Pneumocystis Jiroveci (Carinii) Infection

Shelli Farhadian, MD PhD
Lydia Barakat, MD

Objectives:
1. Identify pulmonary opportunistic infections in HIVinfected patients
2. Recognize the clinical presentation of PJP
3. Learn about treatment modalities for PJP

Case:

Ms PJ is a 45 year old woman who presents to the ED with four weeks of cough. She had previously been followed at the local HIV clinic, where she originally presented ten years ago, with candida esophagitis and a CD4 count of 49. She was started on anti-retroviral therapy, as well as TMP/SMX and azithromycin for primary opportunistic infection prophylaxis. Ms PJ had done well over the years, with a rise in her CD4 count above 200 and reduction in viral load to undetectable, and prophylactic antibiotics were stopped. Three years ago, she was briefly incarcerated, and was subsequently lost to follow-up. She has not seen any providers since her incarceration.

On admission, she tells you that she has had four weeks of a dry cough and shortness of breath that is worse with exertion. She has had intermittent fevers at home and 10 pound weight loss over the last three months. She is a non-smoker and denies injection drug use. Ms PJ lives in New Haven and has not recently travelled outside of the area.

On initial exam, she is in mild respiratory distress. She in thin, weighing 50 kg. She has fever to 101.1, heart rate of 90, blood pressure 110/75, respiratory rate 30, and SpO2 90%, which decreases to 81% with ambulation. She has oral thrush. No rash or skin lesions. She has no palpable lymphadenopathy. She has fine inspiratory crackles throughout both lungs. She had RRR with no S3. No lower extremities edema.

The rest of the exam is unremarkable. Initial laboratory testing reveals a CD4 count of 177 per mm^3 and WBC count 10,000. Chest X-ray shows diffuse, bilateral interstitial infiltrates.

Question 1:
Which of the following are the most likely possible diagnoses for this patient? What aspects of the history and exam support the most likely diagnosis?
a. Pneumocystis jirovecii pneumonia, bacterial pneumonia, cryptococcus pneumonia
b. Pneumocystis jirovecii pneumonia, bacterial pneumonia, pulmonary TB
c. Pulmonary embolism, pulmonary TB, Histoplasma pneumonia

d. Bronchogenic carcinoma, pulmonary aspergilloma, pulmonary TB

Answer b.
Respiratory symptoms are a common complaint of HIV patients and they can represent both infectious and non-infectious diseases. Immunocompromised hosts are susceptible to the most common bacterial and viral causes of pneumonia, and these can occur at any CD4 cell count level. As CD4 cell counts fall, the risk for infection caused by opportunistic bacterial, fungal, viral, and parasitic pathogens rises. Pulmonary symptoms in an HIV patient may also indicate neoplastic disease, such as Kaposi sarcoma, Non-Hodgkin lymphoma, and bronchogenic carcinoma. HIV patients are also susceptible to non-HIV related pulmonary disease, such as pulmonary embolism, asthma, and COPD.

CD4 count is a good measure of the immunocompromised status of the patient, and can help identify specific pathogens that are more common based on CD4 levels. 90% of patient with Pneumocystis jirovecii (PJP, formerly PCP) have CD4 <200. CD4 levels of 100-200 are also associated with recurrent bacterial pneumonia, as well as disseminated TB. At CD4 <100, patients become more susceptible to pneumonia from toxoplasma and cryptococcus, and at CD4 <50, CMV, MAC, and fungal pathogens such as histoplasma and coccidiodes, become more concerning.

Certain aspects of the clinical history and initial exam can help distinguish between these different causes of cough and dyspnea in an HIV patient, and point to PJP as the most likely diagnosis. Her presentation is sub-acute, which is more classic for PJP than for bacterial pneumonia (the median duration for PJP symptoms is 28 days). The lack of a productive cough is also more characteristic of PCP than of bacterial pneumonia, which more typically presents more acutely with 3-5 days of shaking chills and purulent sputum. Bacterial pneumonia is more common in HIV patients that are injection drug users than in HIV patients who do not use injection drugs. A history of oropharyngeal candidiasis is also a risk factor for PCP. The patient has a history of incarceration, putting her at increased risk for TB. Although pulmonary TB in HIV patients can have different presentation (cavitary lesion, interstitial infiltrate, etc.) at CD4 counts less than 200, TB is often disseminated and/or extrapulmonary.

Physical exam findings can help differentiate between various infectious processes: focal lungs findings might suggest a bacterial pneumonia, whereas 50% of patients with PJP have a clear lung exam. Desaturation with exercise is typically seen in PJP. Finally, remember that up to 25% of patients with PJP have an initially clear chest X ray. Ultimately, because there is overlap in clinical presentation for many of these disease states, it is always preferable to obtain a specimen for a definitive diagnosis.

Question 2
What further studies would you obtain at this point?
a. induced sputum culture, chest CT-scan, ABG
b. bronchoscopy with broncheoalveolar lavage, LDH, ABG
c. open lung biopsy, chest CT-scan, LDH

Answer b.
Bronchoscopy with broncheolar lavage has the highest sensitivity for diagnosis of PJP (0-99%) compared to induced sputum (50-90% sensitivity) and is therefore the best choice. There is no need for tissue biopsy to make the diagnosis of PJP even though it is 100% sensitive and specific. Detection of the PJ forms and cysts are made by Methamine Silver stain, immunofluorescence staining, and Wright-Giemsa staining.

LDH and arterial blood gas should be checked as they can help assess the severity of PJP disease, and are therefore good prognostic markers. Blood cultures should be drawn.

Case continued: Initial laboratory results show PaO2 70mmHg, A-a gradient 43, LDH 400. Methenamine silver stain of induced sputum shows a cluster of cystic inclusions consistent with Pneumocystis jirovecii infection

Question 3
What is the best treatment approach to this patient?
a. TMP-SMX: 15-20mg/kg/day TMP component by IV, then 2 DS tabs PO every 8 hours
b. TMP-SMX: 1 DS tab per day
c. TMP-SMX: 15-20mg/kg/day TMP component by IV, then 2 DS tabs PO every 8 hours, PLUS prednisone
d. TMP-SMX: 1 DS tab per day PLUS predniso**ne**

Answer: c
The first choice for treatment of PCP is trimethoprim-sulfamethoxazole. Ms PJ will require 3 weeks of therapy, Mild cases can be treated with oral TMP/SMX as outpatient but moderate to severe cases should be treated initially with IV and then transitioned to oral antibiotics once her breathing begins to improve and she can better tolerate oral medication. The oral dosage is TMP/SMX 2 DS (800mg/160mg)tabs every 8 hours for 21 days followed by PJP prophylaxis dose of 1 DS tab per day. If the patient has an allergy or intolerance to TMP-SMX, other oral treatment regimens for moderate disease are TMP-dapsone, or clindamycin and primaquine. Randomized trials found no difference in survival in patients who were treated with these three different regimens. Other treatment modalities include IV Pentamidine and Atovaquone.

Adjunct corticosteroids are recommended for patients with A-a gradient of 35mmHg or more or PaO2 of 70mmHG or less. Steroids are thought to help decrease inflammation that typically occurs after 2-3 days of PCP treatment. A 2006 Cochrane review found a significant mortality benefit (44% risk reduction at one month) for corticosteroid use in patient with PCP and severe hypoxemia, although the magnitude if this benefit is decreased when ART is widely available. Use of steroids does not seem to increase the risk for development of other opportunistic infections, with the exception of muco-cutaneous herpes simplex virus and candida esophagitis.

Question 4
When would you start anti-retroviral treatment (ART)?
a. immediately
b. within 2 weeks
c. in 3 months
d. after PCP resolves

Answer b. In the past there had been some concern for initiating ART in patients with an opportunistic infection because of the possibility for drug-drug interactions or the development of an immune reconstitution syndrome. A study of 4412 patients with PCP showed that early ART improved survival. A5164 was a randomized trial of early ART (started within two weeks of an opportunistic infection) versus deferred ART that demonstrated that early ART reduces mortality. Therefore, the International AIDS Society recommends the early ART strategy. This patient should be started on ART during this hospitalization.

Case continued: Your patient is started on 40mg prednisone twice a day as well as TMP-SMX. She initially feels worse, but by day 7 she is improving, with better oxygenation and she is transitioned to oral TMP-SMX. On day 10 you initiate ART. The patient does well and is discharged to home. Three weeks later, she develops recurrent fever and worsened dyspnea.

Question 5
What are possible complications of PCP and its treatment? How can you tell if this person has Immune Reconstitution Inflammatory Syndrome (IRIS)?

The overall mortality for HIV infected patients with PJP is 15-27% and increases to 55% for patients admitted to the ICU. Patients with PJP are at risk for developing respiratory failure, even with use of adjunct corticosteroids. Hypoxemia tends to worsen over the first 2-3 days, due to an inflammatory response to dying fungi. This initial inflammatory response improves with steroids and with time of treatment. Patients with PJP are also at risk for spontaneous pneumothorax in 10% of cases.

In this patient, her symptoms worsen three weeks after starting ART therapy, a time frame that is consistent with development of IRIS. IRIS is an inflammatory reaction that can occur following initiation of ART in patients with HIV. As the HIV viral load falls upon initiation of ART, the body is able to generate T-lymphocytes. The resultant inflammatory response can lead to a paradoxical worsening of underlying opportunistic infection. In a patient with PCP started on ART, IRIS can present as high fevers and worsened respiratory symptoms after a patient had initially been doing well on PCP treatment. Risk factors for IRIS are a low CD4 count and the presence of an opportunistic infection when ART is initiated.

References:

*Thomas, Charles and Limper, Andrew. “Pneumocystis Pneumonia” N. Engl. J. Med. 2004;350:2487

*Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR 2009;58 (No. RR-4) April 10, 2009:[pages 6-10].

Additional References:

Ball, Susan C. "Pneumocystis pneumonia in a person with a low CD4 count after stopping antiretroviral therapy." The AIDS reader 17.12 (2007):583-6, 593.

Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection.
Cochrane Database Syst Rev. 2006

Croda J, and al. Benefit of antiretroviral therapy on survival of human immunodeficiency virus-infected admitted to the intensive care unit. Crit.Care Med. 2009;37(5):1605

Dworkin M, Hanson, D and al. Survival of Patients with AIDS, after diagnosis of Pneumocystis carinii Pneumonia, in the United States. JID 2001;183:183:1409

Huang L. Pulmonary Manifestations of HIV. HIV InSite Knowledge Base Chapter. January 2009. http://hivinsite.ucsf.edu/InSite?page=kb-04-01-05

Kovacs JA, Gill VJ. And al. New insights into transmission, diagnosis, and drug treatment of Pneumocystis carinii pneumonia. JAMA 2001;286(19):2450

Safrin S, Finkelstein DM, Feinberg J, Frame P, Simpson G, Wu A, Cheung T, Soeiro R, Hojczyk P, Black JR Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. Ann Intern Med. 1996;124(9):792.

Smego RA, NagarS, and al. A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia . Arch. Intern. Med 2001;161(12):1529

Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, Gatell JM, Günthard HF, Hammer SM, Hirsch MS, Jacobsen DM, Reiss P, Richman DD, Volberding PA, Yeni P, Schooley RT, International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA. 2010;304(3):321.

Wilkin, A, and JFeinberg. "Pneumocystis carinii pneumonia: a clinical review." Am Fam Physician 60.6 (1999):1699-708, 1713.

Zaman MK, White DA. Serum lactate dehydrogenase levels and Pneumocystis carinii pneumonia. Diagnostic and prognostic significance. Am Rev Respir Dis. 1988 Apr;137(4):796-800

Zolopa, A, Andersen, J, Powderly, W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS ONE 2009; 4:e5575. Epub 2009 May 18.