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Outcomes of *Pneumocystis* pneumonia with respiratory failure in HIV-negative patients

Yousang Ko [a,b], Byeong-Ho Jeong [a], Hye Yun Park [a], Won-Jung Koh [a], Gee Young Suh [a,c], Man Pyo Chung [a], O Jung Kwon [a], Kyeongman Jeon [a,c,*]

[a] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[b] Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea
[c] Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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ABSTRACT

Purpose: The outcomes and predictors of mortality from *Pneumocystis* pneumonia (PCP) in HIV-negative patients requiring mechanical ventilation (MV) for respiratory failure were evaluated.
Materials and Methods: This retrospective observational study enrolled 48 patients with PCP requiring MV in the medical intensive care unit (ICU). Multiple logistic regression analysis was used to identify independent predictors of in-hospital mortality.
Results: The main conditions underlying the PCP were malignancies (60%) or post solid organ transplant (35%). Excluding four patients whose initial treatment was changed due to adverse reactions, 21 (44%) of 44 patients did not respond to the initial treatment. During the ICU stay, additional complications developed: shock in 22 (46%), ventilator-associated pneumonia in 16 (33%), and acute kidney injury in 15 (31%). Ultimately, 31 (65%) patients died while hospitalised. In multivariate analysis, hospital mortality was independently associated with severity of illness on ICU admission, failure of initial antimicrobial treatment for PCP, and newly developed shock during ICU stay.
Conclusions: PCP in HIV-negative patients requiring MV for respiratory failure remains a serious illness with high mortality. Failure of the initial antimicrobial treatment for PCP as well as severity of illness was independent predictors of poor outcomes.

1. Introduction

Pneumocystis pneumonia (PCP), the disease caused by *Pneumocystis jirovecii*, is an opportunistic infection in patients with human immunodeficiency virus (HIV) infection [1]. Patients with mild symptoms of PCP can often be treated as outpatients. However, the development of worsening pneumonia with respiratory failure in these patients is the most common reason for admission to an intensive care unit (ICU) [2,3]. In addition, the mortality increases substantially with the need for mechanical ventilation (MV) [4–6], although the overall mortality has decreased with improved ICU care without the effects of highly active antiretroviral therapy in severely ill patients with PCP admitted to the ICU [6].

PCP is also increasing in patients without HIV infection, as the numbers of patients undergoing transplantation and receiving immunosuppressive therapy and antitumour chemotherapy continue to increase [7–12]. However, the clinical course of PCP differs in patients with or without HIV infection [13]. Typically, HIV-negative patients with PCP present with abrupt-onset respiratory failure [7,9], while HIV-positive patients follow a more insidious course [2,14]. Furthermore, the organism burden and inflammatory response in the lungs differ markedly between the two groups, which contributes to the observed difference in outcomes [15]. Recent reports have indicated that the outcome of patients with respiratory failure requiring MV is worse in HIV-negative patients than in patients with HIV infection [16,17]. Although there are some data on the high mortality, however, data on the predictors of mortality from PCP in HIV-negative patients requiring MV for respiratory failure are limited. Therefore, we evaluated the outcomes and predictors of mortality from PCP in HIV-negative patients requiring MV for respiratory failure.

2. Patients and Methods

We retrospectively reviewed the medical records of all consecutive patients with PCP requiring MV for respiratory failure admitted to the medical ICU of Samsung Medical Centre (a 1,961-bed, university-affiliated, tertiary referral hospital in Seoul, South Korea) between January 2005 and December 2011. The Institutional Review Board of Samsung Medical Centre gave approval for the study to review and

* Corresponding author. Division of Pulmonary and Critical Care Medicine, Department of Medicine and Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 135–710, Republic of Korea.
E-mail address: kjeon@skku.edu (K. Jeon).

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publish information from the patients' records. Informed consent was waived because of the retrospective nature of the study.

2.1. Study population

All consecutive patients older than 20 years admitted to the medical ICU were screened for inclusion in this study. For inclusion, the patients had a microbiologically confirmed diagnosis of PCP and required mechanical ventilation for respiratory failure. In patients with multiple admissions for acute respiratory failure due to PCP during the study period, only the first ICU admission was evaluated. Patients were excluded if they had a positive HIV antibody test.

The diagnosis of PCP was based on the clinical symptoms and abnormalities on chest radiograph or computed tomography (CT), along with the morphological identification of the organism in bronchoalveolar lavage (BAL) fluid or lung tissue obtained by transbronchial lung biopsy (TBLB) or video-assisted thoracic biopsy. BAL fluid samples were stained using Gram and Ziehl-Neelsen methods and then cultured for bacteria, mycobacteria, and fungi. Multiplex nested polymerase chain reaction (PCR) assays were used to detect influenza viruses A and B; parainfluenza viruses 1, 2, and 3; respiratory syncytial virus; and adenovirus [18]. Quantification of CMV DNA in BAL fluid was also performed using quantitative real-time PCR [19]. In addition, CMV and adenovirus were cultured using standard techniques. Microbiological identification of *P. jirovecii* was confirmed by documenting the organism with Wright-Giemsa or Gram-Weigert stain, or the cysts with Gomori methenamine silver or calcofluor white stain [2].

2.2. Data collection

The following ICU admission data were extracted from the medical records: general demographic information, underlying disease, medications during the previous month, PCP prophylaxis, need for renal replacement therapy, need for vasopressor support, anti-PCP medication, and newly developed organ failure during the ICU stay. We also collected laboratory data, including the white blood cell count and absolute neutrophil count (ANC), alveolar-arterial oxygen gradient [D(A-a)O_2], and arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio (PF ratio). Illness severity was assessed using the Simplified Acute Physiology Score 3 (SAPS 3) and Sequential Organ Failure Assessment (SOFA) score [20,21]. Finally, we documented outcomes such as the lengths of the ICU and hospital stays, and ICU and in-hospital mortality.

The doses of corticosteroids used for immunosuppression and as adjunctive therapy for PCP were expressed as the prednisolone-equivalent dose [10]. Adjunctive corticosteroid therapy was defined as use started within 72 h of initiating specific anti-PCP treatment and consisting of at least 40-mg prednisone twice daily for 5 days, regardless of the subsequent tapering schedule, and of the use of corticosteroid before the onset of PCP [22]. Anti-PCP therapy treatment failure was defined as: (1) progressive clinical deterioration as demonstrated by the inability to maintain a stable PaO_2 despite an increase in the FiO_2, and (2) progressive deterioration of vital signs with a requirement for increased FiO_2 after 7 days of therapy [23,24]. Breakthrough PCP infection was defined as PCP diagnosed in a patient receiving prophylactic agents with known activity against *P. jirovecii* administered for at least 7 days before the diagnosis of PCP [25].

2.3. Statistical analysis

The data are presented as medians and interquartile range (IQR) for continuous variables and number (percentage) for categorical variables. The data were compared using the Mann–Whitney *U*-test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Multiple logistic regression analysis was used to identify independent predictors of in-hospital mortality, as measured by the estimated odds ratios (OR) with 95% confidence intervals (CI). Variables with a *P*-value less than 0.2 on univariate analyses [26], as well as *a priori* variables of age and sex were entered into a multiple logistic regression model in which in-hospital mortality was the outcome variable of interest. To reduce the risk of multicollinearity, one closely correlated variable was a candidate for inclusion in the final model. Kaplan–Meier estimation was used to determine the 90-day survival curves for failure of the initial antimicrobial treatment for PCP. All tests were two-sided, and a *P*-value of less than 0.05 was considered to indicate statistical significance. Data were analysed using IBM SPSS Statistics version 20 (IBM, Armonk, NY).

3. Results

During the study period, 61 patients with PCP were admitted to the ICU for respiratory failure requiring MV. Of these, 13 patients were excluded from this study because they had HIV infections. Therefore, 48 HIV-negative patients with PCP who required MV for respiratory failure in the ICU were included in the analysis.

The baseline characteristics of the 48 HIV-negative patients are summarised in Table 1. There were 33 (69%) males and 15 (31%) females, with a median age of 53 (IQR 45–68) years. The main underlying conditions associated with the development of PCP were malignancies (60%) or post solid organ transplant (35%). All patients were immunosuppressed before developing PCP. All patients but one

Table 1
Baseline characteristics of 48 HIV-negative patients with *Pneumocystis* pneumonia requiring mechanical ventilation for respiratory failure

Characteristics	No. of patients (%) or median (IQR)
Age, years	53 (45 – 68)
Gender, male	33 (69)
Underlying disease	
Malignancy	29 (60)
Hematologic	18
Solid	11
Solid organ transplant	17 (35)
Kidney	8
Liver	6
Heart	3
Others*	2 (4)
Immunosuppressive agent use, previous month†	
Corticosteroid	47 (98)
Prednisolone-equivalent dose, mg	41.8 (22.3 – 61.5)
Chemotherapy	24 (50)
T-cell immunosuppressant	22 (46)
Prophylaxis for pneumocystis	14 (29)
Infiltration on chest radiograph	
Unilateral	2 (4)
Bilateral	46 (96)
Laboratory findings on ICU admission	
White blood cells,/μL	7490 (3928 – 10990)
Neutrophils,/μL	5190 (2045 – 9590)
Lymphocytes,/μL	369 (162 – 580)
PaO_2/FiO_2 ratio, mmHg	134.6 (115.1 – 182.3)
D(A-a)O_2, mmHg	38.5 (19.3 – 52.5)
Albumin, g/dL	2.5 (2.2 – 3.0)
LDH, IU/L	823 (659 – 1166)
Organ failures on ICU admission	
Shock	14 (29)
Renal failure requiring renal replacement therapy	1 (2)
Severity of illness	
SAPS 3	46 (37 – 58)
SOFA	7 (5 – 8)

IQR, interquartile range; ICU, intensive care unit; LDH, lactate dehydrogenase; SAPS 3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment.
* Others include drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and Behçet's disease.
† One or more agent may be listed.