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PNEUMOCYSTIS CARINI PNEUMONIA IN HIV PATIENTS: A REVIEW

Dr. Sudheesh Raveendran*, Dr. Zhiyan Lu, Dr. Vineeth Vijayarajavan, Dr. Khaing Zar Thin

Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China.

***Corresponding Author: Dr. Sudheesh Raveendran**

Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China.

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ABSTRACT

The status of the PCP outbreak, including the epidemiology, clinical presentation, radiographic findings, diagnosis, and management of PCP were reviewed to present a better understanding of PCP.

KEYWORDS: Pneumocystis carini pneumonia (PCP), Human immunodeficiency virus (HIV), P. Carini, Pneumocystis.

1. INTRODUCTION

PCP is a potentially life-threatening pulmonary infection that occurs in immunocompromised patients who have a low CD4 cell count. Especially with HIV infected patients. The organism causing PCP had named as Pneumocystis carini (jirovecii). Patients with Pneumocystis pneumonia mostly present with fever, cough, dyspnea and malaise Which are not unique to PCP. The average duration of pulmonary symptoms is about 2 - 3 weeks before presentation for medical attention. PCP patients have a severe respiratory disease with a high mortality rate. Sometimes PCP may cause mutation with the dihydropteroate synthase gene that made drug resistant for Trimethoprim-sulfamethoxazole. Trimethoprin – sulfamethoxazole which had considered as the first-line agent for treatment for PCP. Moreover, the incidence rate of non-HIV PCP is increasing worldwide with the increment in the use of some targeted agents for the treatment of collagen diseases, inflammatory bowel diseases, and malignancies. PCP in some geographic locales even today remains the most common acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection. The recognition of an outbreak of PCP had in 1981, and it considers as a fraught moment in the field of medicine. Opportunistic fungal pathogens, PCP in particular, have contributed significantly to the morbidity and mortality of HIV-infected patients. Finally, the development of effective combination antiretroviral therapy (ART) has reduced the incidence of opportunistic infections in HIV-infected patients worldwide. PCP commonly occur in HIV-infected patients with late presentation for cART or virological and immunological failure after receiving cART. Moreover, opportunistic fungi remain an important cause of disease, in particular for patients with undiagnosed HIV infection and patients without access to, or who fail to adhere to, ART.[1,2]

In immunocompetent hosts, an array of immune mechanisms averts disease caused by Pneumocystis fungi. Potential fungal pathogens had identified by pattern recognition receptors of innate immune cells. These, in turn, produce cytokines and interleukin-12, which may cause the activation of CD41 helper T (TH) cells.

Production of interferon-g by TH1 cells then trigger cell-mediated, adaptive cytotoxic immunity. The downstream effects of interferon-g production included recruitment of leukocytes to the site of infection and enhanced macrophage phagocytosis and killing, commonly ending in the elimination of the invading fungi. The clinical presentation and radiographic findings of opportunistic fungal infections of PCP are frequently nonspecific; diagnosis relies on maintaining a high indication of detecting. The intensity and duration of immunosuppression in HIV-infected patients is a major risk factor for PCP. PCP is inversely related to a patient's CD41 TH cell count. Moreover, for other infections, like coccidioidomycosis, the clinical manifestations differ among patients with low CD41 TH cell counts than for immunocompetent patients. Diagnosis commonly relies on the confirmation of the fungus by microscopy or culture, except in select instances in which antigen or serum antibody testing can be definitive.

Extrapulmonary manifestations of Pneumocystis infection are rare, however. In this review, we aim to discuss the most recent and relevant information as well as a discussion of topics on epidemiology, clinical presentation, radiographic findings, diagnosis, and management of PCP.[3,4]

2. Pathophysiology and Epidemiology

Pneumocystis is a genus of host obligate ascomycete fungus. Pneumocystis fungi had typically found in the

lungs of a healthy adult. Mostly Kids at the age of 3 or 4 are believed to have been exposed to the Pneumocystis fungi. There are numerous species of Pneumocystis, each of which is peculiar to a particular mammalian host species. Human transmission had found in cases of recurrent pneumonia in which the genotype of Pneumocystis fungi in the same patient differed in prior stages. It is host obligated; it cannot be cultured or grown outside of the human body. The disease occurs when both cellular immunity and humoral immunity are defective.

Once it gets into the body through inhaling, the trophic form of Pneumocystis fungi will attach to the alveoli of the lung. Multiple host immune defects allow the replication of Pneumocystis fungi and development of sickness that may be uncontrolled. Activated alveolar macrophages without CD4+ cells are ineffectual to eliminate Pneumocystis fungi. On electron microscopy, Increased alveolar-capillary permeability is visible. Moreover, there is as yet no reliable evidence for an environmental reservoir for this organism other than the human host. In immunocompetent patients, Pneumocystis fungi do not cause any clear clinical syndrome.[5,6]

Pneumocystis is unlikely to cause anything more than mild, self-limiting respiratory symptoms. Some research conducted in animal models proved that Pneumocystis fungi spread from host to host via airborne transmission, likely to develop among human in the same manner. It is possible for the detection of Pneumocystis fungi in immunocompetent adults, especially those with COPD or cystic fibrosis, to harbour an asymptomatic colonization with Pneumocystis fungi. However, Pneumocystis fungi are mostly hard to detect in the respiratory specimen of a healthy adult. The consequences of chronic colonization may be progressive impairment of lung function over time. Moreover, that may result in Physiologic changes such as Hypoxemia with an increased alveolar-arterial oxygen gradient, Respiratory alkalosis, Impaired diffusing capacity and Changes in total lung capacity and vital capacity.[7,8]

PCP had recognized in the hosts with B cell defects, kids with severely combined immunodeficiency disorder, premature or debilitated infants, Oncology hosts who are in taking immunosuppressive drugs, and organ transplant recipients.

Transplantation of heart and lung having the highest incidence, whereas kidney transplantation patients have the lowest incidence. Chemotherapy and combination chemotherapy regimens that would cause myelosuppression affecting CD4+ counts would prompt proper monitoring for PCP over the course of therapy. Additionally, patients put on chronic corticosteroids for maladies, including COPD and Wegener's granulomatosis, could be at risk for PCPPneumocystis fungi cause a devastating and frequently Fatal pneumonia by contrast immunocompromised patients. The risk of Pneumocystis pneumonia increases with the degree of immunosuppression, and lower CD41 TH cell Counts predict the risk of PCP. Three-fourth of PCP case might occur in patients with a CD41 TH cell count less than 200 cells/μL, especially in HIV patients. Immunocompromised hosts with <200 cells/μL cannot eradicate the pathogen with innate immunity alone. HIV patients, organ transplant recipients, allogeneic hematopoietic stem cell transplant recipients, premature babies with protracted mechanical ventilation, chemotherapy hosts, and patients on immunosuppressant medications are all at a higher PCP risk because of the likelihood of a low CD4+ lymphocyte count. At 1980s PCP aroused as the HIV epidemic emerged. Antiretroviral therapy and chemoprophylaxis for PJP with trimethoprim/sulfamethoxazole (TMP/SMX) significantly decreased the incidence of PJP. Also, the impact of PCP In infants and children in developed countries has declined because PCP prophylaxis had initiated in all neonates born to HIV-positive mothers. If PCP is left untreated, associated mortality is approximately 100%; however, those who receive treatment have mortality rates between 5% and 40%. PCP increases with the abrupt onset of respiratory failure and delay in PCP diagnosis.[9-11]

3. Clinical presentation

The clinical presentation of PCP is nonspecific and cannot reliably distinguish from other infectious pulmonary processes. Common symptoms include fever, dyspnea, and a cough that can be either nonproductive or productive of hemoptysis but is rarely purulent. Although the disease can be fulminant, PCP patients with HIV frequently presents with an indolent course. Patients may experience weeks of slowly progressive symptoms, including a sensation of chest discomfort or chest tightness and exercise intolerance. HIV +VE hosts presentation might be different from the presentation of PCP of HIV -VE medically immunosuppressed patients who are more frequently acute and may rapidly progress to respiratory failure within weeks or days. Physical examination is also not specific. Chest auscultation may reveal end-inspiratory crackles but is frequently normal. The Severe disease might show the signs of Hypoxemic respiratory failure. Hypoxemia is characteristic and can be mild.PCP rarely cause extrapulmonary manifestations in patients receiving aerosolized pentamidine for prophylaxis. Complication likely to ARDS may occur in PCP hosts.[9,11,12]

4. Radiographic findings

4a. X-ray Findings

The chest radiographic findings may see normal in patients with early mild disease of PCP. Chest imaging has a vital role in the diagnosis of PCP. Diffuse bilateral infiltrates extending from the region of perihilar can see in PCP hosts, and it can describe as reticular, granular, or ground glass opacities (FIG 1). Chest radiographs classically demonstrate bilateral, diffuse, often perihilar,

fine, reticular interstitial opacification, which may appear somewhat granular. This opacification progresses to air-space consolidation over four days. This appearance may be followed by coarse reticulation as the infection resolves. Less common findings include patchy asymmetric infiltrates and pneumatoceles. Pleural effusions and intrathoracic adenopathy are rare. However, the chest radiograph in a patient with early disease may be normal. With late or severe disease, the chest radiograph may show frank alveolar consolidation. Cysts may be visible in the acute or post infective period.

Unusual but not inconsistent features of PCP on chest radiography include focal asymmetric interstitial or alveolar opacities, nodules, pneumatoceles, cavities, and pneumothoraxes. in some of the cyst walls, the radiologic and pathologic correlation demonstrate persistent infection. Spontaneous pneumothorax is the frequently seen infection in PCP hosts with cysts. Spontaneous pneumothorax has had a significantly higher mortality rate especially in PCP patients on ventilation. Pneumothoraces occur bilateral offend. Moreover, the Progression of a spontaneous pneumothorax is the main factor for the treatment and prognosis of PCP hosts because this stage tends to be refractory to conventional tube drainage, frequently requiring pleurodesis or surgical intervention.[9,13]

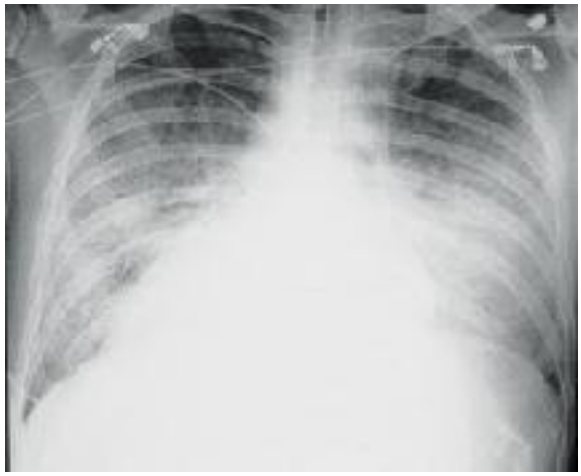


Fig 1: Bilateral interstitial infiltrates in an HIV +ve patient with PCP[13]

4b. High resolution computed tomography(HRCT)

HRCT chest scanning is more sensitive than chest radiography for the detection and exclusion of PCP.The main finding of PCP on HRCT scans is ground-glass attenuation which represents an exudative alveolitis of 90% in PCP patients.

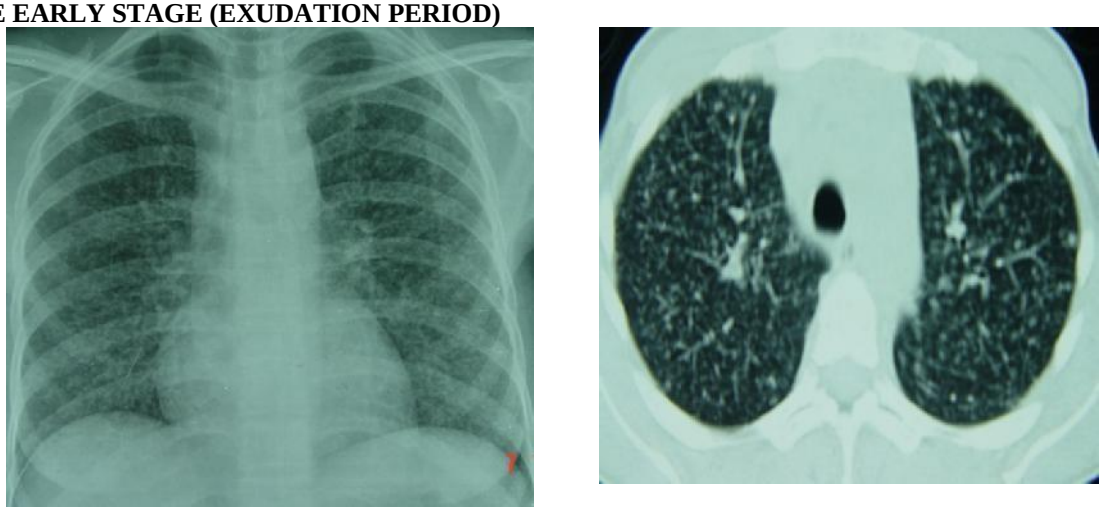
HRCT of the chest scans is a very delicate test for PCP with a high -VE "P" value.The classic structure of PCP on an HRCT scan is bilateral and regularly patchy but sometimes diffuse and homogenous, ground glass opacities. Pulmonary ground glass opacities are the increased attenuation of lung parenchyma without obscuring pulmonary vascular marking on CT images [Fig 4]. It may be the result of a wide variety of interstitial and alveolar disease. PCP commonly occurs in a bilateral and symmetrical to the perihilar region. Geographic or mosaic in shape situated with areas of normal lung adjacent to areas of the affected lung. HRCT manifestation of PCP had classified into five types: A) symmetrical diffuse shadow with ground glass density with hilus as the centre in bilateral lungs; decreased transparency of bilateral lungs with a demonstration of overlapping pulmonary vascular shadows; pulmonary lobular lesion by HRCT with fusion; a gas containing transparent regions between the lungs. Moreover, an irregular margin could appear at the pulmonary borders. B) scattered multiple linear and reticular shadow in both lungs, with thickened pulmonary markings; interlobular septal and intralobular interstitial thickening and thickened broncho vascular bundle by HRCT with confined ground glass like density and without any shadows of nodules. C) obviously increased pulmonary markings in both lungs, with possible multiple wire reticular shadows and diffuse small nodular shadows; after administration of SMZ therapy, no foci had seen in the lungs. D) multiple parenchymal shadows in both lungs, with increased pulmonary markings in the middle and lower lungs fields and with blurry flaky shadows. E) pulmonary interstitial fibrosis in a strip like shadows of increased density in the late stage, with a demonstration of emphysema and pneumothorax.[14,15]

It has internationally reported that nearly 10% of PCP patient shows negative findings by chest x-ray but with abnormal findings by HRCT. As with chest radiography, an HRCT scan of the chest in advanced disease may show consolidation, nodules, or pneumatoceles. Due to the rapid progress of PCP as well as its complex pathological changes, CT scanning demonstration is diverse with specificity. Mainly, in a symptomatic patient with a normal chest radiograph, the absence of ground glass opacities on HRCT significantly diminishes the probability of PCP. According to different pulmonary CT scanning demonstrations in various stage of illness. PCP is divided into early stage (exudative and infiltrative stage), middle stage (fusion and parenchymal stage) and advanced stage (absorption and fibrosis stage). However, ground glass opacities on HRCT are not specific for PCP and could see in other cardiopulmonary pathologic conditions including viral pneumonia, pulmonary edema, and diffuse alveolar haemorrhage.[14-16]

Early manifestation includes intrapulmonary multiple military nodules, mainly distributed in both middle and lower lung fields. It might accompany by lengthened hilar shadow, which should differentiate from military tuberculosis [Fig 2]. The middle stage is a period of infiltration. As the disease progress, military and patchy shadows fuse and expand into a dense infiltrative shadow with even density, showing a diffuse ground glass like change. The typical manifestations include bilaterally symmetrical foci with the hilus as the Centre. The foci infiltrate from the hilus to bilateral pulmonary

interstitium, progressing from the both middle lung to both lower lungs. HRCT can more clearly demonstrate the foci, showing a map or gravel road like appearance, with a clear demonstration of gas containing bronchus penetrating the foci. Pulmonary apex is involved later. The exterior stripe of the lung field has increased transparency, showing typical willow leaf sign or moon bow sign, which is the manifestation of emphysema. In the advanced middle stage, parenchyma is highly affected. Parenchyma appears like flaky shows, more prominent in middle and lower lobes of the lungs. Hilar shadows might enlarge in both lungs. CT scan shows thickened bronchial walls and large flaky parenchymal shadows in concentric and symmetrical distribution with bronchial shadows in them. Absorption period is a period of recovery from initial damage. It shows patchy shadows and thickening of both hila. CT scan shows flaky, mass like ground glass opacities in both lungs with few cords like shadows in them and reticular changes In advanced stage (pulmonary fibrosis period) the lobar septa of both lungs are significantly thickened, with cords liked pulmonary fields, grid like changes and decreased transparency. It can be complicated by pulmonary pseudocyst, with thin and clear cystic wall. Since the advanced pulmonary stage is almost irreversible, it is a critical period in the diagnosis and management of PCP. After fibrosis; administration of HAART is very less efficient, and there are high chances of mortality [Fig 3].[16-18]

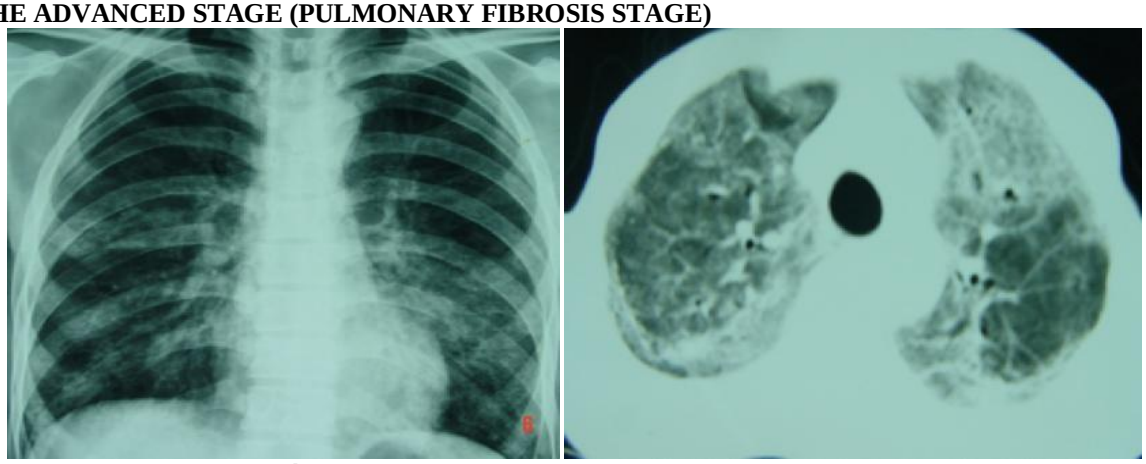
IN THE EARLY STAGE (EXUDATION PERIOD)



A **B**

FIG 2: A) HIV/AIDS related pneumocystis carinii pneumonia. DR demonstrates scattered military increased density shadow in both lungs, with even size, density and distribution. The shadow of both hila is dense, with sharp both Costo phrenic angles. FIG 2 B) CT scanning demonstrate scattered military nodular shadow in both lungs, which is more obvious in upper lung fields. The trachea is unblocked.[17]

IN THE ADVANCED STAGE (PULMONARY FIBROSIS STAGE)



A **B**

Fig 3: A HIV/AIDS related PCP. DR demonstrates multiple patchy shadows with increased density in both lungs which are more obvious in both middle and lower lungs. The hilar shadows in both lungs are enlarged, with sharp Costo phrenic angles. Fig 3B. CT scanning demonstrates multiple patchy mass like parenchymal shadows in both lungs, ground glass opacities in the apical segment of both upper lobes with multiple transparent areas in the medial part of the right middle lobe. The trachea is unobstructed.[17]

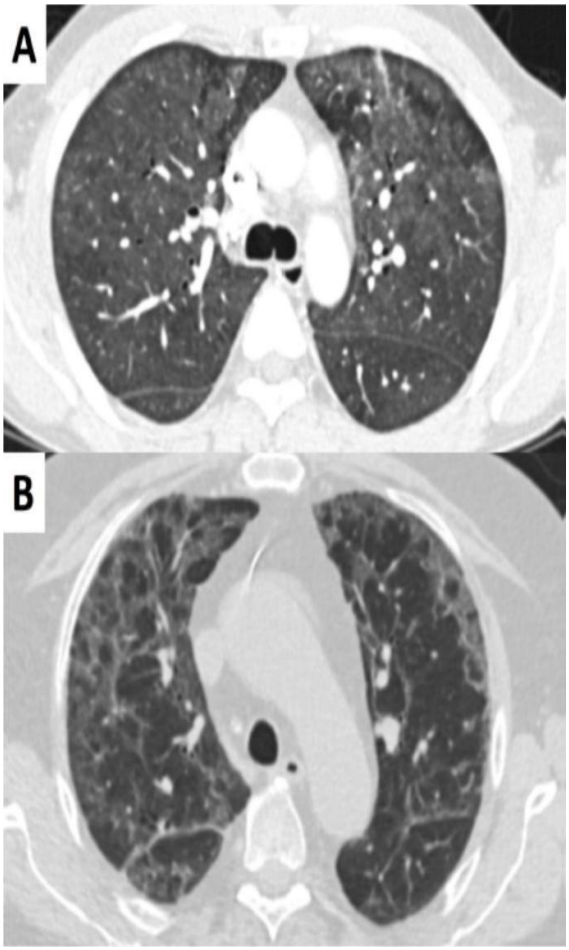


Fig 4: A) HIV +VE male patient with PCP with typical diffuse ground glass opacities in both lungs. B) HIV negative male who developed PCP with multifocal patchy groundglassopacitiesandreticulation.[14]

5. Diagnosis Of PCP

Serum levels frequently vary in PCP patients but also varies in the diagnosis of other diseases caused by bacteria, mycobacteria, and other fungi. The marker (1-3) b-D-glucan is a component of the fungal cell wall and could see in the serum PCP hosts. Lactate dehydrogenase is a nonspecific biomarker of cellular damage because b-glucan levels extend over between those with PCP and without PCP, and results of the test were also positive in other fungal infections. These tests can be useful to support a clinical suspicion for PCP but on their own are not specific enough for definitive diagnosis in most cases. The serologic method cannot distinguish the difference between PCP and other fungal pneumonia, so the test result will not is specific. The test could lead to inappropriate therapy because a substantial number of patients might be treated for PCP infection even though another pathogen was the causative agent that result in misdiagnosis. So it cannot replace the classic gold standard diagnostic procedures for PCP infections. B-Glucan is +VE with certain other fungi; So, that made all the results are nonspecific this is the main disadvantage of this test. The serologic method has hypothesized that might used as a preliminary screening test in patients with primary suspicion of PCP infection or as an alternative diagnostic procedure in patients with respiratory failure, or even in children in whom invasive procedures for specimen collection are not easy to perform, carrying an associated risk of complications. Serologic tests, Radiological findings and clinical presentation are not specific for PCP. PCP predominantly diagnosed by respiratory specimens. So, this specimen making a vital role in the diagnosis of PCP.[19,20]

PCP can detect by Minimal invasive procedures such as sputum induction & bronchoalveolar lavage(BAL) and by open lung biopsy before the emergence of AIDS. Sputum induction & bronchoalveolar lavage(BAL are now the methods of choice. Pneumocystis has rarely identified in spontaneously expectorated sputum. Diagnostic yield is higher with induced sputum, that is, sputum provoked by inhalation of an aerosol of hypertonic saline solution, and sensitivity is 74% to 83%. However, a negative result for Pneumocystis in induced sputum should be followed by bronchoscopy. The sensitivity and specificity of BAL fluid obtained during fiberoptic bronchoscopy can give 100% for the diagnosis of PCP. Bronchoscopy with BAL is useful because it samples the alveolar contents with a sensitivity that exceeds 95 percent. There is no method for culturing Pneumocystis because PCP does not grow in virtue. So cytopathologic examination is the only way out. The diagnosis had done by the microscopic visualisation of trophic or cystic forms of Pneumocystis. A variety of histologic stains can be used under light microscopy to identify Pneumocystis because PCP cannot be cultured routinely and is identified by stains demonstrating the cyst wall or the trophozoite. A confirmatory diagnosis of PCP infections might require the identification of cystic or trophic forms in appropriate specimens, both of which can be visualised using GMS, cresyl violet, Gram-Weigert, toluidine blue, Wright-Giemsa, and Diff-Quick staining. The Diff-Quick and Wright-Giemsa stains identify the nuclei of Pneumocystis organisms of all developmental stages. Grocott-Gomori methenamine silver, toluidine blue O, and cresyl violet stain the wall of the cystic form but not that of the trophic form[Fig.5]. Other stains, such as the chemifluorescence calcofluor white (that binds to b-polymers of Pneumocystis and other fungi) and Papanicolaou (which help the identification of the foamy eosinophilic exudate that surrounds Pneumocystis), can be used. The use of direct immunofluorescent antibody stains(direct fluorescent antigen testing) for Pneumocystis is also effective because of its high sensitivity and binding ability to both trophic and cystic forms. In depth knowledge of the histological features is important to avoid an unwanted investigation and therapy. Total resection should attempt in every case, and strictly follow up should be carried out to prevent postoperative morbidity and recurrence. It is useful to make a diagnosis as quickly as possible so that targeted therapy can start.[21-23]

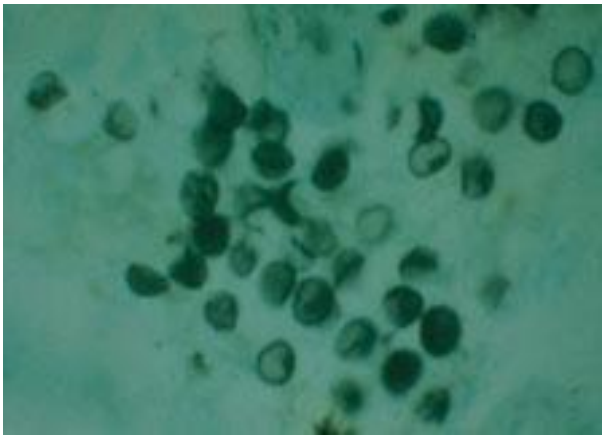


Fig 5: Methenamine silver stain of a bronchoalveolar lavage[BAL] specimen showing a cluster of P. Carini cysts.[22]

More recently, Molecular assays had developed for the detection of Pneumocystis DNA by polymerase chain reaction (PCR) is offered by some laboratories for use on respiratory specimens like P. Carini in bronchoalveolar lavage fluid, induced sputum, or oral wash samples. In one study shows PCR assay targeting MSG gene having a sensitive of 90% and a specificity of 85 % for diagnosis of PCP. PCR testing detects the presence of Pneumocystis DNA not only in those patients with pneumonia caused by Pneumocystis but also in patients who solely colonized and who have symptoms that can be attributed to another confirmed diagnosis or have no symptoms at all. A negative PCR test result, however, significantly decreases the likelihood that a patient has PCP. Currently, PCR has not used in clinical practice yet, But it is effectively using in some research study about the drug resistance, Pneumocystis colonization, and transmission of the disease. More research is going through PCR so soon, or later we can expect PCR in clinical practice that will make a new impact in the field of medicine.[24,25]

New diagnostic techniques for PCP have investigated over S-Adenosylmethionine (AdoMet). Adenosylmethionine is a molecule that Pneumocystis requires for methylation reactions and polyamine synthesis and is scavenged by from its hosts. Two studies showed that AdoMet levels are decreased in humans with PCP with a sensitivity and specificity of 0.88 and 1.0. Moreover, it's a non-invasive, rapid assay for diagnosing PCP and following response to treatment. However, in a subsequent prospective study of 31 HIV-negative patients with and without PCP, AdoMet levels failed to distinguish between with PCP patients and without PCP patients, and it is not reliable. More research studies about it are going now.[26,27]

Pulmonary biopsy (either percutaneous or open) should consider when bronchoalveolar lavage is negative. Authentication of P carinii should seek by use of special stains in all lung biopsy material from HIV infected patients with PCP. Biopsy for the diagnosis of PCP commonly done by transbronchial biopsy through a fiberoptic bronchoscope. However, recently video-assisted thoracoscopic biopsy is used widely because of the convenient of the practitioner. A range of atypical histological appearances may see in patients with HIV infected with PCP. Histopathologically, PCP had characterized by a pattern of diffuse alveolar damage, a vacuolated and foamy exudate that fills alveolar air spaces, a lymphocytic interstitial infiltrate, and hyperplasia of type 2 pneumocytes. PCP typically identified in HIV infected patients who have had 1-3-β-d-glucan levels >80 pg/ml (if available), CD4+ T cell count of <200 cells/µl. Moreover, signs and symptoms that are common of the PCP infection; especially dyspnea, cough, and diffuse, infiltrates present on a chest X-ray or chest CT, especially on bilateral, interstitial, or alveolar regions. A confirmatory diagnosis of PCP done through the specimen (identification of cystic or trophic forms). Because of the high diagnostic and sensitivity yield of bronchoscopy with BAL, a biopsy is not mandatory to confirm the diagnosis of PCP. Pathologic confirmation is mandatory when other infections or co-infections are suspected or need to exclude.[21,28,29]

6. Management of PCP

Treatment for PCP should start in the patient when clinical suspicion for PCP conclude that P. Carini is likely the causative pathogen. Furthermore, it is then necessary to treat the PCP infection before complications get severe. Treatment will not is delayed, as the yield for diagnosis of PCP from BAL fluid is unchanged for up to 14 days after starting treatment. Cotrimoxazole, namely trimethoprim- sulfamethoxazole (TMP-SMX) is the most common drug used for prophylaxis and the therapy of PCP. TMP-SMX had utilised as an effective treatment option for many years because of its low cost, clinical efficacy against PJP, and bioavailability in both intravenous (IV) and oral formulations. The recommended strength for treatment in both adults and children is 1:5 fixed dose combination of 15 to 20 mg/kg/d(based on the TMP component), and 75 to 100 mg/kg/d(based on the SMX component). That may administered orally or intravenously (IV)may give into 3 to 4 doses per day for 21 days(The total recommended dose duration).

Minimal courses duration has resulted in higher rates of treatment failure. TMP/SMX is the preferred agent for treatment of PCP(first line choice)because of its excellent oral bioavailability, and IV therapy is often preferred initially for cases of moderate to severe PCP. Use of trimethoprim- sulfamethoxazole (TMP- SMX) might limit by adverse reactions, including rash, fever, transaminitis, nephritis, hyperkalemia, and cytopenias. If a patient has chronic PCP infection (acute respiratory failure, hemodynamic instability, the need of ventilator support), they should treat with IV TMP/ SMX because of the possibility of low drug absorption in the critically ill.[30,31]

There are alternative treatment options if TMP-SMX not tolerated or if treatment fails then IV pentamidine had given. IV pentamidine given at 4 mg/kg once daily infused over 60 minutes has equivalent efficacy to IV TMP-SMX but greater toxicity. Adverse reactions of pentamidine include infusion site phlebitis, severe hypotension during infusion, prolonged QT, torsades de pointes, pancreatitis, hypoglycemia or hyperglycemia, hepatitis, transaminitis, nausea and vomiting, fever, nephrotoxicity, hypocalcemia, hypomagnesemia, hyponatremia, diabetic Mellitus, and leukopenia. Given the variety and severity of these toxicities, IV pentamidine has commonly reserved for use in patients who do not tolerate and no respond, TMP-SMX. It is necessary to monitor blood glucose and creatinine levels and to watch for QT prolongation, especially during the last several weeks of the therapy.[32,33]

Other alternative therapies include clindamycin with primaquine. Clindamycin could administer intravenously(IV), 600 to 900 mg 3 times daily. Moreover, orally, 400 to 600 mg 3 times daily. Primaquine is only available in an oral formulation and is given 15 - 30 mg once daily. Clindamycin with primaquine has equivalent efficacy to TMP-SMX for initial treatment of mild to moderate PCP(second choice for PCP therapy), and there is evidence to suggest that it is more efficient than IV pentamidine as a salvage therapy, In addition to TMP-SMX, clindamycin-primaquine could use as an alternative regimen. In patients that do not show any improvement after 4 to 8 days of treatment, then therapy failure must be considered. On that occasion, clindamycin-primaquine could consider. Anemia, neutropenia, methemoglobinemia, hemolysis and rash is a common complication of this therapy.[34,35]

Trimethoprim and dapsone are as effective as oral TMP-SMX for mild or moderate PCP but is ineffective for severe PCP. Trimethoprim, 5 mg per kg orally every eight hours and dapsone, 100 mg orally once in a day. Nausea, vomiting, fever, rash, bone marrow suppression, hepatitis, hemolysis, methemoglobinemia are the complications of this drug, And these drugs had considered as the second choice for the treatment of mild to moderate PCP likewise Clindamycin and primaquine.

Atovaquone, 750 mg of suspension orally twice daily, is inferior therapy compared with TMP-SMX for mild or moderate PCP and is ineffective for severe PCP. It should intake with fatty foods, and it will not prescribe to patients with diarrhoea and malabsorption. Nausea, vomiting and rash are the complications of this drug, and it considers as a third choice drug for the treatment for mild to moderate PCP.[36,37]

The use of corticosteroids with anti-Pneumocystis agents has become the standard of care in the treatment of moderate to severe PCP patients because the Adjunctive corticosteroids decrease the need for ICU admission, mechanical ventilation, and mortality in HIV-infected patients with moderate to severe PCP patients.

Randomized studies revealed that corticosteroids give a better prognosis by improving the survival rate in patients who have had a partial pressure of arterial oxygen when breathing room air less than 70 mm Hg or alveolar-arterial O2 difference >35 mm Hg. Ideally, steroids should start at the time that Pneumocystis-specific treatment is initiated and definitely within the first 72 hours of treatment.

The recommended dosing schedule is 40 mg of prednisone twice daily for 5 days, then 40 mg once daily for 5 days, and 20 mg once daily for the 21 days should follow up. If the patient cannot take the dosages orally, then methylprednisolone is given intravenously at 75% of prednisone dose. Complication these corticosteroids are osteonecrosis and metabolic complication like Impaired blood glucose regulation, type 2 diabetes mellitus (T2DM), prediabetes, and gestational diabetes. So, this therapy has rarely used in the treatment of mild PCP. Microbial degradation may trigger further inflammation which may lead to a chronic inflammatory response in the lungs that can deteriorate after the therapy start over. Adjunctive corticosteroid therapy can blunt this inflammatory response, reduce oxygen deterioration and the incidence of respiratory failure. With appropriate therapy early clinical deterioration is common, attributed to a host inflammatory response provoked by antibiotic-induced lysis of Pneumocystis organisms. If there is no improvement or further clinical decline after at least 5 to 8 days of first line treatment, treatment failure should consider, and it would be important to consider switching to an alternative therapy. Clinical Worsening After Initiation of Therapy because of clinical deterioration, caused by the development of iatrogenic hypervolemia, pneumothorax, and methemoglobinemia would need to be excluded.[38,39]

Smoking and tobacco cessation is strongly recommended in patients with PCP because risk factors and complications from this are very high. A panel of united states PHS and IDSOA has published guidelines on PCP prophylaxis. They recommended that patients with CD41 TH cell counts <200 cells/mL TMP-SMX is the agent of choice for PC P prophylaxis in the absence of a contraindication.

Commonly for TMP - SMX, 1 double-strength tablet (160 mg TMP and 800 mg SMX) once daily has been the regimen of choice, but 1 single-strength tablet (80 mg TMP and 400 mg SMX) once daily is also effective. A daily dosing regimen is right for the cross protection against Toxoplasma gondii infections and other bacterial infections. Another choice is 1 double-strength tablet can be taken 3 times weekly. Sometimes TMP-SMX cannot be used because of adverse effects of drug resistant organisms such as pneumococcus or Staphylococcus aureus. On that occasion, alternative options for

prophylaxis should follow up that is aerosolized pentamidine, 300 mg once monthly; dapsone, 100 mg once daily; dapsone, 50 mg once daily with pyrimethamine, 50 mg once weekly. These regimens are protected against T gondii infection, but not other bacterial infections(less efficient than prophylaxis with TMP-SMX). Atovaquone, 1500 mg oral suspension once daily with food. Atovaquone has a low toxicity profile and is an alternative if the patient cannot tolerate TMP-SMX or dapsone. Aerosolized pentamidine, 300 mg in 6 mL sterile water via Respirgard nebuliser every 4 weeks. Aerosolized pentamidine, better tolerated than dapsone or TMP-SMX. Also, it is less effective than other prophylactic agents with Side effects of a cough and bronchospasm. As a result of ART, the PCP prophylaxis can be drop out if the CD41 TH cell count > 200 cells/mL for at least three months. Although PCP can occur when CD41 TH counts >200 cells/mL, the benefit of continuous PCP chemoprophylaxis is diminished or may be outweighed by the risk of drug toxicity for those receiving daily systemic corticosteroid treatment follow up (at least 20 mg daily for at least 1 month).[32,36,40,41]

7. CONCLUSION

Clinical manifestations of HIV-infected patients with PCP frequently depend on the degree of immunosuppression and the CD4 1 TH cell count. Primary and secondary prophylaxis depends on CD41 TH cell counts and geographic location and local prevalence of disease. An accurate diagnosis is important because treatments are different.[40,41] In this review, we mainly focused on epidemiology, clinical presentation, radiographic findings, diagnosis, and management of PCP with new relevant information that can aid a clinical practitioner in his clinical practice. A correct diagnosis can avoid much more empirical investigation and save much time. In this review, we cover up almost all newly relevant measures that are quite useful for the early detection and prevention of PCP.

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