REVIEW ARTICLE

Pneumocystis pneumonia: Recent Update

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Introduction:

Pneumocystis carinii pneumonia (PCP) is an opportunistic infection that occurs in immuno-suppressed populations, primarily patients with advanced human immunodeficiency virus infection. In 2002, taxonomists renamed the human species of pneucystis as P. jirovecii and recommended that P. carini be used only to describe the not species of pneumocystis1.

Pneumocystis is commonly found in the lungs of healthy people, but being a source of opportunistic infection it can cause a lung infection in people with a weak immune system. Pneumocystis pneumonia is especially seen in people with cancer, HIV/AIDS and the use of medications that affect the immune system. The causal agent is known as *P. jirovecii*. Also the older name Pneumocystis carinii, (which now only applies to the Pneumocystis variant that occurs in animals), is still in common usage. As a result, Pneumocystis pneumonia (PCP) is also known as Pneumocystis jirovec pneumonia and (incorrectly) as Pneumocystis carinii pneumonia.[2,3,4].

P carini and fungi have similar cyst wall ultra structures (eg mitochondria with lamellar cristae) and have cyst forms containing intracystic bodies resembling those of ascospores formed by Ascomycetes. The 16s rRNA subunit, protein synthesis elongation factor, FF-3 and thymidilate synthase of *P.cariniis* most homologous with that of Ascomycetes. In contrast cell wall of *P. carini* does not contain ergosteral whish is processed by fungi and very fragile[5]. Regarding nomenclature, when the name of Pneumocystis pneumonia changed from *P. carinii pneumonia* to *P. 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 Pneumocystis (jirovecii) Pneumonia.

Pneumocystis carinii is a common microorganism that exists in rats, guinea pigs, monkeys, dogs, sheep, humans, and other animals. Most people are infected with Pneumocystis carinii during childhood and develop no symptoms. In rare cases, Pneumocystis carinii has been reported in parts of the body other than the lungs - this is called extrapulmonary pneumocystosis.

Although advances in the care of HIV infected patients have dramatically lowered its incidence, PCP remains a challenging clinical problem. Physicians need to be familiar with the presentation, diagnosis, treatment and prevention of PCP. Thus the purpose of the study is to update the knowledge regarding microbiology,epidemiology, laboratory diagnosis and prevention of PCP.

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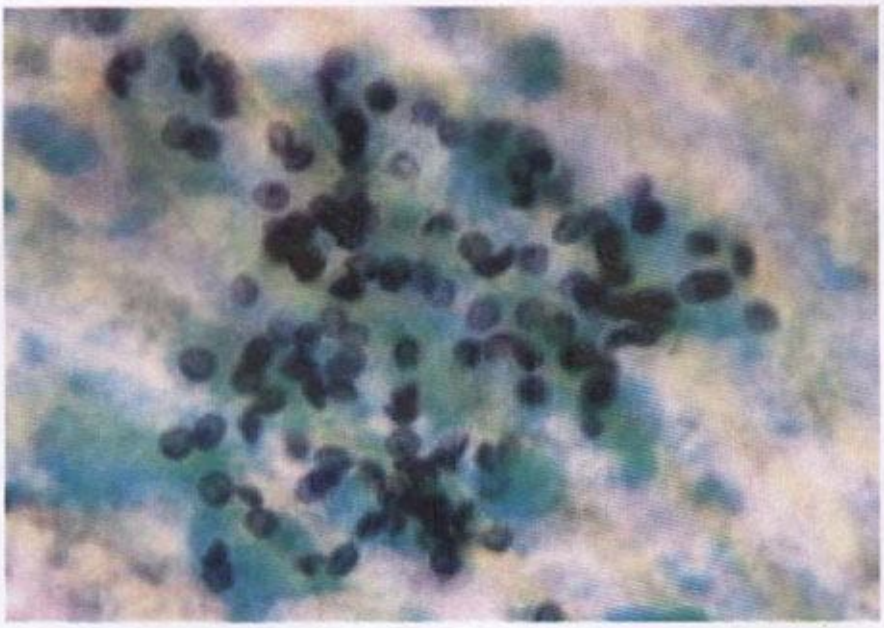


Pneumocystis (carinii) jiroveci

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[6]. PCP can also develop in patients who are taking immunosuppressive medications. It can occur in patients who have undergone solid organ transplantation) or bone marrow transplantation and after surgery[7]. Infections with Pneumocystis pneumonia are also common in infants with hyper IgM syndrome, an X-linked or autosomal recessive trait.

The causative organism of PCP is distributed worldwide[8,9] and Pneumocystis pneumonia has been described in all continents except Antarctica[8]. Greater than 75% of children are seropositive by the age of four, 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[10].

Pneumocystis jirovecii was originally described as a rare cause of pneumonia in neonates. It is commonly believed to be a commensal organism (dependent upon its human host for survival). The possibility of person-to-person transmission has recently gained credence, with supporting evidence coming from many different genotyping studies of Pneumocystis jirovecii isolates from human lung tissue. For example, in one outbreak of 12 cases among transplant patients in Leiden, it was suggested as likely, but not proven, that human-to-human spread may have occurred[11].

Since the start of the AIDS epidemic PCP has been closely associated with AIDS. Because it

only occurs in an immunocompromised host, it may be the first clue to a new AIDS diagnosis. If the patient has no other reason to be immunocompromised (eg. taking immunosuppressive drugs for organ transplant). An unusual rise in the number of PCP cases in North America, noticed when physicians began requesting large quantities of the rarely used antibiotic pentamidine, was the first clue to the existence of AIDS in the early 1980s[12,13].

Causes and Risk Factors of Pneumocystis Carinii Pneumonia (PCP)

In the immune-suppressed person, Pneumocystis carinii causes disease by growing and filling the alveoli of the lungs. Alveoli are small sacs in the lung that are lined with blood vessels. Oxygen inhaled in the lungs diffuses across the walls of the alveoli into the tiny blood vessels that line each sac. Carbon dioxide is expelled from the blood by a similar mechanism.

If a large proportion of alveoli are filled with microorganisms and the fluid by-products of inflammation, the blood can neither get enough oxygen nor get rid of excess carbon dioxide.

The specific mode of transmission in primary infection is unknown but the evidence suggests airborne transmission. After asymptomatic primary infection, presumably inactive organisms are sparsely distributed in the alveoli.

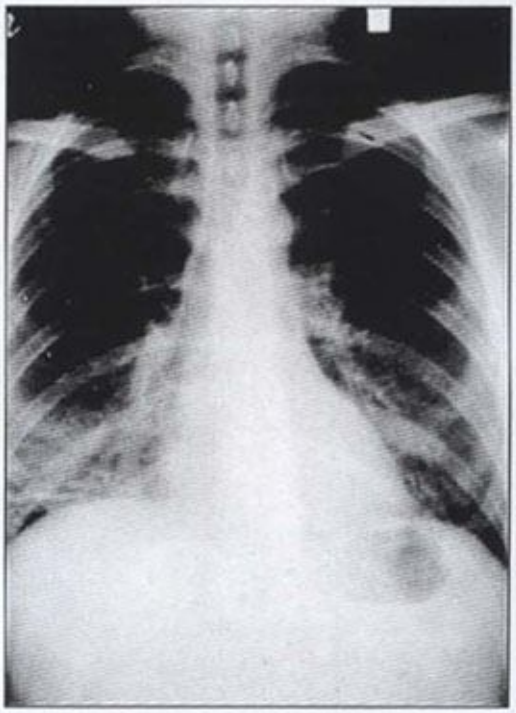
It is unclear whether acute infection in older children and adults results from new infection or from reactivation of latent infection.

Pneumocystis carinii pneumonia usually begins with mild but gradually worsening symptoms. These include:

- Dyspnea (shortness of breath) is the most common symptom.
- Cough associated with PCP usually produces no mucus or only thin, clear mucus (in patients who smoke)
- Tachypnoea (very rapid breathing)
- Fever
- Chill
- Sweat
- Progressive, profound fatigue
- Cyanosis

Respiratory symptoms are not always the first or most prominent sign of PCP. Many people have a few weeks or months of fever, fatigue and weight loss (constitutional symptoms) before respiratory symptoms develop.

Tests used to diagnose PCP include chest X-rays, pulmonary function tests, induced sputum tests, and bronchoscopy.



X-ray of Pneumocystis jirovecii pneumonia

There is increased opacification (whiteness) in the lower lungs on both sides, characteristic of Pneumocystis pneumonia. The diagnosis can 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. The diagnosis can be definitively confirmed by histological identification of the causative organism in sputum or bronchio-alveolar lavage (lung rinse). Staining with toluidine blue, silver stain or periodic-acid schiff or immunofluorescence assay, which will show characteristic cysts[14]. The cysts resemble crushed ping-pong balls and are present in aggregates of 2 to 8 (not to be confused with Histoplasma or Cryptococcus which typically do not form aggregates of spores or cells). A lung biopsy would show thickened alveolar septa with fluffy eosinophilic exudate in the alveoli. Both the thickened septa and the fluffy exudate contribute to dysfunctional diffusion capacity which is characteristic of this pneumonia.

Pneumocystis infection can also be diagnosed by immunofluorescent or histochemical staining of the specimen, and more recently by molecular analysis of polymerase chain reaction products comparing DNA samples. Notably, simple molecular detection of Pneumocystis jirovecii in lung fluids does not mean that a person has Pneumocystis pneumonia or infection by HIV. The fungus appears to be present in healthy individuals also in the general population[15].

Disease course

The risk of pneumonia due to Pneumocystis jirovecii increases when CD4 positive cell levels are less than 200 cells/µl. In these immunosuppressed individuals the manifestations of the infection are highly variable[16] The disease attacks the interstitial, fibrous tissue of the lungs, with marked thickening of the alveolar septa and alveoli and leading to significant hypoxia which can be fatal if not treated aggressively; therefore, LDH levels increase and gas exchange is compromised. Oxygen is less able to diffuse into the blood, leading to hypoxia. Hypoxia, along with high arterial carbon dioxide (CO_2) levels, stimulates ventilation, thereby causing dyspnea.

Treatment:

Antipneumocystic medication is used with concomitant steroids in order to avoid inflammation, which causes an exacerbation of symptoms about four days after treatment begins if steroids are not used. By far the most commonly used medication is co-trimoxazole, but some patients are unable to tolerate this treatment due to allergies. Other medications that are used, alone or in combination, include pentamidine, trimetrexate, dapsone, atovaquone, primaquine, pafuramidine meleate (under investigation), and clindamycin. Treatment is usually for a period of about 21 days.

Pentamidine is less often used as its major limitation is the high frequency of side effects. These include acute pancreatitis, renal failure, hepatotoxicity, leukopenia, rash, fever, and hypoglycaemia.

Preventive therapy is recommended for:[17]

- Patients with AIDS who have CD4 counts below 200
- Bone marrow transplant recipients
- Organ transplant recipients
- People who take long-term, high-dose corticosteroids
- People who have had previous episodes of this infection

Signs and symptoms may be insidious in onset and difficult to distinguish from those of other pathogenic process. Patient must be monitored carefully for clinical response and drug toxicity. Controversy exists over whether PCP represents reactivation pf infection acquired early in life or whether repeated exposure and reinfection cause the disease.

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