## Interactive Case Studies: Improving Clinical Outcomes in Invasive Aspergillosis

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#### Case Study 1: Introduction

- 45-year-old man underwent bilateral lung transplantation for idiopathic pulmonary fibrosis with organ ischemic time of 520 minutes
- Post-transplant immunosuppression
  - Sirolimus (target levels 4-10 ng/mL)
  - Tacrolimus (8-12 ng/mL)
  - Prednisone
- Clinical course complicated by reperfusion edema and renal failure
- 21-day post-transplant dyspnea and fever of 100.8°F were noted
- Chest radiograph was unremarkable
- CT of the chest and bronchoscopy were ordered
  - CT scan was unremarkable

CT = computed tomography.

#### **Bronchoscopic Findings**







Clinical image provided by Nina Singh, MD.

#### Audience Response

What are the options for appropriate antifungal therapy?

- 1. Voriconazole administered orally
- 2. AmB deoxycholate
- 3. A lipid formulation of AmB
- 4. Aerosolized lipid formulation of AmB
- 5. An echinocandin

# Types of IA in Lung Transplants



IA = invasive aspergillosis; IPA = invasive pulmonary aspergillosis. Singh N, et al. *Clin Microbiol Rev.* 2005;18(1):44-69.

#### Time to Onset of IA in Lung Transplants



Tr/BA = tracheobronchitis or bronchial anastomatic infection. Singh N, et al. *J Heart Lung Transplant.* 2003;22(3):258-266.

#### **Bronchial Anastomotic Infections**

- 40% of BAs are due to Aspergillus spp
- Time to onset: ~30 days
- Risk factors
  - Airway ischemia, reperfusion injury
  - Bilateral lung transplantation
  - T-cell—depleting induction therapy
  - Sirolimus-based immunosuppression
    - Defer until wound healing complete (4-6 weeks)

BA = bronchial anastomatic infection. Hadjiliadis D, et al. *Ann Transplant*. 2000;5(3):13-19. Groetzner J, et al. *J Heart Lung Transplant*. 2004;23(6):770-773.

#### Audience Response

Sirolimus is withheld and voriconazole is initiated as therapy for *Aspergillus* BA infection.

Which of the following management options are appropriate at this point?

- 1. Decrease tacrolimus dose by 10% upon initiation of voriconazole
- 2. Decrease tacrolimus dose by 50% upon initiation of voriconazole
- 3. Monitor tacrolimus level
- 4. Monitor tacrolimus and voriconazole levels

#### Drug Interactions Between Immunosuppressants and Azoles: Therapeutic Drug Monitoring

- Enzyme inhibition may be observed immediately, and as early as after the first dose of the inhibitor
- Preemptive dose reduction of immunosuppressants may incur risk of rejection
- Monitor immunosuppressant levels at the start and throughout combination therapy
- Immunosuppressant levels may take up to 7-10 days to return to baseline after discontinuation of the azoles
- Therapeutic drug monitoring for voriconazole
  - Levels affected by nonlinear saturable pharmacokinetics, drug-drug interactions, liver disease, genetic polymorphism of CYP2C19
  - Levels >1 mg/L are correlated with efficacy
  - Levels >5.5 mg/L are correlated with neurologic toxicity

CYP2C19 = cytochrome P450 2C19. Pascual A, et al. *Clin Infect Dis.* 2008;46:201–211.

#### Magnitude of Effect and Dose Adjustment with Concomitant Azole and Immunosuppressant Use

Azole	Potency	Tacrolimus (%)	CsA (%)	Sirolimus (%)
Ketoconazole	++++	50-60	70-80	80-90
Fluconazole ( <u>&gt;</u> 200 mg/day)	+	40	20-50	50-70
Itraconazole	+++	50-60	50-60	—
Voriconazole	++ to +++	~66	50	90
Posaconazole	+++	75-80	0-30	_

CsA = cyclosporin A. Saad AH, et al. *Pharmacotherapy*. 2006;26(12):1730-1744.

#### Unique Issues Pertaining to Aerosolized AmB

- Levels in distal compared with proximal airways significantly greater
- MIC<sub>90</sub> of Aspergillus exceeded in proximal airways for 4 hours only
- 2/51 lung transplant recipients with anastomotic infections and 4 with extrapulmonary infections, all due to *Candida*

MIC<sub>90</sub> = minimum inhibitory concentration for 90%. Monforte V, et al. *Transplantation.* 2003;75(9):1571-1574. Palmer SM, et al. *Transplantation.* 2001;71(12):1772-1776.

#### Considerations in Administering Aerosolized AmB Formulations

- Deposition in single compared with bilateral lung transplants: erratic and nonuniform in native lung
- Regional distribution correlated with perfusion: nonuniform in 3/4 vs 1/3 without bronchiolitis obliterans syndrome

Monforte V, et al. J Heart Lung Transplant. 2001;20:1274-1281.

#### Deposition Profile of Inhaled ABLC in Single Lung Transplants



ABLC = AmB lipid complex. Corcoran TE, et al. *Am J Transplant*. 2006;6:2765-2773.

#### Case Study 1: Conclusions

- Potential drug interactions of antifungal drugs with immunosuppressive agents need consideration
- Antifungal agent selection
  - Locally delivered vs systemic (former appropriate for prophylaxis)
  - Drug distribution and delivery (single vs bilateral transplants)
- Management of immunosuppressive regimen
  - Unique considerations with sirolimus use

#### Case Study 2: Introduction

- 67-year-old patient treated with VBMCP for recurrent multiple myeloma
- Postchemotherapy prophylaxis
  - Trimethoprim/sulfamethoxazole
  - Acyclovir
  - Fluconazole
- Fever developed 7 days later and patient remained unresponsive to piperacillin-tazobactam
- Labs and diagnostics
  - ANC=250 mm<sup>3</sup>
  - Serum Aspergillus GM was shown to be positive (index 3.66)
  - Chest radiograph was unremarkable
  - CT of the chest revealed nodular lesion in left lower-lobe
  - Voriconazole 600 mg/day was initiated

VBMCP = vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; ANC = absolute neutrophil count; GM = galactomannan.

## Case Study: Clinical Progression

- High-grade fever, dyspnea, and worsening hypoxia were noted 11 days after initiation of voriconazole
- CT of the chest showed bilateral pulmonary nodular and parenchymal infiltrates
- ANC=2500 mm<sup>3</sup>
- Intubation and mechanical ventilation for progressive respiratory failure were required

#### Audience Response

What are the most appropriate interventions at this point?

- 1. Repeat and await results of Aspergillus GM test
- 2. Perform bronchoscopy and culture BAL fluid
- 3. Add a second mould-active agent (an echinocandin)
- 4. Add corticosteroids
- 5. Both 1 and 2

BAL = bronchoalveolar lavage.

#### Case Study: Follow-Up

- Serum Aspergillus GM index returned at 1.25
- Methylprednisolone was initiated intravenously
- Follow-up CT scans showed gradual reduction and ultimately resolution of pulmonary infiltrates

# IRS in Aspergillosis

- Fatal hemoptysis after GM-CSF—induced marrow recovery
- 8/20 neutropenic patients with IA developed severe pulmonary complications if neutrophil recovery occurred over 5 days (P<.001)</li>

- 5/8 patients died

- 19/67 (28%) of patients with hematologic malignancy, or HSCT and IA developed worsening hypoxia, progressive infiltrates, requirement of mechanical ventilation up to 8-15 days after resolution of neutropenia
  - 2 required corticosteroids
  - All 19 had declining GM titers
  - 3/19 died

IRS = immune reconstitution syndrome; GM-CSF = granulocyte monocyte colony-stimulating factor; HSCT = hematopoietic stem cell transplantation. Groll AH, et al. *Mycoses*. 1992;35:67-75. Todeschini G, et al. *Eur J Clin Invest.* 1999;29(5):453-457. Miceli MH, et al. *Cancer*. 2007;110(1):112-120.

# **Evolution of IPA**



- 4-fold increase in volume of lesions between days 0-7, and 3-fold increase from days 0-14
- PMN count increased from a median of 0 on day 0 to 2850/mm<sup>3</sup> on day 14
- No correlation with antifungal regimen
  - Most patients received itraconazole (with or without AmB) or voriconazole

PMN = polymorphonuclear. Caillot D, et al. *J Clin Oncol*. 2001;19:253-259.

#### Hepatosplenic Candidiasis as a Manifestation of IRS

- Occurs after chemotherapy-induced neutrophil recovery (8-20 days)
- Imaging findings show inflammatory lesions with granulomatous changes on histopathology
- Biomarkers (circulating mannoprotein) negative in 87%
- Erratic response to antifungal agents; requirement of prolonged therapy
- Th 1/2 imbalance: high IL-10 levels

Th 1/2 = time needed to reach half of the maximal systolic thickening; IL-10 = interleukin-10. Cheng VCC, et al. *Clin Infect Dis.* 2000;30:882-892. Girmenia C, et al. *J Med Microbiol.* 2004;53:103-106. Roilides E, et al. *J Infect Dis.* 1998;178:1734-1742.

#### Monitoring for IA in High-Risk Patients

- Neutropenic patients with hematologic malignancy or allogeneic HSCT recipients
  - Monitor twice weekly using the GM assay
  - GM index of >0.05: sensitivity 79%, specificity 89%, and overall accuracy 89%
- Approach in patients with 2 consecutive positive values
  - Evaluate for IA using CT imaging of the lungs and histopathologic or culture evidence of infection
  - Consider etiologies of false-positive or inaccurate test if no evidence of IA

Pfeiffer C, et al. *Clin Infect Dis.* 2006;42:1417-1427.

#### Causes of Inaccurate Aspergillus GM Assay

- True false-positivity due to GM contamination
  - Beta-lactam antibiotics, most notably piperacillin-tazobactam
  - Plasmalyte or sodium gluconate-containing IV solutions
  - Contamination of blood samples or collection tubes with cotton or cardboard
- Cross-reactivity with cell wall GM
  - Penicillium, Paecilomyces, Cladosporium, Alternaria, Trichophyton, Geotrichum
  - GI colonization with *Bifidobacterium*
  - Histoplasma capsulatum: reactivity in 50% of the samples testing positive for histoplasma antigen assay
- False-negativity
  - Treatment antifungal agents, particularly mould-active drugs

#### GI = gastrointestinal. Wheat LJ, et al. *Clin Vaccine Immunol.* 2007;14(10):1387-1388.

# Utility of BAL Compared with Serum for the Diagnosis of Suspected IPA

- Overall sensitivity 61% and specificity 98% in HSCT recipients
- SOT recipients: sensitivity 61%-100%, specificity 91%-98%
  - Median GM index value significantly higher for Aspergillus disease
    (2.33) vs colonization (0.16) or no disease (0.12)
  - BALs performed for symptomatic cases yielded higher values than surveillance BAL samples
  - 4/13 patients with "false-positive" tests subsequently developed IPA
- Serum-positive in only 27% of cases where BAL yielded the diagnosis

SOT = solid organ transplant. Musher B, et al. *J Clin Microbiol*. 2004;42:5517-5522. Husain S, et al. *Transplant*. 2007;83(10):1330-1336. Clancy CJ, et al. *J Clin Microbiol*. 2007;45:1759-1765. Wheat LJ, et al. *Clin Vaccine Immunol*. 2007;14(10):1387-1388.

#### Correlation of Aspergillus GM Index with Outcome in IA



Woods G, et al. Cancer. 2007;110(4):830-834.

#### Case Study 2: Conclusions

- Approach to the establishment of IA diagnosis in patients with hematologic malignancy, HSCT, and SOT recipients
- Utility of Aspergillus GM assay and its interpretation
- Recognize IRS as a potential contributor to worsening presentation in the evolution of infection
  - Differentiation from progressive disease
  - Use of corticosteroids?