Pneumocystis jiroveci management in IC HOST

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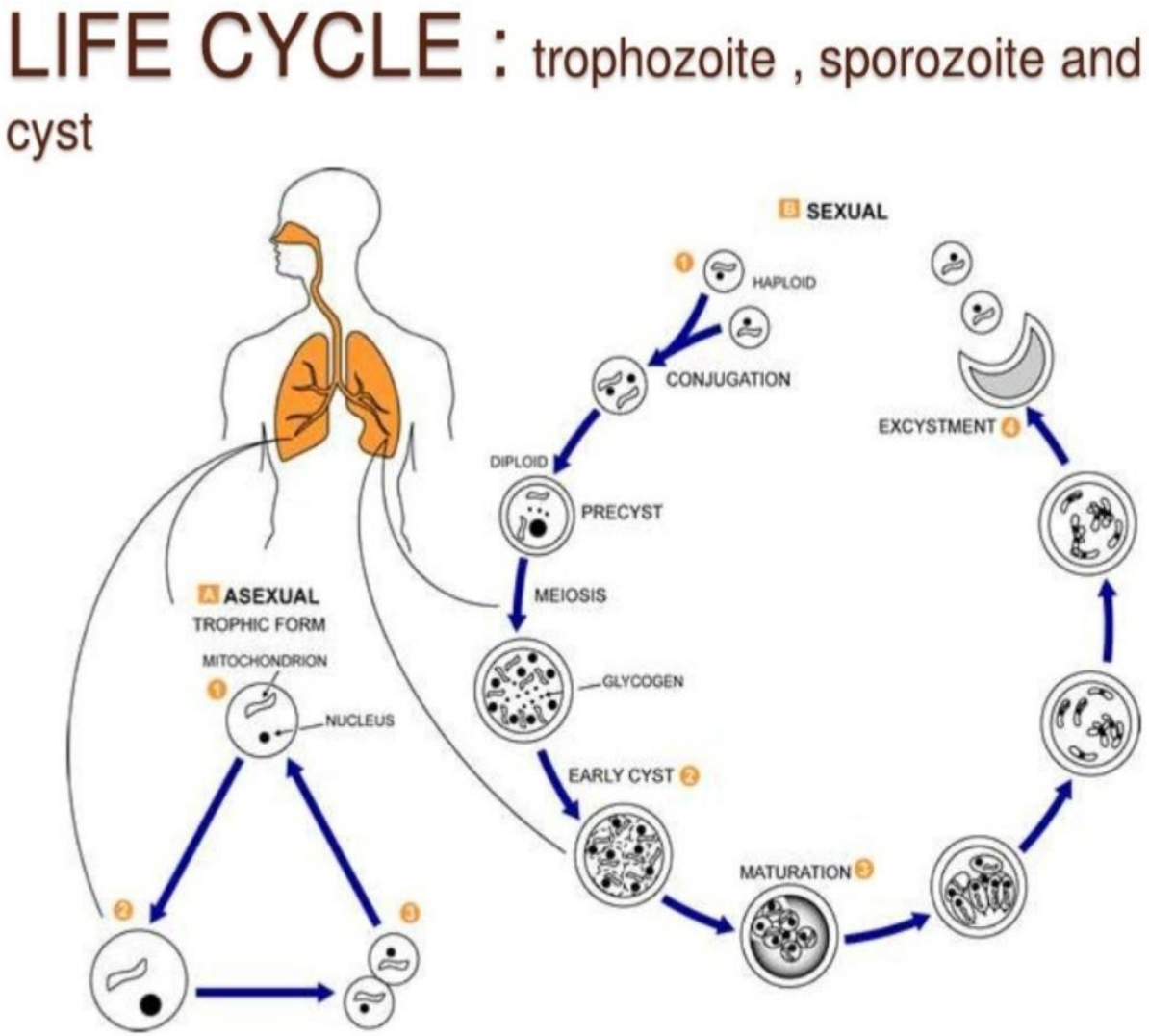
Pneumocystis jiroveci

- Pneumocystis jiroveci, formerly P carinii, remains an important opportunistic fungal pathogen in immunocompromised patients

Pneumocystis jiroveci



Pneumocystis jiroveci

PATHOPHYSIOLOGY …

Development of PCP

- Disease occurs when **both cellular immunity and humoral immunity are defective**.
- Once inhaled, the trophic form of *Pneumocystis* organisms attach to the alveoli.
- Multiple host immune defects allow for uncontrolled replication of *Pneumocystis* organisms and development of illness.
- Activated alveolar macrophages without $CD4^+$ cells are unable to eradicate *Pneumocystis* organisms.
- Increased alveolar-capillary permeability is visible on electron microscopy.

Pneumocystis jiroveci

PATHOPHYSIOLOGY …

Risk Factors for PCP in HIV-negative Patients

- Patients taking steroids or other immunosuppressants.

Eg.Patients with

- ✓ Haematological malignancy.
- ✓ Organ transplant recipients.
- ✓ Connective tissue diseases such as rheumatoid arthritis.
- Congenital immune deficiency - eg, thymic aplasia, SCID, hypogammaglobulinaemia.
- Severe malnutrition (poor nutrition in HIV-positive individuals increases risk).
- Pre-existing lung disease

Pneumocystis jiroveci

PATHOPHYSIOLOGY …

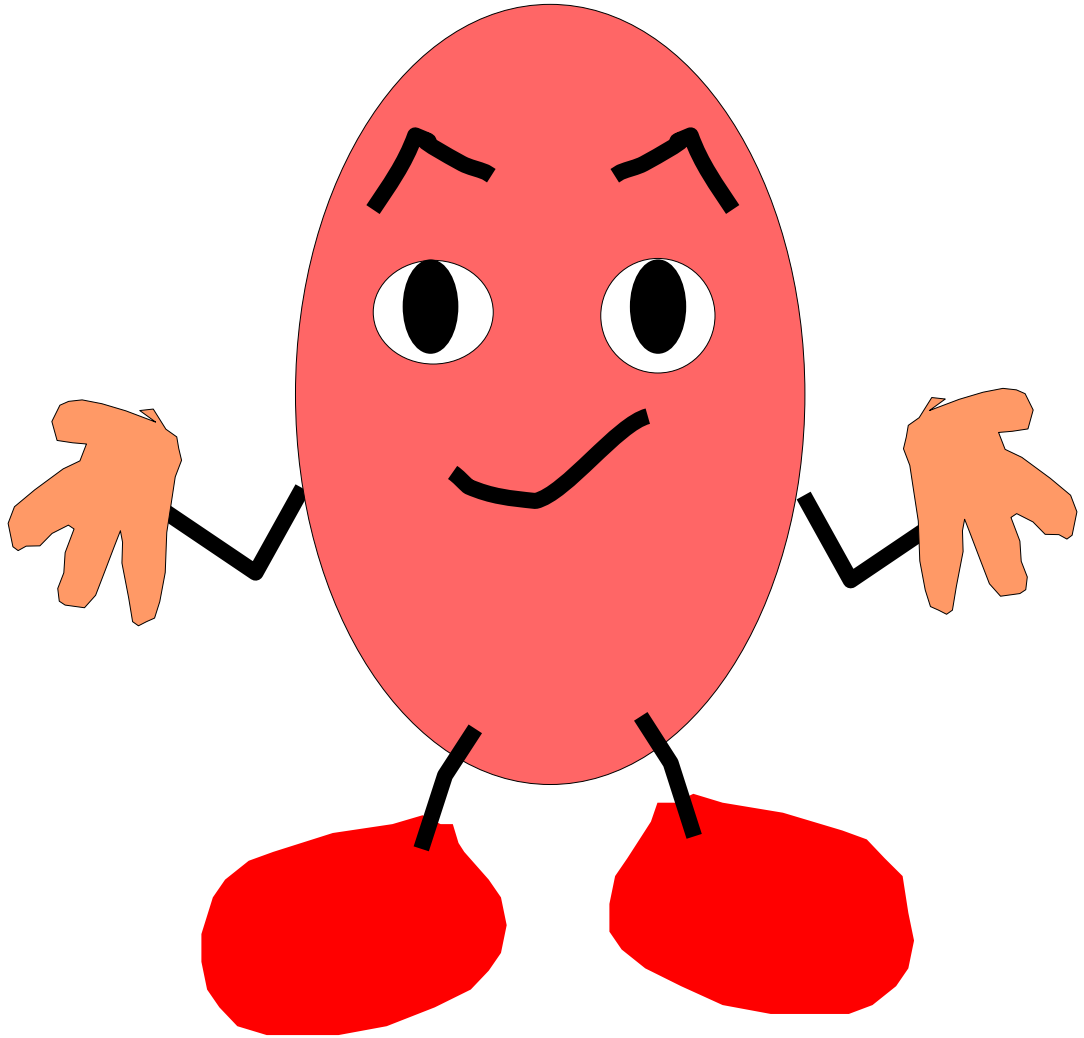
Risk Factors for PCP in HIV-Positive Patients

- CD4+ T-lymphocyte cell count < 200 per mm^3 (200×10^6 per L)
- Unexplained fever of > 37.7℃ (100℉) for > two weeks
- History of oropharyngeal candidiasis
- Previous episode of PCP
- Other AIDS-defining illness

Risk Factor	Comments
Immunosuppressive therapies	
Corticosteroids	Retrospective case series on non-HIV-infected patients with PJP have identified corticosteroids as a common feature in up to 90%. The median dose and duration of therapy in one series equivalent to 30 mg/day of prednisone for 12 wk.[24,25]
Chemotherapy	PJP reported with numerous chemotherapeutic agents including methotrexate, fluorouracil, and bleomycin. Risk for infection related to intensity and duration of neutropenia.[5] Purine analogs, fludarabine and cladribine, and the anti-metabolite cytarabine are independent risk factors for PJP.[74,75]
Antibody therapies	Antilymphocyte antibodies for graft rejection or in induction are linked to the highest risk of PJP being in the 1-6 mo post–transplant time period.[76] Alemtuzumab may confer the highest risk for PJP of antibody therapies.[77]
Mycophenolate mofetil	Mycophenolate may have anti-*Pneumocystis* effects in animal models and uncontrolled human data, leading to theories about it being protective[78,79]; definitive data are lacking.
Calcineurin inhibitors	Limited data suggest greater risk with cyclosporine A compared with azathioprine in renal transplantation.[80] Retrospective study with higher incidence of PJP among renal transplant recipients on tacrolimus-based regimens compared with cyclosporine A.[3]
Sirolimus	Sirolimus associated with a clinical syndrome of interstitial pneumonitis that may be confused with PJP.[81]
Other clinical factors	

CMV disease	Systemic immunosuppressive effects of CMV is an independent risk factor for PJP[51]; CMV, and PJP coinfection well-reported.[23,82,83]
Allograft rejection	PJP has been related to the degree and intensity of immunosuppression in transplant recipients,[3] and directly linked to treatment for and number of episodes of acute rejection.[83]
GVHD	Patients greater than 6 m out from HSCT are more likely to develop PJP when still being maintained on immunosuppressant therapies for ongoing GVHD.[84]
Low $CD4^+$ T-cell counts	In HIV infection, the risk for PJP is directly linked to the fall of $CD4^+$ T-cell counts to <200 cells/mL or <20% of the total circulating lymphocytes.[85] About 73% of PJP diagnosis in SOT recipients occurred in patients with $CD4^+$ T-cell counts of <200 cells/ml and associated with absolute lymphocyte count $<500 \times 10^6$ cells.[86,87] Lymphopenia and decreased $CD4^+$ T-cell counts are a risk factor for PJP in HSCT recipients,[88] solid tumor patients receiving chemotherapy,[89] and autoimmune disease and haematological malignancy.[90] Low $CD4^+$ T-cell counts may reflect other processes such as viral coinfection or exogenous immunosuppression.[23,51]
Neutropenia	Prolonged neutropenia has been suggested as a potential risk factor for the development of PJP in transplant recipients.[51]

CLINICAL MANIFESTATIONS



Signs and symptoms

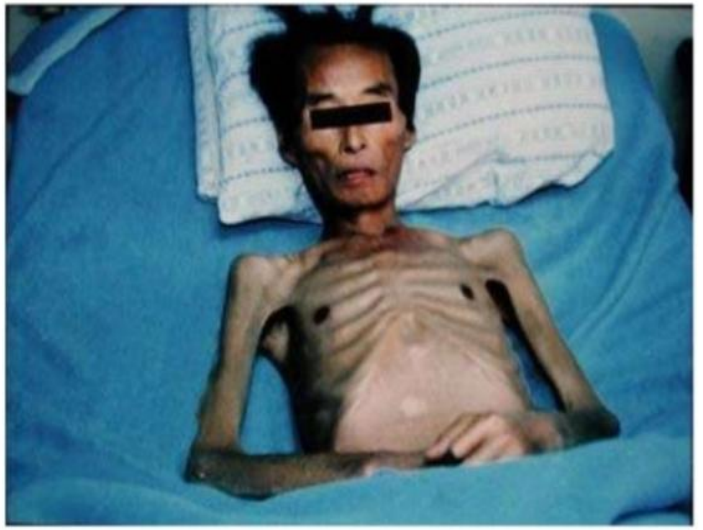
Sign or Symptom of PJP	Incidence
Fever	81%-87%
Dyspnea	66%-68%
Cough	71%-81%
Chest pain	23%-24%
Abnormal lung auscultation on examination	30%-34%
Abnormal chest radiography	92%-96%
Hypoxemia	78%-91%

Signs and symptoms

CLINICAL MANIFESTATIONS

Symptoms of PCP include the following:

- Progressive exertional dyspnea (95%)
- Fever (>80%)
- Nonproductive cough (95%)
- Chest discomfort
- Weight loss
- Chills
- Hemoptysis (rare)



Signs and symptoms

CLINICAL MANIFESTATIONS …

B. Grading severity of PCP by oxygenation

Severity	$[A\text{-}a]Do_2$ (mm Hg)	Pao_2 (mm Hg)
Mild	< 35	> 70
Moderate	35 to 45	> 70
Severe	> 45	70 - 50

$[A\text{-}a]Do_2$ = alveolar-to-arterial oxygen difference;
Flo_2 = fraction of inspired oxygen;
$Paco_2$ = arterial partial pressure of carbon dioxide;
Pao_2 = arterial partial pressure of oxygen

Signs and symptoms

CLINICAL MANIFESTATIONS …

Extrapulmonary manifestations

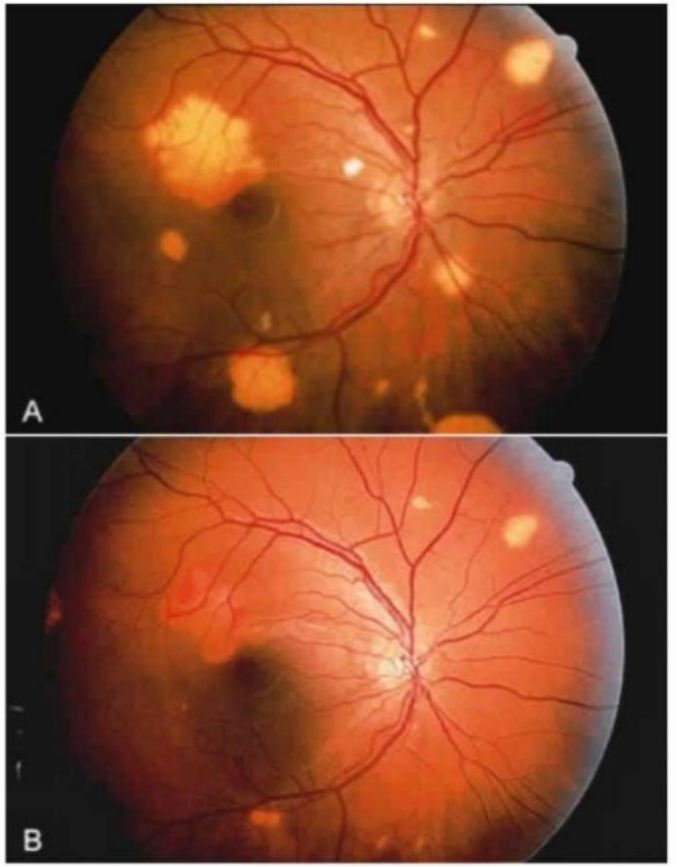
present in patients receiving aerosolized pentamidine for prophylaxis or in patients with advanced HIV infection who are not taking any prophylaxis.

- Central nervous system & Gastrointestinal tract
- Bone marrow (may have necrosis with resultant pancytopenia)
- Lymphadenopathy
- Eyes (may have retinal cotton-wool spots)
- Thyroid (may present as a rapidly enlarging thyroid mass)

Complications

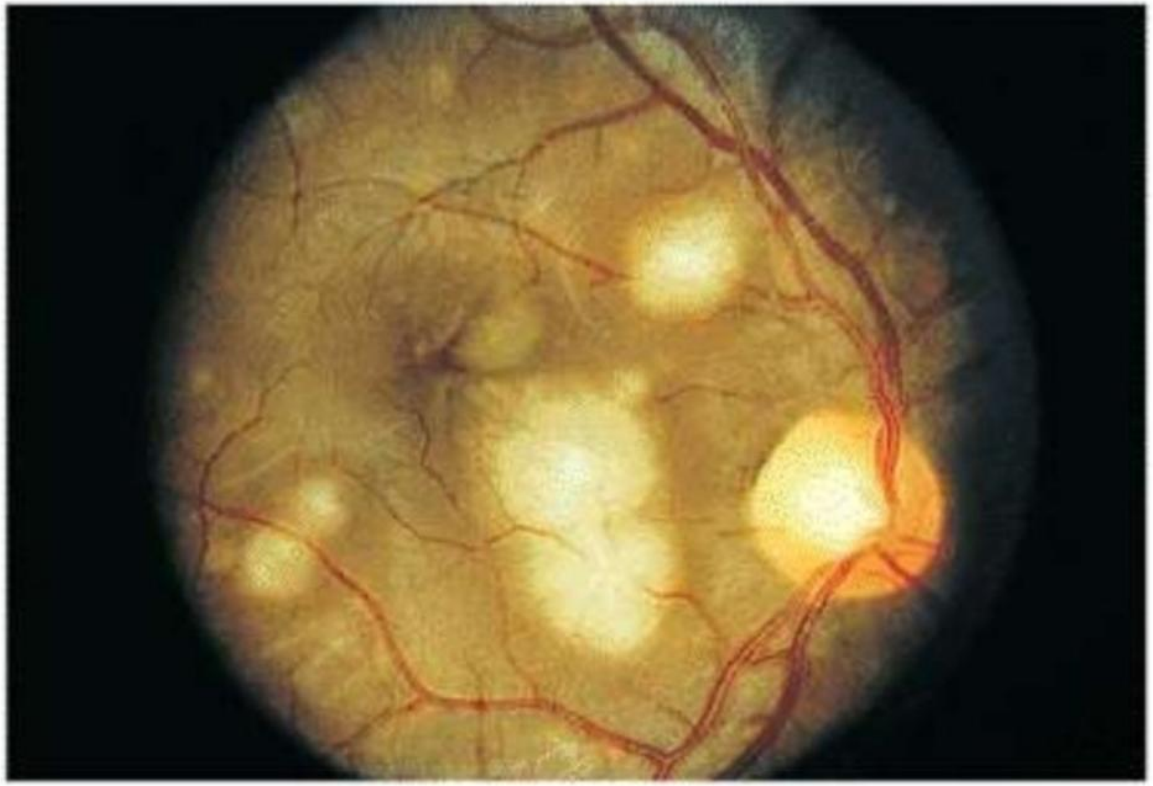
- A pathophysiologic process similar to acute respiratory distress syndrome (ARDS) may occur in patients with severe PCP. These patients may require intubation. This greatly diminishes the prognosis.

Signs and symptoms



Acute (**A**) and healed (**B**) *Pneumocystis carinii* choroiditis in a patient with AIDS

Signs and symptoms



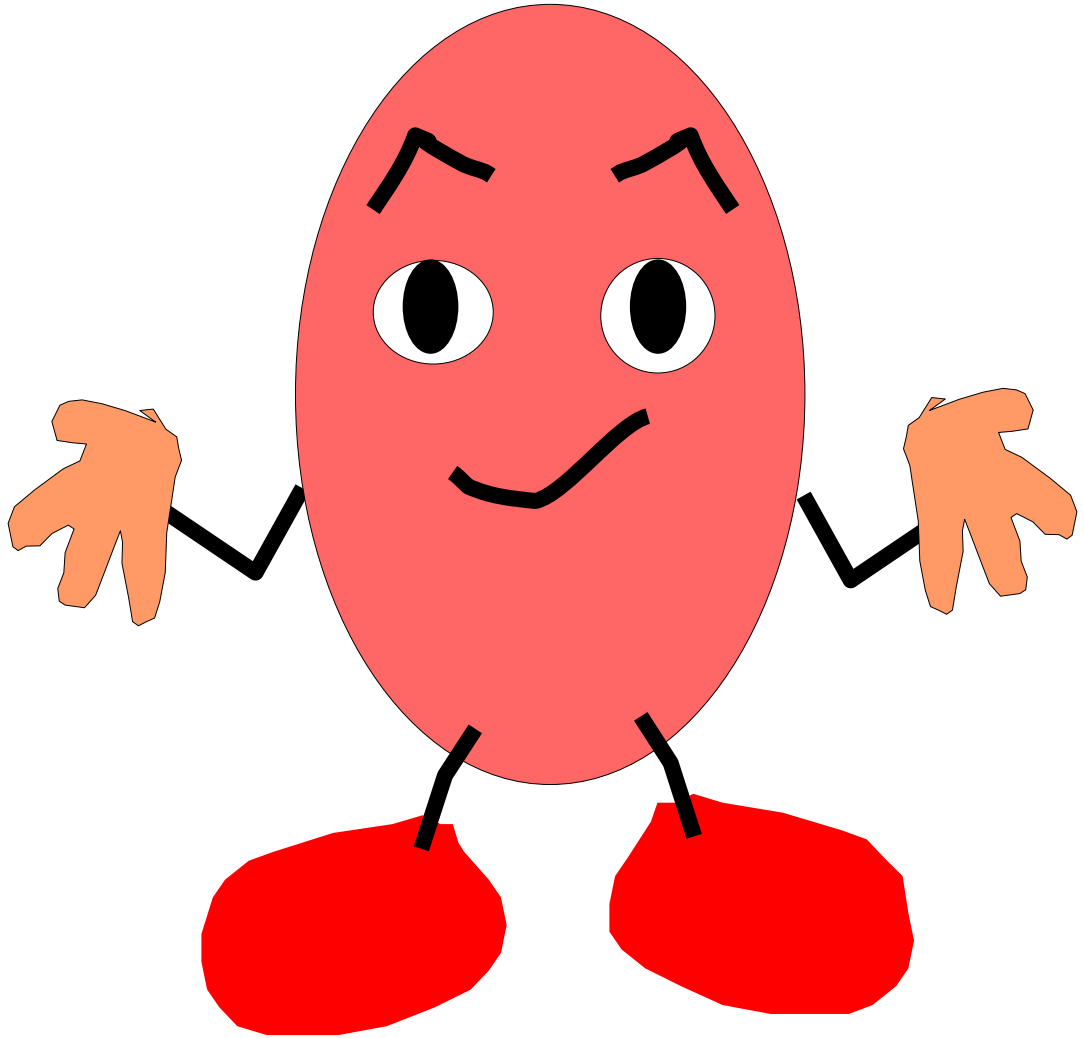
Pneumocystis carinii choroiditis in a patient with acquired immunodeficiency syndrome. Multifocal, whitish lesions are seen at the level of the choroid. Macular involvement often reduces vision, although the lesions are asymptomatic and clear promptly with appropriate antibiotic therapy

Differential diagnosis

DIFFERENTIAL DIAGNOSES

- Cytomegalovirus
- Lymphocytic Interstitial Pneumonia
- Acute Respiratory Distress Syndrome
- Mycoplasma Infections
- Pneumonia, Viral
- Pulmonary Embolism
- **Other Problems to Be Considered**
- Legionellosis
- Tuberculosis
- *Mycobacterium avium* complex (MAC) inection

Diagnosis



Specimen/Technique	Recommended usage
Diagnostic specimen	
Bronchoalveolar lavage	Allows detection of multiple etiologies; yield ≥80%[43,91]
Transbronchial biopsy	Increases yield of BAL, other lung pathology
Open Lung biopsy or video-assisted thoracoscopy (VATS)	Gold standard for diagnosis, generally not required[92-94]
Induced Sputum	Alternative specimen to BAL, yield ≥50%[94,95]
Other Respiratory specimens[a]	Not a good alternative, low organism burden[96]
Diagnostic technique	
Immunofluorescence assays	Most sensitive microscopic diagnostic method; increased yield over other stains
Real-time quantitative PCR, nucleic acid testing	Quantification in BAL; cannot distinguish infection from carriage[40,46,97]
Silver, polychrome, or calcofluor stains	Exclusion of PJP by negative BAL only
Serum	
Lactic dehydrogenase (LDH)	Not specific, generally positive in PJP[98]
β-D-glucan	Not specific, useful as adjunctive diagnostic tool; β-D-Glucan is component of *P jiroveci* cell wall[40,98]
Genotyping, sequencing	Investigation of suspected outbreaks
Dihydropteroate synthase mutations	Not recommended

Pneumocystis pneumonia

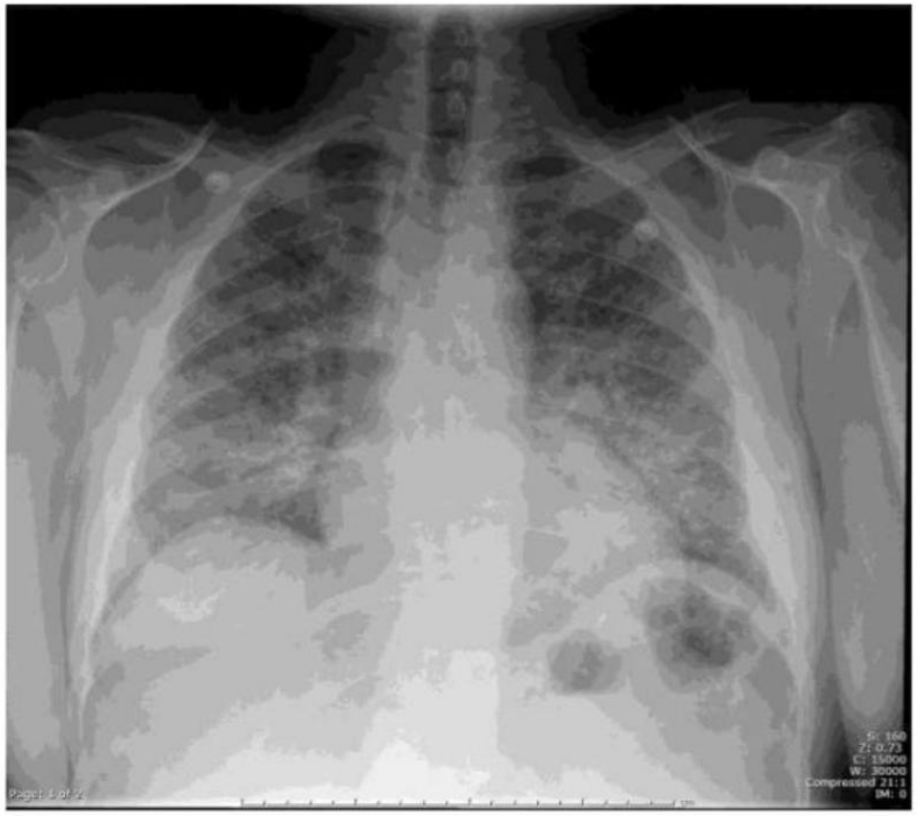
- Early PJP is manifested by fine, bilateral, perihilar, diffuse infiltrates that progress to an interstitial alveolar butterfly pattern; from the hilar region, the infiltrates often spread to the apices or bases.
- This pattern often progresses despite therapy with progressive consolidation over 3-5 days.
- Unusual patterns are common including nodules, unilateral infiltrates, pleural effusions, pneumothoraces, lymphadenopathy, or lobar consolidations.
- P jiroveci can superinfect fungal or mycobacterial cavities.

Pneumocystis pneumonia

RADIOLOGICAL FINDINGS

- The chest radiographic findings may be normal in patients with early mild disease.
- **Diffuse bilateral infiltrates extending from the perihilar region** are visible in most patients with *P jiroveci* pneumonia (PJP).
- Less-common findings include patchy asymmetric infiltrates and pneumatoceles.
- Pleural effusions and intrathoracic adenopathy are rare.
- Pneumothorax may develop in patients using aerosolized pentamidine. Apical disease may also be found in patients using aerosolized pentamidine for prophylaxis.

Pneumocystis pneumonia



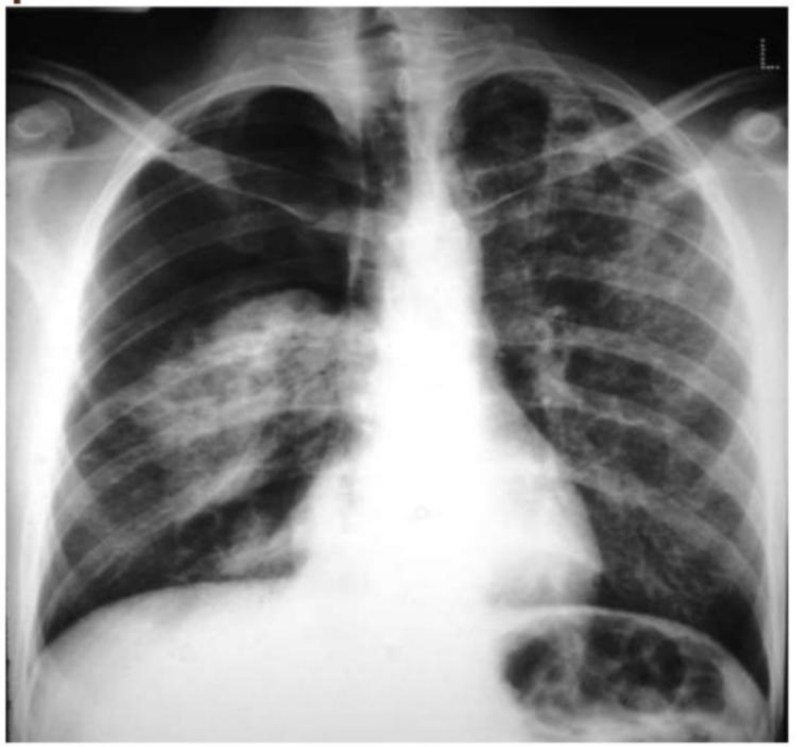
Chest radiograph demonstrating diffuse bilateral infiltrates in a patient with Pneumocystis jiroveci pneumonia.

Pneumocystis pneumonia

X-ray of a patient with Pneumocystis jirovecii Pneumonia in a setting of AIDS

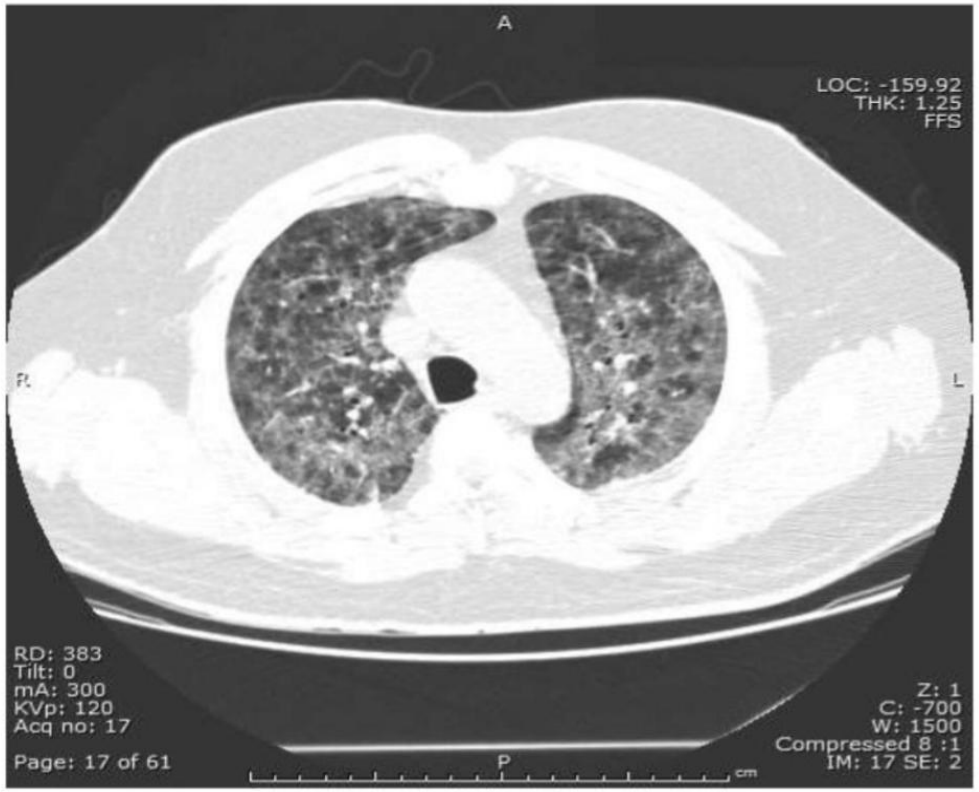
Pneumocystis pneumonia

Pneumothorax in PCP (right sided), a relatively common complication.



Pneumocystis pneumonia

RADIOLOGICAL FINDINGS



CT scan of chest, with classic patchy areas of ground-glass attenuation

Agents	Dosing	Comments
Trimethoprim-sulfamethoxazole (TMP-SMX)	Adults/Adolescents: 15-20 mg/kg/day of the TMP component given IV in divided doses every 6-8 h; lower doses may be sufficient. In milder disease, two double-strength tablets can be given po tid Children: >2 months 3.75–5 mg/kg/dose of the TMP component and 19-25 mg/kg/dose of the SMX component given IV every 6 h. In milder disease, the same daily dosing can be given po tid-qid	TMP-SMX remains the drug of choice; most effective systemic therapy for PJP. Correct for renal function and maintain hydration. May consider adjunctive corticosteroids (below). (strong recommendation, moderate evidence).
Pentamidine	All ages: 4 mg/kg/day IV initially with dose reduction to 2-3 mg/kg/day if needed	Infusions given over 1-2 h period once daily; prolonged half-life may complicate amelioration of side effects after cessation of therapy; side effects include pancreatitis, hypoglycemia, hyperglycemia, bone marrow suppression, renal failure, and electrolyte disturbances. Avoid in setting of pancreas transplant. (strong recommendation, moderate evidence).
Atovaquone	Adults/Adolescents: 750 mg po bid (higher doses to 1500 mg bid commonly used) Children: 1-3 mo and 24 mo-12 y: 30-40 mg/kg (max 1500 mg), orally, daily or divided into 2 daily doses. 4-24 mo: 45 mg/kg (maximum 1500 mg), orally, daily or divided into 2 daily doses.	Atovaquone available in oral suspension only with variable oral absorption and tested only in mild-and-moderate PJP infection. (strong recommendation, low evidence).
Primaquine and clindamycin (not studied adequately in children to recommend)	Primaquine 15-30 mg po qd in combination with clindamycin 600-900 mg IV or po q6-8 h	This combination tested in patients with mild-to-moderate PJP infections in AIDS. Long-term use of clindamycin can increase infection by *Clostridium difficile*. Primaquine should be avoided in the setting of G6PD deficiency. (strong recommendation, moderate evidence).

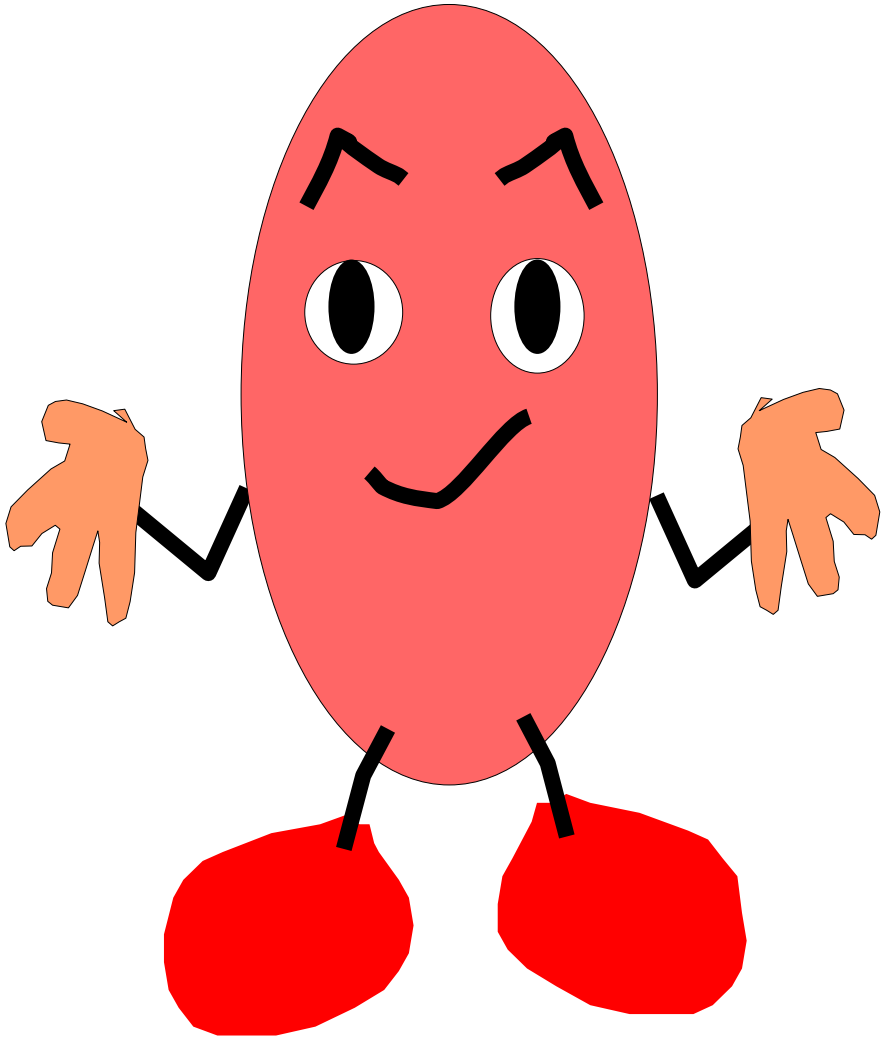
Dapsone and trimethoprim (not studied adequately in children to recommend)	Dapsone 100 mg po qd used in combination with trimethoprim 15 mg/kg/day po divided tid Children: dapsone: 2 mg/kg/dose po qd with TMP 5 mg/kg/day/dose po tid	Combination has been used in some patients with sulfa allergies; dapsone may elicit allergic reactions in sulfa intolerant. Check G-6-PD deficiency. (weak recommendation, low evidence).
Pyrimethamine and sulfadiazine (not studied adequately in children to recommend)	Pyrimethamine load of 100-200 mg po, followed by 50-100 mg po qd in combination with sulfadiazine 4 g po qd in divided doses	Limited data available; supplement with folinic acid 10 mg po qd to reduce toxicity. (weak recommendation, low evidence).
Macrolide and SMX	Macrolides such as clarithromycin or azithromycin in combination with sulfamethoxazole may be synergistic in vivo [99]	Few data to support this combination. (weak recommendation, low evidence).
Caspofungin and TMP-SMX	Adults/Adolescents: 70 mg IV loading dose of caspofungin on day 1, followed by 50 mg IV qd after in combination with TMP-SMX (dose reduced in the setting of moderate to severe hepatic dysfunction) Children: caspofungin: 0 to <3 mo: 25 mg/m^2 IV qd: 3 mo-17 y: 70 mg/m^2 on day 1 (max: 70 mg/dose); followed by 50 mg/m^2 (max: 50 mg/dose) IV qd in combination with TMP-SMX (dose reduced in the setting of moderate to severe hepatic dysfunction)	Echinocandins have activity against *Pneumocystis* in animal models.[100,101] Case reports in combination with TMP-SMX for PJP in solid organ and bone marrow transplantation.[102,103] Clinical efficacy compared with TMP-SMX unknown. (weak recommendation, low evidence).
Trimetrexate with folinic acid (*no longer available*)	Trimetrexate 45 mg/m^2/day IV (or 1.5 mg/kg/day IV in patients <50 kg) administered concomitantly with folinic acid 20 mg/m^2 po or IV every 6 h (80 mg/m^2 total daily); Folinic acid therapy should extend for at least 3 d beyond cessation of trimetrexate	Severe bone marrow suppression without folinic acid supplementation; inferior outcomes compared with TMP-SMX.

Agents	Dosing	Comments
Adjunctive agents		
Corticosteroids	Adolescents and Adults: 40-60 mg of prednisone (or equivalent) po/iv bid-tid with taper after 5-7 d over a period of 1-2 wk Children: 1 mg/kg po bid for 5 d, then 0.5 mg/kg po bid for 5 d, then 0.5 mg/kg po qd for 10 d	Corticosteroids are best administered within 72 h of patient presentation in the setting of hypoxia (pAO_2 < 70 mm Hg). (strong recommendation, low evidence).
Colony-stimulating factors	Standard dosing	Use of GM-CSF as an adjuvant has been tried in animal models of PJP with some success.[104] No clinical data in humans are available.

TREATMENT

- Trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line therapeutic agent and drug of choice for documented PJP (strong, high).•
- Alternative agents are less effective and include intravenous pentamidine isethionate, atovaquone, primaquine and clindamycin (strong, high).•
- Pentamidine therapy may cause pancreatitis, hypo- and hyperglycemia, and electrolyte disturbances and should generally be avoided in pancreas recipients (strong, moderate)
- • Adjunctive corticosteroids are best administered within 72 hours of presentation in the setting of hypoxia (pAO2 < 70 mm Hg) (strong, low).•
- The duration of antimicrobial therapy should be at least 14 days; longer courses are often required (strong, low).

PREVENTION



PREVENTION

CHEMOPROPHYLAXIS …

Chemoprophylaxis in patients without HIV infection

- Patients with an underlying primary immune deficiency (eg, severe combined immunodeficiency, hypogammaglobulinemia)
- Patients with a persistent CD4 count less than 200/µL
- Solid organ transplant recipients
- Hematopoietic stem cell transplant (HSCT) recipients,
- Patients receiving daily systemic corticosteroid therapy (at least 20 mg daily for at least 1 month)
- Patients with cancer, vasculitides, or collagen vascular disorders
- Patients receiving cytotoxic or immunosuppressive treatments such as cyclosporine or the purine analogs fludarabine or cladribine

PREVENTION

CHEMOPROPHYLAXIS

Chemoprophylaxis in patients with HIV Infection

- Adults, adolescents, and pregnant patients with a CD4 count of less than 200/µL
- oropharyngeal candidiasis
- CD4% <14%
- History of AIDS-defining illness
- CD4 count >200 but <250 cells/mm^3 and if CD4 cell count monitoring (e.g., every 3 months) is not possible

Prophylaxis may be **discontinued** in patients with HIV infection whose CD4 count exceeds 200/µL for 3 consecutive months while on HAART.

Prophylaxis should be **restarted** if the CD4 count drops below 200/µL.Prophylaxis should be continued for life in patients who developed PJP while their CD4 level exceeded 200/µL.

Agents	Dosing
Trimethoprim-sulfamethoxazole (TMP-SMX, cotrimoxazole)	Adults/Adolescents: Can be given as either 80 mg TMP/400 mg SMX (single strength) or 160 mg TMP/800 mg SMX (double strength) po (double strength) either daily or three times weekly Children: trimethoprim, 5-10 mg/kg and sulfamethoxazole, 25-50 mg/kg orally (max dose 320 mg TMP and 1600 mg SMX) given once daily 7 d a week or daily dose divided and given twice daily twice or three times weekly
Dapsone	Adults/Adolescents 50-100 mg po qd Children: 2 mg/kg (max 100 mg), orally, once daily or 4 mg/kg (max 200 mg), orally, every week
Atovaquone	Adults/Adolescents 1500 orally, daily Children: 1-3 mo and 24 mo-12 y: 30-40 mg/kg (max 1500 mg), orally, daily 4-24 mo: 45 mg/kg (maximum 1500 mg), orally, daily
Pentamidine	All ages: 300 mg administered through aerosolized nebulizer q 3-4 wk
Clindamycin and pyrimethamine (not studied adequately in children to recommend)	Up to 300 mg of clindamycin po qd with 15 mg of pyrimethamine po qd (some clinicians have administered this regimen 3 times weekly instead of daily)

TAKE  MESSAGE

- **Despite effective antimicrobial therapy**, mild to moderate episodes of PCP still carry a mortality risk upto **9 %**.
- The mortality rate approaches **100% without therapy**.


Thank
You!