Pneumocystis Pneumonia

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Abstract

Pneumocystis carinii pneumonia (PCP) is an opportunistic infection that occurs in immunosuppressed populations, primarily patients with advanced human immunodeficiency virus infection. The classic presentation comprises of nonproductive cough, shortness of breath, fever, bilateral interstitial infiltrates and hypoxemia but it may present with an atypical presentation. Diagnostic methods of choice include sputum induction and bronchoalveolar lavage. The drug of choice for treatment and prophylaxis is trimethoprim-sulfamethoxazole, but alternatives are often needed because of adverse effects or, less commonly, treatment failure. Adjunctive corticosteroid therapy improves survival in moderate to severe cases. Complications such as pneumothorax and respiratory failure portend poorer survival. Prophylaxis dramatically lowers the risk of disease in susceptible populations. Although PCP has declined in incidence in the developed world as a result of prophylaxis and effective antiretroviral therapy, its diagnosis and treatment remain challenging.

History

Pneumocystis carinii was first described in 1909 by Carlos Chagas, who mistook it for a cystic form of *Trypanosoma cruzi* in a guinea pig experimentally infected with T. *cruzi*.[1]

In 1910, Antonio Carini observed similar cysts in rats with experimental trypanosomiasis, but suspected the cysts were from an unknown organism. He sent samples to his colleague, Laveran, for further examination. In 1912, Laveran's students, Delanoe and Delanoe, found similar cysts restricted to the lungs of *Trypanosoma*-free sewer rats, and named the new organism *Pneumocystis carinii*.[1]

Years later, Dr. Otto Jirovec and his group isolated the organism from humans, and the organism responsible for PCP was renamed after him as Pneumocystis jirovecii in 2001 .[2]

Regarding nomenclature, when the name of Pneumocystis pneumonia changed from Pneumocystis carinii pneumonia to Pneumocystis jirovecii pneumonia, it was at first felt that it could no longer be referred to as "PCP." However, because the term PCP was already in common usage, it was rationalized that the term PCP could continue to be used, as it stood for **P**neumo**c**ystis (jirovecii) **P**neumonia . As a result, *Pneumocystis* pneumonia (PCP) is also known as ***Pneumocystis jiroveci[i]*** **pneumonia** and (incorrectly) as ***Pneumocystis carinii*** **pneumonia**.[3,4,5,6]

Pneumocystis first came to attention when it was found to cause interstitial pneumonia in Central and Eastern Europe during World War II in severely malnourished and premature infants.[2] Prior to the 1980s, fewer than 100 cases of PCP per year were reported in the United States, occurring in immuno suppressed patients such as patients with cancer treated with chemotherapy and solid-organ transplant recipients receiving immuno suppressive agents.[2]

In 1981, the Centers for Disease Control and Prevention (CDC) reported PCP in 5 previously healthy homosexual males residing in the Los Angeles area.[7] Well over 100,000 cases of PCP were reported in the first decade of the HIV epidemic in the United States in people with no other cause for immunosuppression.[3]

Pneumocystis jiroveci is now one of several organisms known to cause life-threatening opportunistic infections in patients with advanced HIV infection worldwide.

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Epidemiology

The disease PCP is relatively rare in people with normal immune systems, but common among people with weakened immune systems such as premature or severely malnourished children, the elderly, and especially persons living with HIV/AIDS, in whom it is most commonly observed. [8, 9] PCP can also develop in patients who are taking immuno suppresive medications. It can occur in patients who have undergone solid organ transplantation or bone marrow transplantation and after surgery. [10] Infections with *PCP* are also common in infants with Hyper IgM Syndrome , an X-linked or autosomal recessive trait.

The causative organism of PCP is distributed worldwide [11] and *it* has been described in all continents except Antarctica. [11, 12] Greater than 75% of children are seropositive by the age of 4, which suggest a high background exposure to the organism. A post-mortem study conducted in Chile of 96 persons who died of unrelated causes (suicide, traffic accidents, and so forth) found that 65 (68%) of them had pneumocystis in their lungs, which suggests that asymptomatic pneumocystis infection is extremely common. [13]

Airborne transmission of *Pneumocystis* has been documented in animal studies; person-to-person transmission has been suggested by hospital outbreaks of PCP and by molecular epidemiologic analysis of isolates. [14, 15] *Pneumocystis* colonization of immuno-competent individuals has been detected by polymerase chain reaction (PCR) techniques**.**

Microbiology

The taxonomic classification of the *Pneumocystis* genus was debated for some time. It was initially mistaken as a trypanosome and then later as a protozoan. In the 1980s, biochemical analysis of the nucleic acid composition of *Pneumocystis* rRNA and mitochondrial DNA identified the organism as a unicellular fungus rather than a protozoa. Subsequent genomic sequence analysis of multiple genes including elongation factor 3, a component of fungi protein synthesis not found in protozoa, further supported this notion. [2]

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)

The cysts are small and round to oval in shape, about the size of a red blood cell (5 to 8 µm), and contain four to eight nucleated sporozoites. The cysts collapse easily, which gives them a helmet or banana shape on staining. Extracystic trophozoites, 2 to 5 µm in diameter, are the most commonly seen form and are pleomorphic, often with an eccentric nucleus. [16]

Lack of growth on fungal culture media, response to the antiprotozoal drug pentamidine, and lack of response to most antifungal agents have also supported the notion that it is a protozoan. However, *P. jirovecii* has an affinity for fungal stains, is ultrastructurally similar to fungi, and is phylogenetically closely related to the Ascomycetes yeasts by molecular analysis of its 16S ribosomal RNA [17, 18] and mitochondrial DNA. [19] This is not a purely academic issue. Although *Pneumocystis* does not respond to antifungal drugs such as amphotericin or azoles, β-glucan synthesis in the cyst wall is inhibited by newer antifungal agents such as the echinocandins. [16] Because the organism cannot be reliably grown in culture, its life cycle is not fully understood; both pathogenesis and treatment studies have been conducted in various animal models.

Pathophysiology

The pathogenesis of PCP was originally thought to be reactivation of latent infection as a result of severe immune system depression. However, few data support chronic carriage because the organism is detected neither in lung sections at autopsy of previously healthy individuals nor by polymerase chain reaction (PCR) in bronchoalveolar lavage (BAL) fluid of immunocompetent adults.

The principal host effector cells against Pneumocystis are alveolar macrophages, which ingest and kill the organism, releasing a variety of inflammatory mediators. Proliferating organisms remain extracellular within the alveolus, attaching tightly to type I cells.

Alveolar damage results in increased alveolar-capillary permeability and surfactant abnormalities, including a fall in phospholipids and an increase in surfactant proteins A and D. The host inflammatory

response to lung injury leads to increases in levels of interleukin 8 and in neutrophil counts in bronchoalveolar lavage (BAL) fluid. These changes correlate with disease severity. [20]

On lung sections stained with hematoxylin and eosin, the alveoli are filled with a typical foamy, vacuolated exudate. Severe disease may include interstitial edema, fibrosis, and hyaline membrane formation. The host inflammatory changes usually consist of hypertrophy of alveolar type II cells, a typical reparative response, and a mild mononuclear cell interstitial infiltrate. Malnourished infants display an intense plasma cell infiltrate that gave the disease its early name: interstitial plasma cell pneumonia. [20]

Clinical Manifestations

Early recognition and treatment are imperative. Clinicians must be familiar with both the typical and the unusual manifestations of PCP so that therapy can be instituted promptly . HIV-infected patients are usually ill for several weeks and may have relatively subtle manifestations. Symptoms in non-HIV-infected patients are of shorter duration and often begin after the glucocorticoid dose has been tapered. [20] A high index of suspicion and a thorough history are key factors in early detection.

❖ **Typical Manifestations**

The onset of PCP in HIV-infected individuals is generally insidious and marked by slow, but steady progression of symptoms, including fever, chills, sweats, malaise, fatigue, and ultimately, exertional dyspnea. [21]

The cardinal manifestation is a hacking, typically nonproductive cough that may have been present for weeks or even months. Retrosternal chest tightness, intensified by coughing and inspiration, is also common. Fever occurs in 80 to 90%. Dyspnea develops when oxygenation is moderately to severely impaired.

In contrast, PCP in HIV-seronegative patients, such as those with lymphoreticular malignancies, is typically acute in onset with high fever and evident chest x-ray abnormalities.

Physical findings in AIDS patients are often limited and nonspecific. Tachypnea does not usually occur with mild episodes, whereas respiratory distress, use of accessory muscles, cyanosis, and frank respiratory failure may be seen in severe cases. Auscultation is frequently normal because dry ("cellophane") rales occur in only 30 to 40% of cases and are usually a late finding indicating greater severity. Occasionally, patients have wheezing or overt bronchospasm.

❖ **Atypical Manifestations**

➢ **Pneumothorax and Cavitation** [16]

Pneumothorax, which can be associated with refractory bronchopleural fistulas and chronic lung cavitation, occurs in up to 10% of episodes . HIV-positive patients with spontaneous pneumothorax should be evaluated and treated presumptively for PCP, along with lung re-expansion. Lung destruction and cavitation may appear as solitary, thin-walled cavities, regional honeycombing, blebs, or bullae; these findings are often bilateral, generally occur in the upper lobes, and precede the development of pneumothorax. Although cavitation and pneumothorax were initially associated with aerosol pentamidine prophylaxis, these complications may occur in the absence of aerosol therapy, as well as in nonsmokers, in first episodes, and in patients with previous bronchoscopy or mechanical ventilation and barotrauma.

➢ **Fever of Unknown Origin**

In some AIDS patients, PCP may be manifested as an occult febrile illness with minimal respiratory symptoms. Nonspecific complaints of high fever, night sweats, fatigue, and malaise are prominent.

Other causes of fever of unknown origin in this population, such as occult sinusitis, cytomegalovirus retinitis, disseminated *Mycobacterium avium* infection, and endocarditis, must be excluded. Oxygen desaturation with exercise and histologic evidence of Pneumocystis should be sought.

➢ **Extrapulmonary Infection** [16]

Extrapulmonary infection with Pneumocystis may occur in 0.5 to 3.0% of patients with advanced HIV disease and was more frequently reported in the early 1990s when many patients were receiving aerosol pentamidine prophylaxis.

When extrapulmonary pneumocystosis is diagnosed, more than 50% of patients have concurrent pneumonia. Clinical findings depend on the location of extrapulmonary involvement, although nonspecific

complaints of fever and sweats predominate.

The diagnosis is complicated by the broad range of possible extrapulmonary sites, including the ear (external auditory polyps), mastoids, choroid, cutaneous lesions or digital necrosis from vasculitis, small bowel obstruction, ascites with gastric and duodenal nodules, liver, spleen, hilar or mediastinal lymphadenopathy, thyroid and parathyroid glands, thymus, kidney, heart, pancreas, central nervous system, and bone marrow, resulting in cytopenia. Some sites have been detected only at autopsy.

The lymph nodes, liver, spleen, and bone marrow are the most commonly affected organs. Two extrapulmonary sites are associated with specific symptoms or signs. Thyroid involvement may be accompanied by neck pain, hyperthyroidism or hypothyroidism, and goiter, which may be multinodular or a solitary neck mass .

Choroiditis appears as slightly elevated, yellow-white plaques, without involvement of retinal vessels or evidence of intraocular inflammation. Identification of typical choroidal lesions may provide the first clue of disseminated infection. Although the lung is involved in nearly 90% of cases, choroiditis may be the only evidence of extrapulmonary disease.

Histologic analysis of affected organs shows foci of eosinophilic frothy exudates and the presence of organisms by special stains. Unlike lesions in the lung, these lesions are often calcified (punctate or rim-like) and characterized by vasculitis with frank invasion of vessel walls.

Diagnosis

Because of the nonspecific nature of the clinical picture, the diagnosis must be based on specific identification of the organism. A definitive diagnosis is made by **histopathologic staining**. [22] Traditional cell wall stains such as methenamine silver selectively stain the wall of Pneumocystis cysts, while reagents such as Wright-Giemsa stain the nuclei of all developmental stages.

Immunofluorescence with monoclonal antibodies [23] is more sensitive and specific than histologic staining. **DNA amplification by PCR** [24] may become part of routine diagnostics but may not distinguish colonization from infection.

The successful diagnosis of PCP depends on the collection of proper specimens. In general, the yield from different diagnostic procedures is higher in HIV-infected patients than in non-HIV-infected patients because of the higher organism burden in the former group.

Sputum induction and **oral washes** [25] have gained popularity as simple, noninvasive techniques; however, these procedures require trained and dedicated personnel.

Fiberoptic bronchoscopy with BAL, [26] which provides information about the organism burden, the host inflammatory response, and the presence of other opportunistic infections, continues to be the mainstay of Pneumocystis diagnosis.

Transbronchial biopsy and **open lung biopsy**, [27] the most invasive procedures, are used only when a diagnosis cannot be made by BAL

The diagnosis can also be confirmed by the characteristic appearance of the **chest x-ray** which shows widespread pulmonary infiltrates, and an **arterial oxygen level (pO_2)** strikingly lower than would be expected from symptoms.

Course and Prognosis

In the typical case of untreated PCP, progressive respiratory embarrassment leads to death. Therapy is most effective when instituted early, before there is extensive alveolar damage. If examination of induced sputum is nondiagnostic and BAL cannot be performed in a timely manner, empirical therapy for PCP is reasonable. However, this practice does not eliminate the need for a specific etiologic diagnosis. With improved management of HIV and its complications, mortality from PCP is 15–20% at 1 month and 50–55% at 1 year. Rates of early death remain high among patients who require mechanical ventilation (60%) and among non-HIV-infected patients (40%).

Treatment

The key to successful treatment is prompt suspicion of the diagnosis and early initiation of therapy. Because sputum induction and bronchoscopy are not generally performed after hours and the results of special stains may not be immediately available, patients with typical clinical features of PCP and moderate to severe

hypoxemia should be treated empirically. Such treatment does not impair the ability to make a specific diagnosis because large numbers of organisms are detectable in lung tissue and secretions for weeks after therapy is begun.

Drugs In The Treatment Of PcP

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX), which acts by inhibiting folic acid synthesis, is considered the drug of choice for all forms of PCP . [16, 20, 23] Therapy is continued for 14 days in non-HIV-infected patients and for 21 days in persons infected with HIV. [16] Since HIV-infected patients respond more slowly than non-HIV-infected patients, it is prudent to wait at least 7 days after the initiation of treatment before concluding that therapy has failed. TMP-SMX is well tolerated by non-HIV-infected patients, whereas more than half of HIV-infected patients experience serious adverse reactions.[29]

Parenteral Pentamidine

Parenteral pentamidine is also highly effective. [30] As with TMP-SMX, adverse reactions are common . Impaired renal function and hypoglycemia are dose dependent and are more likely to be seen after 2 weeks of therapy or a total dosage higher than 4 g. Hypotension generally occurs during or shortly after intravenous infusion and may last several hours, although low blood pressure may persist for several months. Infusion-related hypotension can be minimized by slow administration over a 1-hour period. Hypoglycemia is the most insidious reaction and occurs in 10 to 20% of AIDS patients treated with pentamidine; it results from sudden increases in serum insulin caused by lysis of pancreatic beta cells.

Because of the prolonged binding of pentamidine to tissue, precipitous hypoglycemia may occur after use of the drug is discontinued, with fatal reactions reported up to 2 weeks after the last dose. When hypoglycemia is detected, pentamidine should be discontinued, and patients should be monitored closely with daily glucose measurements for several weeks. [16]

Trimetrexate

Trimetrexate [31] is a powerful antifolate drug that binds to the DHFR of Pneumocystis nearly 1500 times more avidly than trimethoprim does, and it is concentrated in the organism. Leucovorin (folinic acid) must be coadministered [31] to protect against bone marrow toxicity. To mimic the sequential DHFR-DHPS blockade provided by TMP-SMX, trimetrexate can be coadministered with oral dapsone, 100 mg daily , although this combination has not been rigorously studied .

Adjunctive Corticosteroids [23, 31]

The major breakthrough in the search for more effective therapies for Pneumocystis has been the irrefutable evidence that mortality with severe episodes can be reduced nearly two-fold by the use of corticosteroids within 72 hours after beginning specific anti- Pneumocystis therapy . With adjunctive corticosteroids, oxygen desaturation occurs less often, and fewer patients require mechanical ventilation. Serious adverse consequences are uncommon, perhaps because the course is limited (21 days) and the taper is rapid; an increase in mucocutaneous herpes infections was seen in the largest study. However, adjunctive corticosteroids can be deleterious if given with empirical anti- Pneumocystis therapy to patients who have undiagnosed concomitant pulmonary fungal infection or tuberculosis; these patients may show initial improvement, which could delay the diagnosis and specific antimicrobial therapy for their other pulmonary condition.

Trimethoprim-Dapsone [31]

Trimethoprim-dapsone, like TMP-SMX, results in sequential blockade of folate synthesis in Pneumocystis . [16] Dapsone, a sulfone, binds to DHPS two-fold more avidly than sulfamethoxazole does. Treatment-limiting neutropenia and transaminase elevations occur less frequently than with TMP-SMX.

Clindamycin-Primaquine [30]

The antibacterial clindamycin and the antimalarial drug primaquine together have excellent activity against Pneumocystis, but neither agent is effective alone, and the mechanism of action is unclear. The combination has been effective as initial therapy for Pneumocystis with response rates in the range of 90%, regardless of whether clindamycin is given intravenously or orally and whether the dose of primaquine base is 15 or 30 mg/day. Awareness of the potential common problems with each of these regimens permits better matching of Pneumocystis

therapy to the patient's clinical status at diagnosis. The U.S. Public Health Service has not recommended adjunctive corticosteroids for mild episodes because the mortality rate is very low.

Atovaquone

Atovaquone is an oral hydroxynaphthoquinone originally developed as an antimalarial. It inhibits the mitochondrial electron transport necessary for the biosynthesis of pyrimidines in protozoa, but its mode of action against Pneumocystis is unknown.[31] Atovaquone must be given with fatty food because blood levels are two- to three-fold lower when it is taken on an empty stomach

Echinocandins

These newer antifungals are active against Pneumocystis animal models but have not been systematically tested for Pneumocystis infection in humans.

TREATMENT OF PCP[20]

Drug(s) , Dose , Route	Adverse Effects
First Choice[a]	
TMP-SMX (5 mg/kg TMP, 25 mg/kg SMX[b]) h PO or IV	Fever, rash, cytopenias, hepatitis, hyperkalemia, q6–8 GI disturbances
Other Agents[a]	
TMP, 5 mg/kg q6–8h, plus dapsone, 100 mg qd PO	Hemolysis (G6PD deficiency), methemoglobinemia, fever, rash, GI disturbances
Atovaquone, 750 mg bid PO	Rash, fever, GI and hepatic disturbances
Clindamycin, 300–450 mg q6h PO or 600 mg q6–8h IV, plus primaquine, 15–30 mg qd PO	Hemolysis (G6PD deficiency), methemoglobinemia, rash, colitis, neutropenia
Pentamidine, 3–4 mg/kg qd IV	Hypotension, azotemia, cardiac arrhythmias,pancreatitis , dysglycemias, hypocalcemia, neutropenia, hepatitis
Trimetrexate, 45 mg/m^2 qd IV, plus leucovorin, [c]20 mg/kg q6h PO or IV	Cytopenias, peripheral neuropathy, hepatic disturbances
Adjunctive Agent	
Prednisone, 40 mg bid x 5 d, 40 mg qd x 5 d, 20 mg qd x 11 d; PO or IV	Immunosuppression, peptic ulcer, hyperglycemia, mood changes, hypertension

[a]Therapy is administered for 14 days to non-HIV-infected patients and for 21 days to HIV-infected patients.

[b]Equivalent of 2 double-strength (DS) tablets. (One DS tablet contains 160 mg of TMP and 800 mg of SMX.)

[c]Leucovorin prevents bone marrow toxicity from trimetrexate.

Supportive Care

Evidence suggests that the degree of alveolar damage is the most important determinant of outcome. As with adult respiratory distress syndrome, which has histologic features similar to those of severe Pneumocystis infection, supportive care is crucial for severely ill patients. Continuous positive airway pressure by facemask improves oxygenation in patients with tachypnea and refractory desaturation with standard masks and may mitigate the need for mechanical ventilation.

Mechanical Ventilation and Intensive Care

The mortality rate for AIDS patients undergoing mechanical ventilation in intensive care units has ranged from 30 to 50%, thus supporting the value of aggressive measures in selected patients. A low albumin level, arterial pH less than 7.35, or need for positive end-

expiratory pressure greater than 10 cm H_2O after 96 hours in the intensive care unit portends a several-fold greater risk for a fatal outcome. Patients with better nutritional status and those who have less severe alveolar damage and a normal pH may benefit most from ventilatory support

Salvage Therapy

After respiratory failure has developed, the prognosis is poor. Although there is some evidence that Pneumocystis can develop resistance to sulfamethoxazole as a result of mutations in the DHPS enzyme, the limited data are conflicting regarding the clinical impact of this phenomenon. Respiratory failure is thought to ensue largely from diffuse alveolar damage. Parenteral TMP-SMX, pentamidine, trimetrexate, and clindamycin-primaquine have all been evaluated for salvage in uncontrolled studies and appear to provide limited benefit. Little reason has been put forward to favor any of these agents, and no data are available to support the use of multiple concurrent therapies.

Prevention

Prophylaxis is indicated for HIV-infected patients with CD4+ T cell counts of <200/L or a history of oropharyngeal candidiasis and for both HIV-infected and non-HIV-infected patients who have recovered from PCP. [16] Prophylaxis may be discontinued in HIV-infected patients once CD4+ T cell counts have risen to >200/ul and remained at that level for 3 months . Primary prophylaxis guidelines for immunocompromise hosts not infected with HIV are less clear .

TMP-SMX is the drug of choice for primary and secondary prophylaxis . This agent also provides protection against toxoplasmosis and some bacterial infections. Alternative regimens are available for individuals intolerant of TMP-SMX. Although there are no specific recommendations for preventing the spread of Pneumocystis in health care facilities, it seems prudent to prevent direct contact between patients with PCP and other susceptible hosts.

Prophylaxis For PCP [20]

Drug(s), Dose, Route	Comments
First Choice	
TMP-SMX, 1 DS tablet or 1 SS tablet qd PO[a]	TMP-SMX can be safely reintroduced in some patients who have experienced mild to moderate side effects.
Other Agents	
Dapsone, 50 mg bid or 100 mg qd PO Dapsone, 50 mg qd PO, plus pyrimethamine, 50 mg weekly PO, plus leucovorin, 25 mg weekly PO	Leucovorin prevents bone marrow toxicity from pyrimethamine.
Dapsone, 200 mg weekly PO, plus pyrimethamine, 75 mg weekly PO, plus leucovorin, 25 mg weekly PO	Leucovorin prevents bone marrow toxicity from pyrimethamine
Pentamidine, 300 mg monthly via Respirgard II nebulizer	Adverse reactions include cough and bronchospasm.
Atovaquone, 1500 mg qd PO	
TMP-SMX, 1 DS tablet three times weekly PO	TMP-SMX can be safely reintroduced in some patients who have experienced mild to moderate side effects.

[a]One DS tablet contains 160 mg of TMP and 800 mg of SMX

Note: DS, double-strength; SS, single-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

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