

Pneumocystis Pneumonia

Dr. Pradeep kumar
II yr Pulmonary Medicine

PNEUMOCYSTIS CARINII PNEUMONIA

Pneumocystis carinii pneumonia (PCP), is commonly termed *Pneumocystis jiroveci pneumonia*, is the 2nd most common opportunistic infection in persons infected with HIV.

Table 1: Pulmonary complications in patients with an HIV infection

Infections	Neoplasia	Other
<p>Pneumocystis jiroveci</p> <p>Bacterial pneumonia <i>S. pneumoniae</i> <i>S. aureus</i> <i>H. influenzae</i> <i>B. catarrhalis</i> <i>P. aeruginosa</i> <i>Rhodococcus equi</i> <i>Nocardia asteroides</i></p> <p>Mycobacteria <i>M. tuberculosis</i> Atypical mycobacteria</p> <p>Other Cytomegalovirus Aspergillus spp. Cryptococcus neoform. Histoplasma capsulatum Toxoplasma gondii</p>	<p>Kaposi sarcoma</p> <p>Non-Hodgkin's lymphoma</p> <p>Hodgkin's lymphoma</p> <p>Bronchial carcinoma</p>	<p>Lymphocytic interstitial pneumonia</p> <p>Non-specific interstitial pneumonia</p> <p>Pulmonary hypertension</p> <p>COPD</p> <p>Bronchial hyperreactivity</p>

CD4 Cell Count Pulmonary Infections

- .>500 cells/mm³ Ac pharyngitis, bronchitis, sinusitis, pneumonia, TB
- .200-500 cells/mm³ Recurrent bact pneumonia
 varicella zoster pneumonitis
- .100-200 cells/mm³ PCP
 Disseminated TB
- .50-100 cells/mm³ Fungal pneumonia
- .<50 cells/mm³ - CMV retinitis, Atypical mycobacteriosis

Pathophysiology

- *Pneumocystis* organisms are commonly found in the lungs of healthy individuals. Most children are believed to have been exposed to the organism by age 3 or 4 years, and its occurrence is worldwide.
- Animal studies have suggested that *Pneumocystis* organisms are communicable; airborne transmission has been reported.
- The organism is found in 3 distinct morphologic stages, as follows:
 - The trophozoite (trophic form), in which it often exists in clusters
 - The sporozoite (precystic form)
 - The cyst, which contains several intracystic bodies (spores)

Mature, thick-walled cyst

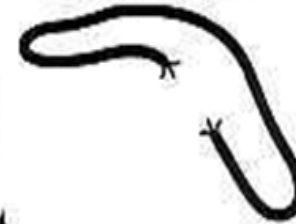


Sporozoites

Excystation



Empty cyst



Intermediate cyst

Trophozoites



Early, thin-walled cyst



Pneumocystis carinii

<http://www.doctorfungus.org>



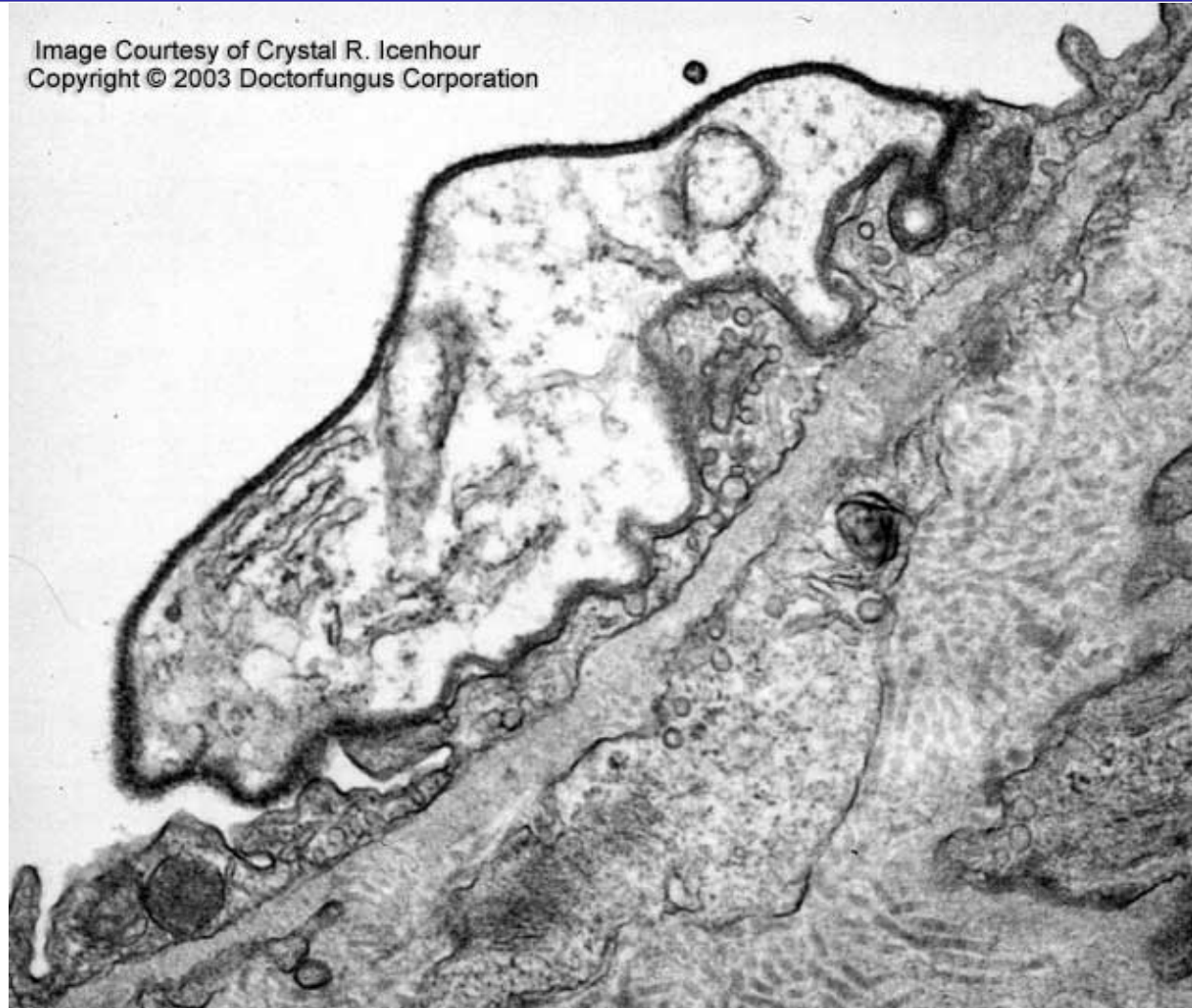
Image Courtesy of Crystal R. Icenhour
Copyright © 2003 Doctorfungus Corporation

- | | |
|---|---|
| <ul style="list-style-type: none">• Genus/Species: <i>Pneumocystis carinii</i>• Image Type: Microscopic Morphology | <ul style="list-style-type: none">• Title: EM Image of <i>Pneumocystis carinii</i>• Disease(s): Pneumocystis pneumonia |
| <ul style="list-style-type: none">• Legend: An electron micrograph of <i>P. carinii</i> cyst from rat lung tissue. | |

Pneumocystis carinii

<http://www.doctorfungus.org>

Image Courtesy of Crystal R. Icenhour
Copyright © 2003 Doctorfungus Corporation



- **Genus/Species:** *Pneumocystis carinii*
- **Image Type:** Microscopic Morphology

- **Title:** EM Image of *Pneumocystis carinii*
- **Disease(s):** Pneumocystis pneumonia

- **Legend:** An electron micrograph of a *P. carinii* troph from rat lung tissue, showing its binding to a type I pneumocyte.

- 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, including the following:
- Activated alveolar macrophages without CD4+ cells are unable to eradicate *Pneumocystis* organisms.
- Increased alveolar-capillary permeability is visible on electron microscopy.
- Physiologic changes include the following:
 - Hypoxemia with an increased alveolar-arterial oxygen gradient & permeability
 - [Respiratory alkalosis](#)
 - Impaired diffusing capacity
 - Changes in total lung capacity and vital capacity

Frequency

- Prior to the widespread use of highly active antiretroviral therapy (HAART), PCP occurred in 70-80% of patients with HIV infection.
- The frequency of PCP is decreasing with the use of PCP prophylaxis and HAART.
- PCP is still the 2nd most common opportunistic infection in patients with HIV infection.
- Patients with HIV infection are more prone to PCP recurrence than patients not infected with HIV.

Mortality/Morbidity

- In patients with HIV infection
 - In this population, PCP once carried a mortality rate of 20-40%, depending on disease severity at presentation. Currently, mortality rates of 10-20% are reported.
 - PCP is still a major cause of death in patients with AIDS.
- In patients without HIV infection
 - PCP carries a worse prognosis in persons without HIV infection; this has not changed significantly in the past 20 years.
 - Mortality rates of 30-50% have been documented in several large studies.
- The higher mortality rate is likely a result of delayed diagnoses and initiation of appropriate treatment



Etiology & Risk Factors

- The following groups are at risk for PCP:

Persons with HIV infection whose CD4⁺ cells fall below 200/ μ L

Persons with primary immune deficiencies

Persons receiving long-term immunosuppressive regimens

Persons with hematologic and nonhematologic malignancies

Persons with severe malnutrition

Clinical History

- The symptoms of *P carinii* pneumonia (PCP) are nonspecific. PCP in patients with HIV infection tends to run a acute or more often subacute indolent course and tends to present much later, often after several weeks of symptoms, compared with PCP associated with other immunocompromising conditions. Symptoms of PCP include the following:
 - Progressive exertional dyspnea
 - Fever
 - Nonproductive cough
 - Chest discomfort
 - Weight loss
 - Chills
 - Hemoptysis (rare)

Physical

- The physical examination findings of PCP are nonspecific and include the following:
- Tachypnea
- Fever
- Tachycardia
- Pulmonary symptoms: Pulmonary examination may reveal mild crackles and rhonchi but may yield normal findings in up to half of patients.
- Additional findings in children with severe disease
 - [Cyanosis](#)
 - Nasal flaring
 - Intercostal retractions
- Extrapulmonary manifestations: Although *Pneumocystis* infection rarely causes extrapulmonary manifestations, they may be present in patients receiving aerosolized pentamidine for prophylaxis or in patients with advanced HIV infection who are not taking any prophylaxis. They may also occur in the absence of lung involvement. Based on most well-documented findings, *Pneumocystis* infection may present in almost any organ system, as follows:
 - CNS
 - 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)
 - GI tract

Differential Diagnoses

- Cytomegalovirus
Lymphocytic Interstitial Pneumonia
Mycoplasma Infections
viral Pneumonia
Pulmonary Embolism
- Legionellosis
Tuberculosis
Mycobacterium avium complex (MAC) infection
- Acute Respiratory Distress Syndrome

Workup

Laboratory Studies

- Lactic dehydrogenase study as part of the initial workup
 - Lactic dehydrogenase (LDH) levels are usually elevated (>220 U/L) in patients with *P carinii* pneumonia (PCP).
 - This study has a high sensitivity (78-100%).
 - The LDH level is elevated in 90% of patients with PCP who are infected with HIV.
 - This study has a much lower specificity because other disease processes result in an elevated LDH level.
 - LDH levels appear to reflect the degree of lung injury.
 - Consistently elevated LDH levels during treatment may indicate therapy failure and a worse prognosis.
- LDH levels should decline with successful treatment

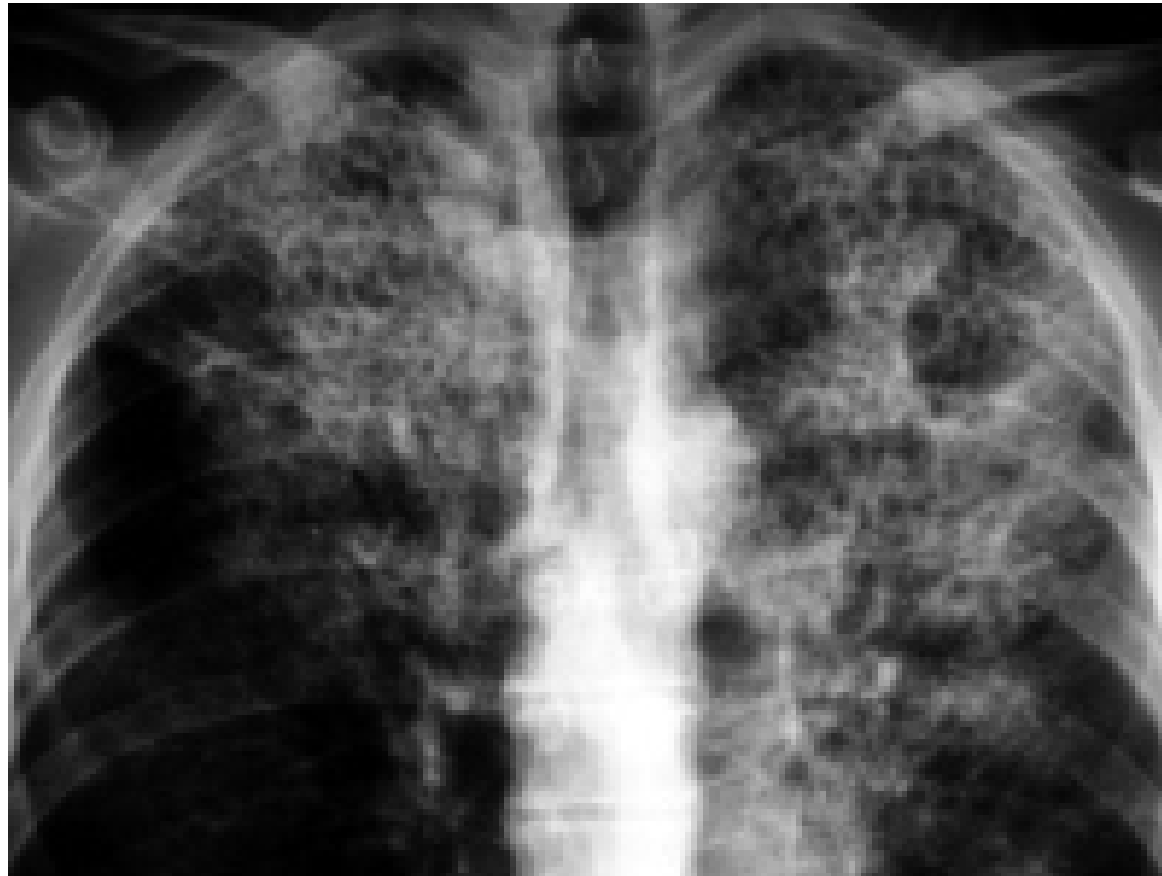
Imaging Studies

- Chest radiography should be obtained in any immunocompromised patient with fever and/or respiratory signs or symptoms. Findings include the following:
 - 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 PCP.
 - 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.
- High-resolution CT scanning of the chest
 - High-resolution CT scanning of chest (HRCT) is helpful when the chest radiography findings are equivocal.
 - The typical appearance is patchy areas of ground-glass attenuation with a background of interlobular septal thickening.
 - HRCT yields a high sensitivity for PCP in patients with HIV infection.
 - Negative (normal or unchanged) CT scan findings alone do not rule out PCP.

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



This image shows the redistribution of *Pneumocystis carinii* pneumonia to the upper lobes following aerosolized pentamidine prophylaxis. ■



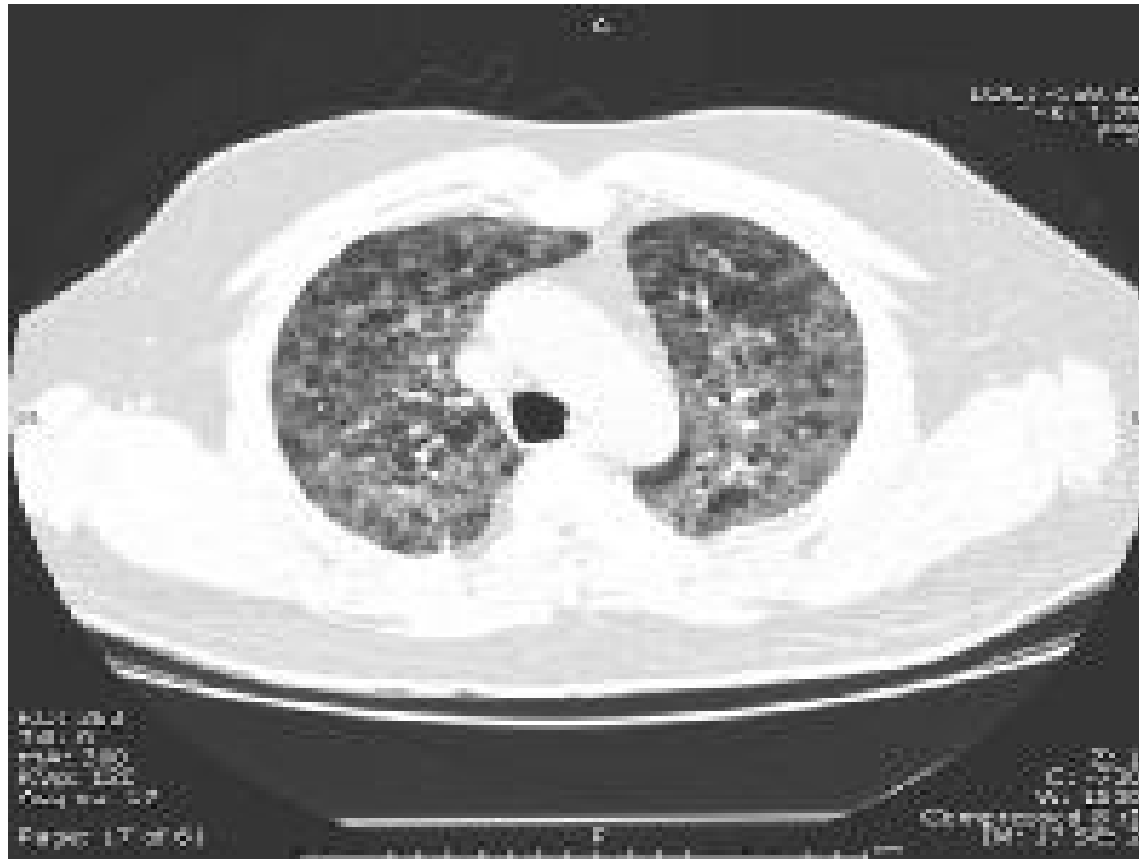
This chest radiograph shows bilateral upper-lobe pneumatoceles after a *Pneumocystis carinii* infection in a patient with acquired immunodeficiency syndrome.



This chest radiograph shows left side pneumothorax after a Pneumocystis carinii infection in a patient with acquired immunodeficiency syndrome



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



Imaging Studies

- Gallium 67 scanning
 - Gallium 67 scan demonstrates an increased diffuse symmetrical pulmonary uptake in patients with PCP.
 - This study is highly sensitive (nearly 100%).
 - The specificity is low (some studies report as low as 20%).
 - The high cost and 2-day time delay in obtaining results have limited its use.
 - A gallium 67 scan is potentially more useful in patients with suspected relapse, as BAL may be less diagnostic in such cases.

Other Tests

- Pulmonary function tests should be obtained as part of the initial noninvasive workup in patients with suspected PCP.
 - Results may demonstrate a decreased diffusion capacity of carbon monoxide (DLCO) of less than 75% predicted.
 - Decreased DLCO has a high sensitivity (89-100%) but poor specificity (53%).
 - PCP is unlikely if DLCO is normal.
 - When combined with normal or unchanged HRCT findings, pulmonary function tests may be used to identify patients unlikely to have PCP; such patients may be managed with observation alone.

Procedures

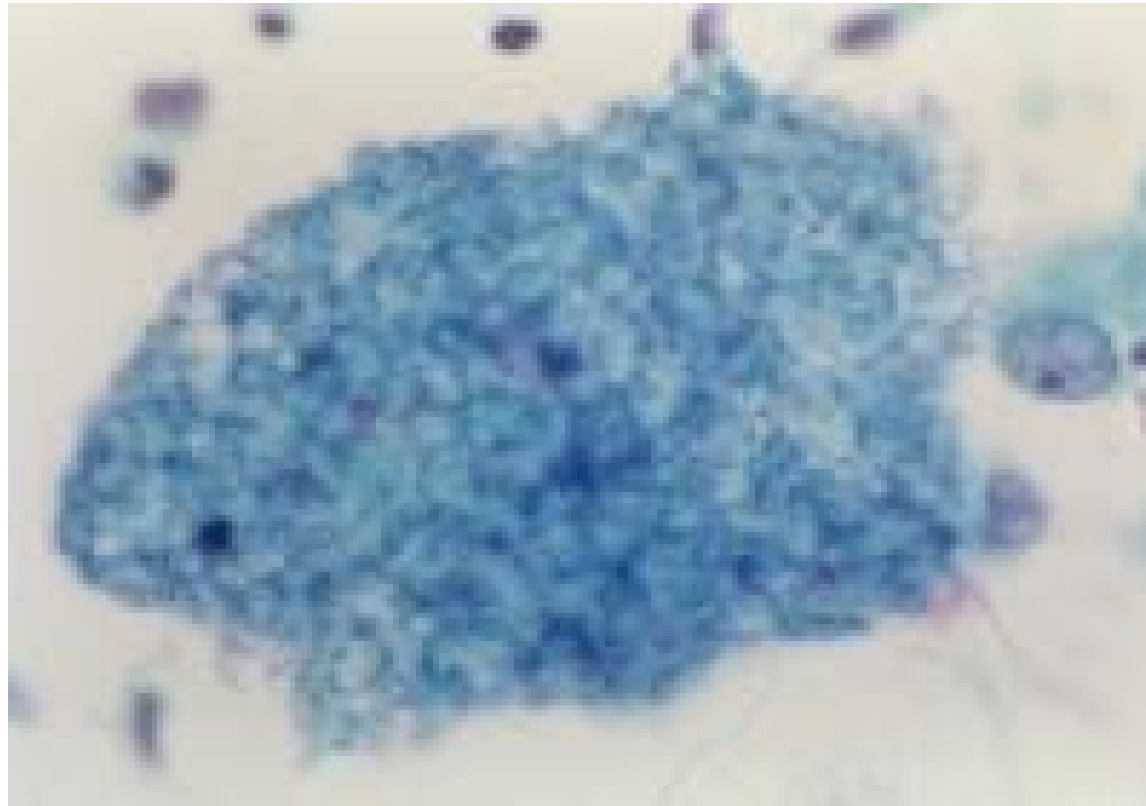
- Obtain sputum sample by sputum-induction for histopathologic testing if PCP is strongly suspected. *Pneumocystis* organisms are frequently found in sputum induced by inhalation of a hypertonic saline solution.
 - Expecterated sputum has a very low sensitivity and should not be submitted for diagnosis.
 - Sputum induction is the quickest and least-invasive method for definitively diagnosing PCP.⁵
 - Sensitivity varies widely (<50% to >90%) and depends on proficiency in using the technique and the experience of the laboratory.
 - Specificity is high (99-100%).
 - This study may be less sensitive in patients without HIV infection, as the immunodeficiency caused by HIV infection typically leads to a greater alveolar load of *Pneumocystis* organisms.
 - It may also be less sensitive in patients receiving aerosolized pentamidine for prophylaxis.

- BAL is the most common invasive procedure used to diagnose PCP.
 - BAL has a diagnostic yield that exceeds 90% (may be increased if multiple lobes are sampled).⁶
 - Obtain BAL if PCP is strongly suspected and the induced sputum sample findings are negative.
 - BAL yields a lower sensitivity in patients receiving aerosolized pentamidine, in which case a transbronchial biopsy may be performed in conjunction with BAL.⁷
 - BAL may be used in patients who are unable to cooperate with an induced sputum sample (eg, because of altered mental status).
 - BAL may be less useful in cases of suspected PCP relapse (see [Imaging Studies](#)).
- Open lung biopsy is the most invasive procedure and yields 100% sensitivity and specificity because it provides the greatest amount of tissue for diagnosis. However, this procedure is reserved for rare cases when bronchoscopy findings are nondiagnostic

Histologic Findings

- Because clinical and radiologic findings are not specific for PCP and because *P jiroveci* cannot be grown in vitro, histopathologic demonstration is necessary before a definitive diagnosis is established. The following are the staining techniques available for respiratory tract secretions:
- Cresyl violet, Giemsa, Diff-Quik, and Wright stain are used to detect both the trophozoite and cyst forms but not the cyst wall.
- Methenamine silver, toluidine blue, and Gram-Weigert selectively stain the wall of *Pneumocystis* cysts .
- Papanicolaou smear may demonstrate a foamy-appearing eosinophilic material surrounding *Pneumocystis* organisms .
- Some facilities prefer to use direct immunofluorescence using monoclonal antibodies to detect *Pneumocystis* organisms because it may be more sensitive than histologic staining.

Papanicolaou smear of
Pneumocystis jiroveci



Drugs used in the treatment of pneumocystis carinii pneumonia

Drug	Dosage	Severity of disease			Major adverse reactions
		Mild	Moderate	Severe	
TMP-SMX	TMP: 15-20 mg/kg/day SMX: 75-100 mg/kg/day IV divided into 3 or 4 daily doses for 21 days OR 2 DS tablets every 8 hours for 21 days	X	X	X	Rash, fever, neutropenia, hyperkalemia, transaminase elevation
Pentamidine	4 mg/kg/day IV for 21 days	X	X	X	Nephrotoxicity, hyperkalemia, hypoglycemia, hypotension, pancreatitis, dysrhythmias, transaminase elevation
Atovaquone	750 mg PO BID for 21 days	X	X		Rash, fever, transaminase elevation
Trimetrexate	Trimetrexate: 45 mg/m ² /day IV for 21 days plus leucovorin: 20 mg/m ² QID IV or PO for 24 days	X	X	X	Rash, neutropenia, thrombocytopenia, transaminase elevation
TMP-Dapsone	TMP: 5 mg/kg PO TID Dapsone: 100 mg/day PO for 21 days	X	X		Rash, fever, gastrointestinal upset, methemoglobinemia, hemolytic anemia, (check patients for G6PD deficiency)
Primaquine-Clindamycin	Primaquine: 15-30 mg/day PO for 21 days Clindamycin: 600 mg every 8 hours IV OR 300-450 mg QID PO both for 21 days	X	X	X	Rash, fever, diarrhea, methemoglobinemia, hemolytic anemia (check for G6PD deficiency)
Corticosteroids	Prednisone: 40 mg BID PO for 5 days 40 mg once daily PO for 5 days 20 mg once daily PO for 11 days		X	X	Hyperglycemia, hypertension, reactivation of herpetic lesions ? increased susceptibility to other infections

Further Inpatient Care

- All patients who require corticosteroids should be admitted to the hospital because of the risk of progressive respiratory compromise.
- Treatment of *P carinii* pneumonia (PCP) may be initiated before the workup is complete in severely ill high-risk patients.
- Appropriate histopathologic testing may still be used to confirm a diagnosis of PCP after treatment is initiated.
- Endotracheal tube aspirates from severely ill patients on mechanical ventilation may be submitted for diagnosis.
- Because of increasing evidence of possible human transmission the CDC Hospital Infection Control Practice Advisory Committee has recommended that patients with PCP not have direct contact with other immunocompromised patients.

Prevention

- Smoking cessation is strongly recommended in patients with HIV infection smokers are at an increased risk of PCP and have a more complicated treatment course.
- Chemoprophylaxis is recommended for the following groups:
 - Adults, adolescents, and pregnant patients with a CD4 count of less than 200/ μ L, oropharyngeal candidiasis, unexplained fever exceeding 100°F for more than 2 weeks, and a prior episode of PCP regardless of CD4 count should receive prophylaxis.
 - Children born to mothers with HIV infection should receive prophylaxis with TMP-SMX beginning at age 4-6 weeks. The drug should be discontinued if they are subsequently determined not to be infected with HIV.
 - Children who are determined to be HIV positive through the first year of life, then as determined by age-specific CD4 levels, should receive prophylaxis.

Chemoprophylaxis

- Two types of outpatient chemoprophylactic therapies exist, as follows:
 - Primary prophylaxis is used in immunocompromised patients without a history of PCP.
 - Secondary prophylaxis is used in patients with a prior bout of PCP.
- Prophylaxis may be discontinued in patients with HIV infection whose CD4 count exceeds 200/ μ L for 3 consecutive months while on HAART. Prophylaxis should be restarted if the CD4 count drops below 200/ μ L. Prophylaxis should be continued for life in patients who developed PCP while their CD4 level exceeded 200/ μ L.

immunocompromised patients without HIV

- Unlike in patients with HIV infection, no specific PCP prophylaxis guidelines exist for immunocompromised patients without HIV infection. In general, chemoprophylaxis should be considered in any of the following patients:
 - Patients with an underlying primary immune deficiency (eg, SCID or hypogammaglobulinemia)
 - Patients with a persistent CD4 count less than 200/ μ L
 - Solid organ transplant recipients
 - Hematopoietic stem cell transplant (HSCT) recipients, with prophylaxis administered (1) for 6 months after engraftment months or (2) for more than 6 months after HSCT in those who are still receiving immunosuppressive therapy (eg, prednisone, cyclosporine) or who have chronic [graft versus host disease](#)
 - Patients receiving daily systemic corticosteroid therapy (at least 20 mg daily for at least 1 mo)
 - Patients with cancer, vasculitides, or collagen vascular disorders and others receiving cytotoxic or immunosuppressive treatments such as cyclosporine or the purine analogs fludarabine or cladribine

Prophylactic regimens include

- Trimethoprim-sulfamethoxazole
 - Dose is one double-strength tablet (160 mg TMP to 800 mg SMX) daily.
- Dapsone: Dose is 100 mg by mouth daily if administered alone
- Dapsone with pyrimethamine (plus leucovorin)
 - Atovaquone
- Dose is 1500 mg by mouth once daily given with food
 - Aerosolized pentamidine
- Dose is 300 mg in 6 mL sterile water via Respigard nebulizer every 4 weeks

Complications & Prognosis

- Hypoxemia and respiratory failure
 - A pathophysiologic process similar to ARDS may occur in patients with severe PCP.
 - These patients may require intubation.
- This greatly diminishes the prognosis
- The prognosis of PCP is worse in patients who present with concurrent pulmonary disease, in patients who develop pneumothorax, and in patients who require mechanical ventilation.
- Other factors that affect prognosis include a delay in diagnosis that leads to delayed treatment

HAART

- Before the availability of HAART [known as highly active antiretroviral therapy, HAART], patients who survived mechanical ventilatory support for PCP rarely lived longer than 1 year. With the use of HAART, the prospects for long-term survival are considerably more hopeful, especially if the patient has not yet received antiretroviral therapy [

Thank you