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***Retrospective Study***

**Treatment of *Pneumocystis* *jirovecii* pneumonia in non****-human immunodeficiency virus-infected patients using a combination of trimethoprim-sulfamethoxazole and caspofungin**

Wu HH *et al*. Non-HIV-infected PJP

Huan-Huan Wu, Shuang-Yan Fang, Yan-Xiao Chen, Lan-Fang Feng

**Huan-Huan Wu, Shuang-Yan Fang, Yan-Xiao Chen, Lan-Fang Feng,** Department of Respiratory Medicine, Dongyang Hospital Affiliated to Wenzhou Medical University, Dongyang 322100, Zhejiang Province, China

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**Corresponding author: Huan-Huan Wu, MD, Doctor,** Department of Respiratory Medicine, Dongyang Hospital Affiliated to Wenzhou Medical University, No. 60 Wuning West Road, Dongyang 322100, Zhejiang Province, China. huanhuan871002@163.com

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**Abstract**

***BACKGROUND***

*Pneumocystis jirovecii* pneumonia (PJP) is an infectious disease common in immunocompromised hosts. However, the currently, the clinical characteristics of non-HIV patients with PJP infection have not been fully elucidated.

***AIM***

To explore efficacy of trimethoprim–sulfamethoxazole (TMP-SMX) and caspofungin for treatment of non-human immunodeficiency virus (HIV)-infected PJP patients.

***METHODS***

A retrospective study enrolled 22 patients with non-HIV-infected PJP treated with TMP-SMX and caspofungin from 2019 to 2021. Clinical manifestations, treatment and prognosis of the patients were analyzed.

***RESULTS***

Five patients presented with comorbidity of autoimmune diseases, seven with lung cancer, four with lymphoma, two with organ transplantation and four with membranous nephropathy associated with use of immunosuppressive agents. The main clinical manifestations of patients were fever, dry cough, and progressive dyspnea. All patients presented with acute onset and respiratory failure. The most common imaging manifestation was ground glass opacity around the hilar, mainly in the upper lobe. All patients were diagnosed using next-generation sequencing, and were treated with a combination of TMP-SMX and caspofungin. Among them, 17 patients received short-term adjuvant glucocorticoid therapy. All patients recovered well and were discharged from hospital.

***CONCLUSION***

Non-HIV-infected PJP have rapid disease progression, high risk of respiratory failure, and high mortality. Combination of TMP-SMX and caspofungin can effectively treat severe non-HIV-infected PJP patients with respiratory failure.

**Key Words:** Acquired immunodeficiency syndrome; Non-human immunodeficiency virus-infected patients; Immunosuppression; caspofungin; Mortality; *Pneumocystis jirovecii* pneumonia

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**Core tip:** *Pneumocystis* *jirovecii* pneumonia (PJP) is common in immunocompromised hosts. However, the clinical characteristics of non-human immunodeficiency virus (HIV) infected PJP patients have not been fully elucidated. This was a retrospective study of non-HIV-infected PJP treated with trimethoprim–sulfamethoxazole (TMP-SMX) and caspofungin. Clinical manifestations, treatment and prognosis of the patients were evaluated. Non-HIV-infected PJP patients are characterized by rapid disease progression, high risk of respiratory failure, and high mortality. Early diagnosis and treatment can improve survival in non-HIV-infected PJP patients. The findings of the current study showed that combination of TMP-SMX and caspofungin is effective for non-HIV-infected PJP patients with respiratory failure.

**INTRODUCTION**

Approximately 75% of patients infected with human immunodeficiency virus (HIV) positive present with *Pneumocystis* *jirovecii* pneumonia (PJP) during the early stages of the infection[1]. Technological advancements in medicine have led to development of effective therapies that have significantly reduced the incidence of PJP in patients with acquired immunodeficiency syndrome (AIDS). For example, the CD4+ T lymphocyte counts have been shown to be accurate in identifying patients at high clinical risk of developing PJP[2]. In addition, prophylaxis interventions have been designed for patients at risk of PJP[3] and sensitive immunofluorescence detection methods are now available for timely detection. The development of combined antiretroviral therapy drugs has significantly reduced incidence of PJP and improved prognosis of HIV-positive PJP (HIV + PJP) patients[4]. Clinically, the number of non-HIV-infected PJP patients has been on the rise annually owing to the increased use of immunosuppressants and organ transplantations[5,6]. The mortality levels of non-HIV-infected PJP patients ranges between 30% and 60%, whereas the mortality of HIV + PJP patients ranges between 10% and 20%[7]. In comparison, management measures for non-HIV-infected PJP are not standardized as is the case for HIV + PJP patients. Moreover, the clinical attention for non-HIV-infected patients is poorer compared with that of HIV + PJP patients.

The aim of this retrospective study was to explore the characteristics of non-HIV-infected PJP treated with trimethoprim–sulfamethoxazole (TMP-SMX) and caspofungin. The findings of this study are expected to improve our understanding of the occurrence of PJP in non-HIV-infected patients, and thus prevent misdiagnosis and reduce mortality rate of non-HIV-infected PJP patients.

**MATERIALS AND METHODS**

***Study design***

A retrospective case review of 22 non-HIV-infected PJP patients admitted to Dongyang Hospital Affiliated to Wenzhou Medical University, a tertiary hospital in Zhejiang, China was carried out between October 2019 and April 2021. Patient data including symptoms, laboratory results**,** dynamic and comprehensive computed tomography data, and clinical course of the disease were extracted from electronic medical records. Information on treatment, response to treatment, outcomes, and any follow-up data were also collected. The study protocol was approved by the Ethics Committee of the Dongyang Hospital Affiliated to Wenzhou Medical University, (No. 2021-YX-127). All data were anonymized prior to analysis.

**RESULTS**

***Patient characteristics***

In total, four women and 18 men diagnosed as non-HIV-infected PJP were enrolled in the study. The median age of these patients was 61.18 ± 16.51 (range 17–84) years (Table 1). All patients tested positive for *Pneumocystis jiroveciiPneumocystis jirovecii* DNA fragments as determined using metagenomic next-generation sequencing (mNGS). Systematic screening did not identify any other respiratory pathogens at the time of hospital admission. All patients presented with dry cough and dyspnea, whereas 13 patients had fever. The median time from onset of illness to admission was 5.68 ± 3.66 (range 1–15) d. On physical examination, the patients presented with heterogeneous and nonspecific clinical signs. Among the comorbidities found were autoimmune disease (*n* = 5), non-Hodgkin’s lymphoma (*n* = 4), lung cancer (*n* = 7; all underwent chest radiotherapy), organ transplantation (*n* = 2), and membranous nephropathy (*n* = 4). All patients developed respiratory failure and received oxygen therapy (oxygen therapy, administered nasally for 11 patients, mask oxygen therapy for 10 patients, and high flow nasal cannula therapy for 1 patient). No patient received invasive mechanical ventilation.

***Technical investigations***

Clinical examination carried out at admission showed that patients had a mean white blood cell count of 9.69 ± 6.22 × 109/L and with a proportion of neutrophils of 0.82 ± 0.14%. In addition, C-reactive protein level was 79.69 ± 64.21 mg/L, lactate dehydrogenase (LDH) level was 408.23 ± 117.87 U/L, and procalcitonin level was 0.23 ± 0.21 ng/mL.

Lung imaging revealed lesions in the upper lobe of lung in the early stage. With progression of the disease, the lesions spread to the lower lobe of the lung. The most common imaging manifestation was widespread ground glass opacity, which had a mosaic or diffuses distribution, mainly in the upper lobe of the lung (Figures 1 and 2).

***Treatment***

Analysis of medical records showed that most of the patients were treated with antibiotics such as cephalosporin prior to admission. However, their symptoms gradually deteriorated leading to development of progressive dyspnea. After hospital admission, patients underwent bronchofibroscopy and alveolar lavage fluid was collected for mNGS analysis.

mNGS analysis was carried out within 48–72 h from the time of sample collection to the time results were reported. After confirmation of PJP, treatment was changed to TMP-SMX (TMP, 15–20 mg/kg/d; SMX, 75–100 mg/kg/d), administered for at least 2 wk, as reported previously[8].Patients received TMP-SMX combined with caspofungin (through intravenous administration of 70 mg QD on the first day and 50 mg QD as the maintenance dose afterwards) for those with respiratory failure or renal insufficiency. In addition, moderate to severe non-HIV-infected PJP patients received glucocorticoid treatment (*n* = 17) for 1 wk.

***Outcomes***

After initiation of therapy, the body temperature gradually returned to normal within 3 d, and their respiratory function improved. Further analysis revealed that the level of inflammatory indices in blood significantly decreased, and the lung lesions gradually disappeared following treatment. All patients had fully recovered before discharge.

**DISCUSSION**

The incidence of PJP is high among immunocompromised HIV-negative patients. This calls for development of novel diagnostic, treatment, and prevention strategies for non-HIV-infected PJP[9-11]. Non-HIV-infected PJP patients have an acute onset, rapid disease progression, poor prognosis, and higher mortality rates compared with HIV-infected PJP patients[12-16].

The population of HIV-negative patients susceptible to *Pneumocystis jirovecii* includes patients who have undergone transplantation, hemato-oncological patients, and those taking immunosuppressive drugs for autoimmune diseases. Approximately 20% of non-HIV-infected PJP patients are those with autoimmune diseases, mainly nodular polyarteritis, granuloma with polyarteritis, dermatomyositis/polymyositis, and rheumatoid arthritis with interstitial pneumonia[17,18]. So far, several drugs such as, long-term use of medium and high-dose glucocorticoids, cyclophosphamide, rituximab, alemtuzumab (a monoclonal antibody used for treatment of chronic B-cell lymphoblastic leukemia and multiple sclerosis), and tumor necrosis factor α antagonists have been linked to the occurrence of PJP[19,20].

The main symptoms of non-HIV-infected PJP patients include fever, dyspnea and dry cough. Moreover, hypoxia and respiratory failure are more common in non-HIV-infected PJP patients compared with HIV-infected PJP patients. However, frequency of LDH elevation is lower, the onset and disease progression are more rapid (often within a few days) in non-HIV-infected PJP than in HIV-infected PJP. For non-HIV-infected PJP patients, physical examination is nonspecific, and lung auscultation is usually normal, but often inconsistent for those with severe clinical manifestations[21]. Computed tomography (CT) scans show ground-glass opacity (GGO), mainly presenting with a central distribution, is a common radiological pattern for PJP patients. These manifestations were observed in patients included in the current study (Figure 1). GGOs may present as a mosaic-like distribution or diffuse distribution, more commonly occurring in the upper lobes of the lungs[22]. In the advanced stages of the disease, CT scans show lung consolidation. Paving stone-like manifestations are observed in 6%–18% of patients[23]. Hollowness and pleural effusion are rare, and if they occur, they often indicate existence of other diseases[23]. Approximately 3%–6% of non-HIV-infected PJP patients may present with lung cyst-like changes of different shapes, sizes, and wall thicknesses, implying that they are susceptible to spontaneous pneumothorax[23]. GGOs in non-HIV-infected PJP patients spread faster compared than in HIV-infected PJP patients.

*Pneumocystis jirovecii* cannot be cultured in the laboratory. Therefore, this infection has been traditionally diagnosed based on microscopic observation of the organisms in respiratory specimens. However, due to the lower pathogen burden in non-HIV-infected PJP patients compared with HIV-infected PJP patients, specimens from non-HIV-infected PJP patients have lower microscopic sensitivity[24,25]. A combination of different diagnostic methods, such as microscopy, polymerase chain reaction, and (1,3)-β-D-glucan detection have been previously adopted to increase the diagnosis rate. Silver staining can detect cysts with high specificity. However, the sensitivity of this method is not satisfactory. PJP patients have a higher number of trophozoites than cysts, thus Giemsa and Diff-Quik stains used for the detection of trophozoites should have high sensitivity. Moreover, the results depend on the skill and experience of the examiner. Advances in technology have led to development of mNGS which can unbiasedly detect various pathogenic microorganisms in clinical samples. This approach ensures rapid screening of pathogens, and provides timely identification of pathogens. Therefore, it is currently applied in the detection of pathogens that cause infectious diseases. Bronchoalveolar lavage fluid (BALF) is the preferred specimen, as BALF provides a higher diagnosis rate, and can be used to identify other pathogens, such as tuberculosis, histoplasmosis and cytomegalovirus infection. Induced sputum testing can be used as an alternative method if the patient cannot tolerate bronchoscopy, however, its diagnostic sensitivity is lower compared to that of BALF (55%–90%)[26,27].

Current guidelines and published reviews state that the first-line treatment for non-HIV-infected PJP is TMP-SMX[7,8,28]. However, prolonged use of TMP-SMX may increase risk of drug resistance and side effects. Some patients cannot tolerate high doses of this treatment however, low-dose therapy is well-tolerated and has fewer side effects[29]. In the current study, one patient developed renal impairment during treatment, but renal function was restored when the dosage was reduced. Therefore, the dose of TMP-SMX should be adjusted based on the renal function of the patient. If the patient is taking immunosuppressants during treatment, the dose of immunosuppressants should be reduced, suspended, or stopped. However, the dose should be individualized. Previous studies have shown that caspofungin alone or in combination with TMP-SMX is effective for HIV-infected PJP patients, and caspofungin can also be used as a remedial drug[30,31]. In the current study, all patients were successfully treated with caspofungin combined with TMP-SMX. This finding indicates that caspofungin can cure PJP; however, these findings should be validated in large-sample clinical studies. According to current guidelines, standard treatment should be used for 2–3 wk[8]. The duration should be appropriately extended until respiratory function is stable for non-HIV-infected PJP patients with severe immunosuppression, high pneumocystis load, and slow clinical improvement[8,28]. Non-HIV-infected PJP patients present with severe inflammation and some studies recommend use of adjuvant glucocorticoid to control it[31]. In the current study, 17 patients underwent adjuvant treatment of glucocorticoids for 7 d with good results. This indicates that patients with moderate to severe disease should be put under adjunctive corticosteroids to improve survival.

**CONCLUSION**

Non-HIV-infected PJP patients manifest with rapid disease progression, respiratory failure, and high mortality. Physicians should be aware that PJP is an important infectious complication in hemato-oncological and post-transplant patients, including who undergo solid organ transplant, allogenic or autologous hematopoietic stem cell transplantation. It is also common in patients taking immunosuppressive drugs. For non-HIV-infected PJP patients with respiratory failure, or patients with renal insufficiency, TMP-SMX combined with caspofungin can alleviate symptoms and accelerate recovery. Several challenges are encountered in the treatment of non-HIV-infected PJP patients, such as difficulty of determining the timing and duration of adjunctive treatment using glucocorticoids and identification of patients susceptible to *pneumocystis jirovecii* infection. Therefore, future studies should explore methods to circumvent these challenges.

**ARTICLE HIGHLIGHTS**

***Research background***

Incidence of non-human immunodeficiency virus (HIV)-infected *Pneumocystis jirovecii* pneumonia (PJP) patients has been increasing annually owing to increased use of immunosuppressants and organ transplantation. In addition, management of non-HIV-infected PJP patients is not standardized as it is the case for HIV-infected PJP patients, and the clinical attention is poor compared with that of HIV-infected PJP patients.

***Research motivation***

The aim of this retrospective study was to explore the characteristics of non-HIV-infected PJP treated with trimethoprim–sulfamethoxazole (TMP-SMX) and caspofungin.

***Research objectives***

The findings of the current study will improve understanding of PJP in non-HIV-infected patients, and reduce misdiagnosis rate and mortality rate of non-HIV-infected PJP patients.

***Research methods***

A retrospective case review of 22 non-HIV-infected PJP patients admitted to Dongyang Hospital Affiliated to Wenzhou Medical University was conducted between October 2019 and April 2021. Patient data on symptoms, laboratory results, dynamic and comprehensive computed tomography, and clinical course of the disease were extracted from electronic medical records. Additional data on treatment, response to treatment, outcomes, and any relevant follow-up data were also collected.

***Research results***

A total of 22 cases of non-HIV-infected PJP were included in the current study. Clinical manifestations of patients mainly included fever, dry cough, and progressive dyspnea. All patients presented with an acute onset and respiratory failure. The most common imaging manifestation was ground glass opacity around the hilar, mainly located in the upper lobe. All patients underwent diagnosis using next-generation sequencing, and were all treated with TMP-SMX and caspofungin. Seventeen patients received short-term adjuvant glucocorticoid therapy. All patients recovered and were discharged from hospital.

***Research conclusions***

Non-HIV-infected PJP patients are characterized by rapid disease progression, high risk of respiratory failure, and high mortality. The findings of the current study showed that a combination of TMP-SMX and caspofungin is an effective treatment option for severe non-HIV-infected PJP patients with respiratory failure.

***Research perspectives***

The timing and duration of adjunctive treatment using glucocorticoids and identification of patients susceptible to *Pneumocystis jirovecii* infection at an early stage to start effective prophylaxis drugs.

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**Footnotes**

**Institutional review board statement:** The study protocol was approved by the Ethics Committee of the Dongyang Hospital Affiliated to Wenzhou Medical University (No. 2021-YX-127).

**Conflict-of-interest statement:** The authors declare that they have no competing interests.

**Data sharing statement:** All data generated or analyzed during this study are included in this published article.

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**Figure Legends**

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**Figure 1 A 76-year-old man with rheumatic polymyalgia who under 8 mg/wk methotrexate treatment attended our hospital with complaints of cough and fever.** A: The patient presented with respiratory failure and received 3 L/min oxygen therapy nasally. Computed tomography (CT) indicated bilateral infiltration dominantly in the hilum. The patient received bronchoscopy the day after admission. Next-generation sequencing analysis of the bronchoalveolar lavage fluid was positive for *Pneumocystis jirovecii*. The patient was diagnosed with severe non-human immunodeficiency virus-infected *Pneumocystis jirovecii* pneumonia. Daily oral administration of 12 mg/kg trimethoprim (TMP) and 60 mg/kg sulfamethoxazole (SMX) [oral administration of two tablets of TMP (80 mg) and SMX (400 mg), four times daily] and caspofungin (intravenous administration of 70 mg QD for the first day and 50 mg QD for maintenance) was initiated and continued for 14 d without any adverse events; B: The respiratory status of the patient improved gradually. CT at 14 d after start of treatment showed restoration of respiration. The patient was discharged on day 18 of hospitalization.



**Figure 2 A 62-year-old woman with membranous nephropathy who was undergoing treatment with 15 mg/d methylprednisolone was admitted to our hospital with complaints of cough and dyspnea.** A: The patient presented with respiratory failure and received 5 L/min mask oxygen therapy. Computed tomography (CT) showed bilateral infiltration dominantly in the hilum. The patient received bronchoscopy 1 d after admission. Next-generation sequencing of using bronchoalveolar lavage fluid sample was positive for *Pneumocystis jirovecii*, thus the patient was diagnosed with severe non- human immunodeficiency virus-infected *Pneumocystis jirovecii* pneumonia. Daily oral administration of trimethoprim–sulfamethoxazole (TMP-SMX) [oral administration of two tablets of TMP (80 mg) and SMX (400 mg), twice daily, adjusted based on renal function] and caspofungin (intravenous administration of 70 mg QD for the first day and 50 mg QD for maintenance) was initiated and continued for 14 d without any adverse events; B-D: The respiratory status of the patient improved gradually, and CT showed that respiratory function was restored at the last day of treatment.

**Table 1 Clinical characteristics of *Pneumocystis jirovecii* pneumonia cases**

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| **Characteristics** | **Patients, *n* (%)** | **Median value (range)** |
| Demographics |  |  |
| Male/female | 18/4 |  |
| Age, median (range, yr) |  | 61.18 ± 16.51 |
| Underlying disease | 22/22 |  |
| Clinical manifestations  |  |  |
| Fever | 13/22 |  |
| Cough | 22/22 |  |
| Dyspnea | 22/22 |  |
| Laboratory tests |  |  |
| WBC (normal 4 × 109–10 × 109/L) |  | 9.69 ± 6.22 |
| Percentage of neutrophils |  | 0.82 ± 0.14 |
| CRP (normal 0–8 mg/L) |  | 79.69 ± 64.21 |
| PCT (normal 0–0.5 ng/mL) |  | 0.23 ± 0.21 |
| LDH (normal 120–250 U/L) |  | 408.23 ± 117.87 |
| Oxygenation index |  | 209.55 ± 35.03 |
| CD4+ T lymphocyte counts |  | 0.81 ± 0.52 |
| Imaging |  |  |
| Diffuse ground glass opacity | 19/22 (86.36%) |  |
| Streak like dense shadow | 3/22 (13.64%) |  |
| Complete CT recovery in survivors | 22/22 (100.0%) |  |

CRP: C-reactive protein; CT: Computed tomography; PCT: Procalcitonin; WBC: White blood cell; LDH: Lactate dehydrogenase.