Pneumocystis Jiroveci Pneumonia (PJP)

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HIV-negative vs HIV-positive PJP
Pneumocystis Jiroveci Pneumonia (PJP) presents differently, depending on whether the patient is HIV-negative or HIV-positive ([HIV(-)PJP versus HIV(+)PJP]. HIV causes PJP pneumonia to present in a more indolent manner, with a higher burden of organisms. This makes HIV(+)PJP somewhat easier to diagnose and to treat. Alternatively, HIV(-)PJP tends to present in a more fulminant fashion with a lower burden of organisms – presenting a greater diagnostic and therapeutic challenge.

**epidemiology**

**HIV**

- Previously, PJP was extremely common and a leading cause of death in HIV. However, with increased use of anti-retroviral therapy, the frequency of PJP has decreased substantially. Patients who are *unaware* of their HIV status (and thus untreated) continue to present with PJP.
- 95% of patients have a CD4 count <200.
- PJP can occur as a component of immune reconstitution inflammatory syndrome (IRIS), following initiation of anti-retroviral therapy for HIV.

**other forms of immunosuppression**

- **Steroid** accounts for >90% of patients in this category.
  - Involves a minimum exposure of roughly >15 mg prednisone daily for >2 months.
  - Patients are at especially high risk if:
    - They are being treated for rheumatologic diseases or glioblastoma.
    - Steroid is combined with other immunosuppressives (e.g., cyclophosphamide).
  - PJP may manifest when patients are tapering off steroids (when immune system is reconstituting).
- **Malignancy**
  - #1) Hematologic malignancy (especially acute leukemia, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia)
  - #2) Chemotherapy (especially fludarabine, cladribine, cytarabine, and temozolomide)
- **Organ transplantation (solid or hematopoeitic stem cell)**
  - PJP most commonly occurs 4-6 months post-transplantation.
- **Immunosuppressive medications**, for example, ([Tasaka S, 2020](https://pubmed.ncbi.nlm.nih.gov/32185915/)).
  - Alkylating agents (cyclophosphamide, temozolomide)
  - Anti-metabolites (methotrexate, cytarabine, fluorouracil)
  - Purine analogs (azathioprine, cladribine, fludarabine, mycophenolate mofetil)
  - Calcineurin inhibitors (cyclosporine, tacrolimus)
  - mTOR inhibitors (everolimus, sirolimus, temsirolimus)
  - TNF-alpha inhibitors (e.g., adalimumab, certolizumab, etanercept, infliximab, golimumab)
  - IL-6 inhibitors (sarilumab, tocilizumab)

**clinical presentation**

**HIV(+)PJP**

- This typically evolves gradually, over weeks or months (e.g., may cause insidious weight loss).
- Classical symptom trial:
  - Fever (~90%) – fevers, night sweats, and fatigue can be a predominant feature.
  - Cough (95%) – generally dry or productive of clear sputum.
  - Progressive dyspnea (95%).
- Oral thrush coinfection is common (thrush may be a sign of underlying HIV).

**HIV(-)PJP**

- This presents more acutely (typically about one week from symptom onset to respiratory failure) ([Tasaka S, 2020](https://pubmed.ncbi.nlm.nih.gov/32185915/)).
- Common features include fever, dry cough, and hypoxemic respiratory failure.
- This often progresses to requiring mechanical ventilation.

**chest CT scan**

![Chest CT scan](https://emcrit.org/ibcc/pjp/attachment/cxrpjp/)

**typical findings**

- Central ground glass opacities are the most common finding.
  - Distribution is most often perihilar (often sparing the peripheral lung). However, a diffuse distribution may also be seen.
  - Infiltrates may be patchy, involving only some lobules (creating a mosaic attenuation pattern).
  - It can be associated with a septal thickening (with an overall appearance that mimics heart failure).
  - Severe cases may progress to patchy bilateral consolidation (which will have a more nonspecific, ARDS-y appearance).
- Thin-walled cysts occur in ~30%.
  - They are most often located in the upper lobe, in a sub-pleural location.
  - Cysts predispose to the development of pneumothorax.
  - Cysts are seen more often seen in HIV(+)PJP, rather than HIV(-)PJP.

![Chest X-ray showing diffuse bilateral infiltrates due to Pneumocystis jiroveci pneumonia in an HIV-infected patient with AIDS with a CD4+ T lymphocyte count of 15/µL.](https://emcrit.org/ibcc/pjp/attachment/cxrpjp/)

**less common findings**

- Nodular patterns can occur (may be solitary or multiple; usually upper-lobe predominant; nodules can cavitate).

![HRCT scans of Pneumocystis jiroveci pneumonia](https://emcrit.org/ibcc/pjp/attachment/pjpctscans/)

**Fig. 1.** High-resolution computed tomography findings of *Pneumocystis jiroveci* pneumonia (PCP). (A) PCP in a patient with rheumatoid arthritis receiving methotrexate therapy. Diffuse ground glass opacity (GGO) is distributed in a panlobular manner, in which GGO is sharply demarcated from the adjacent lung by interlobular septa. (B) PCP in a patient with human immunodeficiency virus infection. Diffuse GGO is distributed in an inhomogeneous manner without sharp demarcation. Subpleural sparing is also indicated. (C) PCP in a patient with malignant lymphoma. Among GGO, patchy consolidation is located along the bronchovascular bundle. (D) PCP in a cancer patient who was receiving chemotherapy and high-dose corticosteroid. Cysts are observed within the affected area, suggesting that they were formed by PCP.


Salzer HJF et al. 29035251
Upper lobe infiltrates may occur in patients who received inhaled pentamidine for PJP prophylaxis (since the upper lobes are less well ventilated and thus receive lower doses of pentamidine).

**findings which are generally not consistent with PJP**

- If seen, these findings suggest either another superimposed process, or an alternative diagnosis entirely:
  - Lymphadenopathy
  - Pleural effusion

**HIV evaluation**

- PJP pneumonia can be the presenting finding of AIDS.
- For patients with unknown HIV status, there should be a low threshold for evaluating for HIV (e.g., if CT scanning suggests possible PJP).
  - The Centers for Disease Control recommends fairly broad screening for HIV (https://www.cdc.gov/hiv/guidelines/testing.html), so this is reasonable whenever there is a question of possible HIV.
  - The presence of absolute lymphopenia (e.g., absolute lymphocyte count below ~1,500 cells/μL) might suggest the possibility of HIV. However, lymphopenia isn't very good test for HIV, so this cannot be relied upon.

**serum beta-D glucan**

**basic properties of assay**

- Beta-D glucan is a cell wall component present in most fungi (except cryptoccocus or zygomycetes).
- This is not specific for PJP, but rather can be seen with a variety of fungal infections (e.g., aspergillus, histoplasma, cryptoccocus, or candida).
  - Even colonization with candida may generate a positive assay (Morjaria et al. 2019 (https://pubmed.ncbi.nlm.nih.gov/30561560/)).
- Causes of a false-positive assay include:
  - Treatment with intravenous immunoglobulin (IVIG).
  - Exposure to cellulose membranes (used in hemodialysis, or processing of albumin/blood products).
  - Exposure to gauze packing.
  - Some bacterial infections (e.g., Pseudomonas).
  - (Note: assay is not affected by piperacillin-tazobactam).
The largest and most recent study evaluated 438 cancer patients at Memorial Sloan Kettering (Morjaria et al. 2019 (https://pubmed.ncbi.nlm.nih.gov/30561560/)).

- Exact numbers are a little fuzzy because of the existence of some patients with "possible" PJP.
- Using a cutoff of >80 pg/ml had a sensitivity of 88% and specificity of 85%. Within this patient population, a value <80 pg/ml had a negative predictive value of 95% (however, negative predictive value depends on the pre-test probability of disease, so it will vary among patients and populations).
- Using a cutoff of >200 pg/ml had a sensitivity of 70% and specificity of 100%. In the presence of a positive PCR, this strongly argues for invasive disease (rather than colonization).
- Receiver – operator curve is shown above.

The largest study involves analysis of 252 patients with AIDS and opportunistic infections: (Sax et al. 2011 (https://pubmed.ncbi.nlm.nih.gov/21690628/#affiliation-1)).

- Among all patients: 173/252 patients were diagnosed with PJP
  - Patients with PJP had beta-D-glucan levels with median of 408 pg/ml (IQR 209-500 pg/ml).
  - Patients without PJP had beta-D-glucan levels with median of 37 pg/ml (IQR 31-235 pg/ml).
  - A cutoff value of 80 pg/ml yielded a sensitivity of 92% and specificity of 65%.
  - Receiver – operator curve is shown above.
- Among patients presenting with respiratory symptoms: 139/159 patients were diagnosed with PJP (Wood et al. 2013 (https://pubmed.ncbi.nlm.nih.gov/23698062/)).
  - A cutoff value of 80 pg/ml yielded sensitivity of 93% and specificity of 75%.

Lactate dehydrogenase

- Lactate dehydrogenase (LDH) historically was used as a test to evaluate for HIV(+) PJP. However, more recent studies have found that it has poor performance for this (Sax et al. 2011 (https://pubmed.ncbi.nlm.nih.gov/21690628/#affiliation-1)).
- Elevated lactate dehydrogenase is extremely nonspecific (especially in the context of critical illness or malignancy).
- LDH probably adds nothing meaningful to the diagnostic evaluation.
inflammatory markers

- Not generally part of the evaluation of PJP (performance is unclear).
- One study showing typical results is shown below.
  - If procalcitonin is obtained for another reason, a value >>10 ug/L suggests an alternative or superimposed diagnosis (not solely PJP).

![Graph showing distribution of inflammatory markers in PJP](https://emcrit.org/ibcc/pjp/attachment/pjobronch/)

bronchoscopy

conventional stain (i.e., silver stain)

- Sensitivity ~97% for HIV(+)PJP, but considerably lower in HIV(-)PJP.

![Microscopic image of black Pneumocystis jirovecii cysts](https://emcrit.org/ibcc/pjp/attachment/pjobronch/)

PCR for PJP

- PCR has increased sensitivity compared to conventional stain (sensitivity approaches 100%, specificity varies depending on population).
- Specificity is limited by colonization.
  - Up to 20% of healthy adults may be colonized with Pneumocystis jirovecii. Colonization may be even more common among patients with HIV ([Davis et al. 2008](https://pubmed.ncbi.nlm.nih.gov/18024536/)).
  - A beta-D-glucan assay may help sort out whether a positive PCR reflects reflect colonization or invasive infection ([Morjaria et al. 2019](https://pubmed.ncbi.nlm.nih.gov/30561560/)).

PCR for other pathogens

- Consider PCR for CMV in patients with HIV, as this may occur with PJP (or it may develop clinically as patients are recovering from PJP pneumonia).
**induced sputum ??**

- Across different hospitals, there is considerable variation in specimen quality. This test is highly operator-specific, making it difficult to state any universal statistics regarding sensitivity and specificity (reported numbers for sensitivity in the literature range anywhere from 55% to 95%) ([Sax et al. 2011](https://pubmed.ncbi.nlm.nih.gov/21690628/#affiliation-1)).
- If PCR shows organism, this increases likelihood of PJP, but a negative induced sputum has unclear sensitivity.
- Overall role in diagnosis is unclear currently.

**endotracheal aspirate ??**

- There is not much data regarding this.
- In HIV(+) PJP, one study found 12/13 (93%) sensitivity using endotracheal aspirate with immunostaining techniques ([Alvarez et al. 1997](https://pubmed.ncbi.nlm.nih.gov/9201045/)). Note that these authors instilled saline into the endotracheal tube, so this was a bit of a tracheal wash.

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**early-invasive approach**

- Traditionally, diagnosis has centered around bronchoscopy with bronchoalveolar lavage. The main drawback of this strategy is that bronchoscopy may be a risky procedure in patients with severe hypoxemia.
- Bronchoscopy has the greatest utility in patients with a broader differential diagnosis, for example due to:
  - i) More profound immunosuppression (which could place the patient at risk for a variety of opportunistic infections).
  - ii) Nonspecific chest CT findings (e.g. patchy consolidation which could be consistent with pneumocystis, dimorphic fungi, or invasive mold).

**empiric therapy +/- delayed bronchoscopy**

*Noninvasive strategy to critically ill patient with suspected PJP pneumonia*

- **Appropriate candidate for noninvasive strategy**
  - Performing bronchoscopy would involve high risk of deterioration (e.g. intubation).
  - Differential is reasonably narrow (e.g. bacterial pathogens or PJP) = so empirical coverage is possible without incalculable broad tx.
  - Patient prefers more invasive diagnostic/therapeutic approach (consider shared decision-making if possible)

- **Broad-spectrum empiric coverage of possible pathogens**
  - Prednisone 40 mg BID, azithromycin, ceftriaxone, trimethoprime-sulfamethoxazole

- **Optimize patient otherwise**
  - Optimize volume status & hemodynamics
  - Treat any other active pulmonary problems (e.g. COPD)

- **Noninvasive evaluation**
  - Sputum and gram stain for culture/gram stain
  - Procalcitonin & 1-3 beta-D glucan
  - Urine pneumococcal & legionella antigens
  - Relevant fungal antigens (e.g. Cryptococcus, blasto, histo).
  - Nasal MESTA PCR
  - PCR for COVID-19, influenza, respiratory viruses PRN
  - CT soon if not already obtained

- **Re-evaluate over 24-48 hours:**
  - Does the noninvasive evaluation reveal a diagnosis?
    - Yes
      - No further need for bronchoscopy.
      - Tolerant antibiotics & treat accordingly.
    - No
      - Consider high-risk bronchoscopy versus ongoing empiric therapy.

- **Is patient stable enough to undergo bronchoscopy at this point in time?**
  - No
  - Yes
    - Consider bronchoscopy

*Noninvasive strategy for possible PJP pneumonia*: In PJP pneumonia, bronchoscopy will remain positive for days (dead organisms and DNA persists). For unstable patients who may not tolerate bronchoscopy well, an initial empiric approach may be safest. The goal is to avoid bronchoscopy entirely, or delay bronchoscopy until it may be better tolerated.
An alternative approach is to initiate empiric therapy for PJP (as well as other pathogens) while simultaneously awaiting the results from non-invasive studies (Wood et al. 2013 [https://pubmed.ncbi.nlm.nih.gov/23698062/]). Factors that could argue for this strategy could include the following:

i) Patient is extremely hypoxemic and not expected to tolerate bronchoscopy well.

ii) Patient is relatively less profoundly immunosuppressed (narrowing the differential diagnosis).

iii) Chest CT scan is somewhat helpful in narrowing the possibilities (e.g., the CT scan shows diffuse ground-glass opacification).

The drawback of this strategy is that if none of the diagnostic tests reveal a pathogen, then the patient may be left on a rather unwieldy regimen of several antibiotics and steroids. In this situation, delayed bronchoscopy (often after a few days when the patient may have started recovering) may be helpful to assist in narrowing antibiotic therapy. Notably, delaying bronchoscopy for a few days should still allow for a good yield for PJP (dead organisms or PCR positivity should still remain, even after viable organisms are gone).

**1st line therapy: trimethoprim-sulfamethoxazole (TMP-SMX)**

- TMP-SMX is front-line therapy (even if the patient was previously on this agent for PJP prophylaxis).
  - Oral TMP-SMX DS may be used for moderate disease (generally two DS tabs q6hr or q8hr).
  - For severe disease or lack of enteral access, intravenous TMP-SMX is indicated. The dose is 15-20 mg/kg per day trimethoprim in 3-4 divided doses either PO or IV.
  - More on trimethoprim-sulfamethoxazole is in the antibiotics chapter here [https://emcrit.org/ibcc/antibiotics/#trimethoprim-sulfamethoxazole].
  - HIV(+)PJP patients often have difficulty tolerating trimethoprim-sulfamethoxazole due to various adverse reactions. This seems to be better tolerated by HIV(-)PJP patients.
  - Patients with prior allergy to TMP-SMX may undergo desensitization, since this is the front-line therapy. However, severe non-allergic reactions (e.g., Stevens-Johnson syndrome) are a permanent contraindication to the use of TMP-SMX.
  - A 21-day course is standard, but improvement should occur within a week (otherwise consider transition to 2nd line therapy).

**2nd line therapy is generally clindamycin-primaquine**

- Usual combination:
  - Primaquine 30 mg PO daily
  - Clindamycin 900 mg q8hr IV (initially).

A primary limitation to this combination is lack of an IV form of primaquine, so this relies on some form of enteral access.

- Primaquine is contraindicated in G6PD deficiency. However, therapy may be started before G6PD results return if the patient is in a low-risk ethnic group.

- Consult an infectious disease specialist for patients not responding to trimethoprim-sulfamethoxazole.

**antiretroviral therapy (ART) for HIV(+)PJP**

- There is benefit to starting reasonably soon (e.g., within ~2 weeks).
- Infectious disease consultants may help clarify the optimal timing and regimen.
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**steroid**

- **indication**
  - **HIV(+)PJP**
    - The classical indication is: PaO2 < 70 mm or A-a gradient > 35 mm.
    - Patients requiring supplemental oxygen to maintain adequate saturation will meet these criteria, so you don’t need to bother getting an ABG on them. Likewise, critically ill patients with severe pneumonia will all meet these criteria.
  - **HIV(-)PJP**
    - The role of steroid is less clear. However, steroid is generally still used in a similar fashion to that in HIV(+).PJP.

- **regimen**
  - Traditional regimen is as follows:
    - Prednisone 40 mg BID days #1-5
    - Prednisone 40 mg daily days #6-11
    - Prednisone 20 mg daily days #12-21
  - An equivalent dose of other steroid may be used as needed (e.g., methylprednisolone in a patient unable to take oral medications).

- **prognosis**
  - Prognosis of PJP in general:
    - HIV(+)PJP carries a ~15% mortality
    - HIV(-)PJP carries a ~40% mortality
  - Prognosis is worse for patients in the ICU and who require mechanical ventilation (especially patients with advanced malignancy).

- **podcast**
  - Follow us on iTunes.

- **questions & discussion**
  - To keep this page small and fast, questions & discussion about this post can be found on another page here.
Delaying initiation of treatment until the diagnosis has been definitively reached (in many situations, it will be appropriate to empirically initiate therapy prior to confirmation of the diagnosis).

A rigid diagnostic approach to PJP which insists on early bronchoscopy for all patients.

Going further:

- Clinical correlations: [Vignette of HIV(-)PJP](https://www.clinicalcorrelations.org/2017/09/20/clinical-vignette-pneumocystis-pneumonia-in-a-patient-without-aids/) by Martin Fried
- Radiopaedia: [PJP pneumonia](https://radiopaedia.org/articles/pulmonary-pneumocystis-jiroveci-infection?lang=us) by Dr Daniel J Bell and Dr Behrang Amini et al.
- [PJP pneumonia](https://wikem.org/wiki/Pneumocystis_jirovecii_pneumonia) (WikEM)

The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.