ORIGINAL ARTICLE

# Clinical outcomes of pneumocystis pneumonia from a tertiary care centre in Pakistan

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## Abstract

**Objective:** To assess the predisposing immunocompromised states, administration of pneumocystis jirovecii pneumonia prophylaxis, the disease course and outcomes of patients with pneumocystis jirovecii pneumonia.

**Methods:** The retrospective study was conducted at the Aga Khan University Hospital in Karachi. The medical records of patients diagnosed with pneumocystis jirovecii pneumonia from January 1995 to October 2015 were retrieved. Baseline characteristics, clinical course, treatment, and mortality rates were noted. SPSS 19 was used for data analysis.

**Results:** Of the 37 patients, 24(64.9%) were men and 13(35.1%) were women. The overall mean presenting age was 47.08±16.21 years (range: 19-83 years). Ten (27%) patients were positive for human immunodeficiency virus; 12(32.4%) had an underlying autoimmune disease; 3(8.1%) were transplant recipients; 10(27%) had an underlying malignancy, and 19(51.3%) were on long-term corticosteroid therapy. Only 2(5.4%) patients had received pneumocystis jirovecii pneumonia prophylaxis with trimethoprim-sulfamethoxazole. Moreover, 8(21.6%) patients required intensive care unit admission with a mean stay of 2.03±4.91 days (range: 1-22 days).The overall mortality rate was 7(18.9%).

**Conclusion:** Pneumonia due to *pneumocystis jirovecii* was found to be a life-threatening disease in the immunocompromised population. The high mortality burden and resource intensive management of the disease emphasizes the need for PCP prophylaxis in immunosuppressed individuals.

**Keywords:** *Pneumocystis jirovecii* pneumonia (PCP), Outcome, Prophylaxis. (JPMA 66: 1367; 2016)

## Introduction

Pneumocystis pneumonia (PCP) is a potentially life-threatening fungal infection seen in immunocompromised hosts. PCP was initially described in humans in 1942, but was commonly reported with human immunodeficiency virus (HIV) epidemic in the United States in early 1980s. The main risk factors which predispose to PCP infection include a variety of other immune-deficient states such as haematological malignancies, solid tumours, organ transplantations, connective tissue diseases and use of immunosuppressive medications such as corticosteroids and chemotherapeutic agents.[1-8] The mortality rate for HIV-infected patients who develop PCP is around 10-20% during the first episode of this infection. The death rate may reach as high as 30-60% in non-HIV-infected cases of PCP, with the highest risk of mortality seen in cancer patients.[3,9-11] PCP remains a diagnostic challenge due to its non-specific signs and symptoms, the use of prophylactic drugs which might alter the clinical presentation and other opportunistic infections in an immuno-suppressed patient.[3]

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Infection with HIV and subsequent infection with PCP has been studied in detail and PCP has been recognised as one of the acquired immunodeficiency syndrome (AIDS) defining conditions in HIV-positive individuals. Autoimmune diseases also render individuals susceptible to PCP, not only by disease pathophysiology but also due to the immunosuppressive agents used for treatment. Both haematological and solid organ malignancies as well as transplant recipients also remain vulnerable to PCP secondary to the same phenomenon.[3]

In Western countries, PCP is historically recognised as the HIV-indicator disease.[12] Clinical spectrum of PCP, both in HIV and non-HIV population, from higher income countries has been intricately researched and well documented.[13] On the other hand, low- and middle-income countries (LMICs) have been previously regarded as low PCP prevalent areas and limited data is available about the trends and clinical outcomes of PCP in resource-poor settings.[13,14] Studies from India have shown a low prevalence of PCP of 5-6% with mortality rates as high as 29%.[15,16] Pakistan is a low-income country with an under-developed healthcare system. To the best of our knowledge, we have been unable to find data on PCP-related studies from this country. The current study was planned to assess PCP outcome among hospitalised patients, both in HIV and non-HIV individuals in a large tertiary care hospital. We sought to

define demographics, major predisposing immunocompromised states, administration of PCP prophylaxis and its impact, disease course, presence of co-infection and clinical outcomes in patients affected by PCP.

## Materials and Methods

The retrospective study was conducted at the Aga Khan University Hospital (AKUH), Karachi, and comprised records of patients diagnosed with PCP from January 1995 to October 2015.

The AKUH is a 740-bed, private, tertiary-care hospital which caters to the needs of over 50,000 patients annually. Ethical approval was obtained from the institutional review committee. Hospital records were retrieved by accessing Health Information Management Services (HIMS) in order to identify patients who had received a discharge diagnosis of 'Pneumocystosis'. Patients aged above 18 years who had a laboratory confirmed diagnosis of PCP were included. Direct immune fluorescent test (Bio-Rad, France) was performed on sputum, broncho-alveolar lavage and lung tissue specimens in the clinical microbiology laboratory. Patients who had not undergone laboratory testing and had received empirical therapy without laboratory confirmation for PCP were excluded.

A data collection sheet was prepared in order to collect information on demographics, pertinent past medical history (comorbid conditions, immunocompromised states and HIV status), and details regarding hospital admission, presenting complaints, laboratory and radiographic data, admission to the intensive care unit (ICU), length of stay, treatment regimen, clinical outcome and cause of death. Clinical charts were reviewed and data was entered in EpiData version 6.0 (EpiData Association, Odense, Denmark).

SPSS 19 was used for data analysis. Simple frequency and descriptive analysis was run for patient demographic characteristics as well as for categorical variables, and cross-tabulation was carried out. Independent samples t-test was run in order to evaluate for equality of means within HIV versus non-HIV patients as well as for survivors versus non-survivors and 95% confidence interval (CI) was calculated.

## Results

Of the 112 cases identified, 37(33%) had been laboratory confirmed for PCP. The remaining 75(66.96%) patients had received empirical treatment for PCP along with other likely causes of pneumonia as per the attending physician's discretion without undergoing laboratory testing for PCP.

**Table-1:** Demographics of study population (n=37).

| Variables | Number (%) |
|---|---|
| Age in years, (mean ±SD, range) | 45.77±16.83, 19-83 |
| **Gender** | |
| Male | 24 (64.9) |
| Female | 13 (35.1) |
| **Underlying immune-compromised disease** | |
| HIV-positive | 10 (27.0) |
| **Autoimmune disease (n=12)** | |
| Systemic Lupus Erythmatosus (SLE) | 6 (16.2) |
| Membranous Nephropathy | 2 (5.4) |
| Crescentric Glomerulonephritis | 1 (2.7) |
| Polymyalgia Rheumatica | 1 (2.7) |
| Autoimmune Haemolytic anaemia | 1 (2.7) |
| Idiopathic Thrombocytopenic Purpura | 1 (2.7) |
| **Malignancy (n=10)** | |
| Solid Malignancy | 7 (70.0) |
| Haematological Malignancy | 3 (30.0) |
| **Transplant Recipient (n=3)** | |
| Liver | 2 (66.6) |
| Renal | 1 (33.3) |
| **Immuno-suppressant drugs (n=28)** | |
| Corticosteroids | 19 (67.8) |
| Other immunosuppressive agents (cyclophosphamide, methotrexate) | 9 (32.1) |

HIV: Human immunodeficiency virus
SD: Standard deviation.

The overall mean age was 47.08±16.21 years (range: 19-83 years).Of the study population, 24(64.9%) were men and 13(35.1%) were women. Besides, 10(27%) were HIV-positive, 12(32.4%) had an underlying inflammatory autoimmune condition, 3(8.1%) were transplant recipients (2(66.67%) liver and 1(33.33%) renal), 10(27%) had an underlying malignancy, 19(51.3%) were on long-term steroid therapy,9(24.3%) were receiving an additional form of chemotherapy or immuno-suppressants, and 3(8.1%) had received radiation therapy. Only 2(5.4%) of the patients had received PCP prophylaxis (Table-1).

The mean age of HIV-positive patients was 43.40±7.26 years and that of HIV-negative patients was 48.44±18.40 years. Moreover, 31(83.8%) participants had symptoms of low-grade fever. PCP prophylaxis was given in 2(20%) of the HIV-positive patients and none of the HIV-negative immunocompromised patients.

Oral candidiasis was present in 4(10.8%) patients, whereas 2(5.4%) had concomitant pulmonary tuberculosis and 2(5.4%) had pulmonary nocardiosis. The HIV-positive patients had a mean CD4 cell count of 15.64±9.6 (Table-2).

**Table-2:** Clinical characteristics of patients with *Pneumocystis jirovecii* pneumonia (PCP).

| Clinical characteristics | All patients (n=37) | HIV-positive (n=10, 27.0%) | HIV-negative (n=27, 73.0%) | p-value |
|---|---|---|---|---|
| **Gender** | | | | 0.44 |
| Male | 24 (64.9) | 8 (80) | 16 (59.3) | |
| Female | 13 (35.1) | 2 (20) | 11 (40.7) | |
| Mean age ± SD (years) | 47.08±16.21 | 43.4±7.2 | 48.4±18.4 | 0.4 |
| **Age category** | | | | |
| < 25 years | 2 (5.4) | 0 (0) | 2 (7.4) | |
| 25-39 years | 10 (27) | 4 (40.0) | 6 (22.2) | 0.2 |
| 40-64 years | 18(48.6) | 6 (60.0) | 12 (44.4) | |
| > 65 years | 7 (18.9) | 0 (0) | 7 (25.9) | |
| **PCP prophylaxis** | | | | |
| Yes | 2 (5.4) | 2 (20.0) | 0 (0) | |
| No | 35 (94.5) | 8 (80.0) | 27 (100) | 0.06 |
| Duration of symptoms (days) | 25.5±65.2 | 61.8±114.8 | 10.0±6.4 | 0.044 |
| **Symptoms** | | | | |
| Fever | 31 (83.8) | 10 (100) | 21 (77.8) | 0.16 |
| Dyspnoea | 21 (56.8) | 4 (40.0) | 17 (68.0) | 0.15 |
| Cough | 25 (67.6) | 10 (100) | 15 (62.5) | 0.03 |
| **Laboratory findings** | | | | |
| Haemoglobin g/dl | 11.1±2.5 | 10.9±2.4 | 11.2±2.57 | 0.79 |
| WBC /x103mm3 | 6.7±5.7 | 5.6±2.8 | 7.04±6.32 | 0.86* |
| Neutrophils/mm3 | 79.08±11.26 | 77.5±12.4 | 79.5±11.09 | 0.64 |
| Lymphocytes/mm3 | 15.56±10.47 | 15.6±9.2 | 15.5±10.9 | 0.72* |
| Platelets/mm3 | 206.08±121.29 | 195.6±119 | 209.9±126.2 | 0.82* |
| ICU admission & mechanical ventilation | 8 (21.6) | 1 (10) | 7 (25.9) | 0.4 |
| **Complications** | | | | |
| Pneumothorax | 3 (8.1) | 1 (11.1) | 2 (18.2) | 0.99 |
| Septic Shock | 1 (2.7) | 0 (0) | 1 (9.1) | 0.99 |
| Respiratory failure | 7 (23.3) | 1 (11.1) | 6 (28.6) | 0.24 |
| Average length of ICU stay (days) | 2.03±4.91 | 0.50±1.58 | 2.62±5.62 | 0.25 |
| Average length of hospital stay (days) | 7.43±6.45 | 8±3.7 | 7.22±7.25 | 0.75 |
| **Overall outcome** | | | | |
| Recovered | 30 (81) | 9 (90) | 18 (66.7) | 0.22 |
| Expired | 7 (18.9) | 1 (10) | 9 (90) | 0.64 |

*Mann-Whitney U-test.

Trimethoprim/Sulfamethoxazole (TMP-SMX) was used in high doses to treat all cases and dose was adjusted for creatinine clearance if required as per international recommendations. The adjuvant steroid therapy was given to 20(54%) patients due to hypoxaemia. Besides, 8(21.6%) required ICU admission due to either haemodynamic instability or respiratory failure and 7(18.92%) expired in the ICU. Average length of ICU stay was 2.03±4.91 days (range: 1-22days).

The overall mean hospital stay was 7.43±6.45 days (range: 1-34 days).The overall mortality rate was 7(18.9%), with respiratory failure being the leading cause of death. The mortality rate between HIV-positive and HIV-negative patients was not significantly different (p=0.64).

## Discussion

Our study showed that less than one-third of the HIV-negative patients had haematological malignancies and transplants, while almost half of the patients suffered from autoimmune inflammatory diseases. These findings were similar to those shown by Matsumura et al.[17] In our study, there was a smaller proportion of transplant patients while those had undergone transplants usually received prophylaxis, therefore, contributing towards a smaller number of patients with PCP. Previous studies have shown that infection of PCP in HIV-negative patients not receiving prophylaxis is highest in haematological malignancies and transplantation.[8,18] This study showed that low-grade fever was the most common symptom at presentation for PCP.HIV-positive patients presented

with symptoms like fever, cough and dyspnoea more often than HIV-negative patients. However, this finding failed to reach statistical significance. Lowe et al. conducted a meta-analysis to assess PCP status in LMICs.[14] Some of their findings concluded that the predictive value of signs, symptoms and simple diagnostic tests was poor, and case fatality rates were as high as 30%.[14]

Overall, a small number of patients were laboratory tested for PCP in our setting. This may be misleading and reflect an overall low frequency of PCP. However, it should be noted that a total of 112 cases were initially identified from hospital records who had received the diagnostic International Classification of Disease (ICD) code of PCP. A large number of these cases were excluded as they had not undergone laboratory testing and had received empirical treatment for pneumonia along with PCP. Some of the reasons for not using diagnostic studies such as bronchoalveolar lavage and laboratory tests for these patients were cost constraints, refusal to undergo invasive testing and risk of intubation during the procedure. It has been reported previously that the use of available gold standard diagnostic cytological examination of respiratory samples is low and hence affects reported prevalence rates.[14]

In this study, mortality in HIV-negative patients was twice that of HIV-positive patients. This is in accordance with previous studies which have shown that HIV-negative status is known to be associated with an increased mortality in PCP infection when compared to HIV-positive patients.[8,14,19-22] Since PCP in non-HIV population has a higher mortality rate than in HIV-positive individuals, a rigorous prophylactic regimen is needed. Our study showed that a very small proportion of patients received prophylaxis and were therefore susceptible to PCP.

We also observed that a relatively younger population was affected by PCP and male predominance was obvious. However, HIV-negative patients had an overall mean age greater than that of HIV-positive patients. Similar findings were demonstrated in a previous study.[23] Male predominance has been demonstrated in HIV-positive patients affected by PCP.[23]

The main limitation of our study is the small number of patients who were laboratory-confirmed for PCP. Another limitation is that our study did not take into account controls that might have received prophylaxis and had consequently not suffered from PCP.

## Conclusion

Pneumonia due to *pneumocystis jirovecii* was found to be a life-threatening disease in the immunocompromised population. Given the high mortality burden and resource-intensive management of PCP, attention needs to be called towards instituting a rigorous prophylactic regimen in all type of immunosuppressed patients.

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