease (COPD).

Invasive aspergillosis (IA): symptomatic clinical disease consistent with *Aspergillus* tissue invasion (may occur without growth of Aspergillus on culture). This occurs most commonly in the lungs, but extrapulmonary and disseminated disease may occur.

- **Proven IA**: pathological evidence of fungal tissue invasion (on biopsy) or recovery of Aspergillus from sterile site.
- **Probable IA**: Evidence of *Aspergillus* by culture, PCR or galactomannan AND supportive clinical and radiological evidence within a host with risk factors.
- **Possible IA**: radiographic findings consistent with IA in a host with risk factors, in the absence of *Aspergillus* culture, PCR or galactomannan positivity.

Diagnostic considerations:

- Chest CT +/- sinus CT (Xray imaging is not sufficiently sensitive)
- Broncho-alveolar lavage (BAL) for fungal culture, cytology and Galactomannan (GM):
    - low positive (<0.7) BAL GM is not specific for IA (may be associated with colonization alone).
- Transbronchial lung biopsy for fungal culture and pathology when possible.
    - Serum galactomannan, as per recent laboratory threshold of positivity (sensitivity of only about 70% among those with proven IA)
    -

TREATMENT PRINCIPLES:

Involves multiple modalities: antifungal therapy, reduction of immunosuppression (in discussion with treating team) and surgical debridement of necrotic tissue when applicable. **ID CONSULTATION IN ALL CASES**

PHARMACOLOGICAL THERAPY:

Proven or Probable IA	**Voriconazole**[1,2,3]: 6 mg/kg IV q12h on day 1, followed by 4 mg/kg IV q12h, *OR* 400 mg PO q 12h x 2 doses, then 200 mg PO q 12h	Duration depends on clinical disease and host immunosuppression. minimum duration of therapy is 6 to 12 weeks, however longer courses often required.
Possible IA **If need to cover for both IA and mucormycosis**	**Voriconazole**[1,2,3]: 6 mg/kg IV q12 h on day 1, followed by 4 mg/kg IV q12h *OR* 400 mg PO q 12h x 2 doses, then 200 mg PO q 12h **Posaconazole**[4] delayed-release tablets (300 mg q12h on the first day, then 300 mg once daily) PO (with food)	Duration depends on clinical disease and host immunosuppression. minimum duration of therapy is 6 to 12 weeks, however longer courses often required.

[1]Caution: voriconazole increases levels of tacrolimus, cyclosporine and sirolimus. Review possible drug interactions before starting, stopping or modifying dosing. Adjust dose for patients with BMI >30. Consult pharmacy.
[2]Caution: PO voriconazole preferred to IV among patients with renal insufficiency (CrCl < 50 ml/min).
[3]Dose for adults > 90 lbs (or 40 kg). Lower doses needed for patients weighing < 40kg.
[4]Significant drug-drug interactions and prolongs QTc. Consult pharmacy. Obtain baseline ECG at the start of therapy and 3 days after treatment initiation.

Monitoring/ drug toxicity:

- Check voriconazole trough levels between days 4 and 7 (goal: >1.5 but < 5.5 mcg/mL). Refer to MUHC ASP Azole Therapeutic Drug Monitoring guidelines for details.
- Clinical monitoring for voriconazole toxicity: neurotoxicity (hallucinations, delirium, and delusions), prolonged QTc, hepatotoxicity.
- Check serum trough level of posaconazole 1 week after initiation of therapy (goal: trough >1 mcg/mL). Refer to MUHC ASP Azole Therapeutic Drug Monitoring guidelines for details.

Additional comments:

- Switch from IV to PO when patient able to tolerate PO and clinically stable.
- In severe and refractory cases, combination therapy of triazole (eg: voriconazole or posaconazole) and echinocandin (eg: caspofungin) may be indicated in discussion with ID team.
- Liposomal amphoB may be considered among patients who cannot tolerate triazole therapy, in discussion with ID.

REFERENCES

- Martín-Peña A, et al: Antifungal Combination Therapy for Invasive Aspergillosis. Clin Infect Dis **2014**; 59:1437–1445. Available at: https://doi.org/10.1093/cid/ciu581.
- Patterson TF, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Clin Infect Dis **2016**; 63:433–442. https://pubmed.ncbi.nlm.nih.gov/27481947.
- Donnelly JP, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the EORTC - Mycoses Study Group Education and Research Consortium. Clin Infect Dis **2020**; 71:1367–1376. https://doi.org/10.1093/cid/ciz1008.

Drafted by C. Boodman (ID). Reviewed by M. Semret (ID), D. Vinh (ID), M. Cheng (ID), F. Bourdeau (pharmacy). Approved by ASP committee on May 19th, 2021; approved by P&T committee on June 23, 2021.