Original Article

**Pneumocystis jirovecii** pneumonia in AIDS and non-AIDS immunocompromised patients – an update

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**Abstract**

Introduction: *Pneumocystis jirovecii* (PJ) pneumonia (PJP) is an important opportunistic infection affecting various types of immunocompromised patients and is associated with an increased risk of mortality. PJ is a unique fungal pathogen which is increasingly common and maybe associated with a higher mortality rate in patients without AIDS. We present the characteristics of PJP, diagnosis, and treatment outcomes between AIDS and non-AIDS patients.

Methodology: We conducted a review of studies of AIDS and non-AIDS patients with PJP using PubMed to search for studies until December 2017.

Results: The annual incidence of AIDS-PJP decreased from 13.4 to 3.3 per 1000 person-years in industrialized countries, while the incidence of non-AIDS-PJP varied widely. Both groups had similar clinical manifestations and radiological features, but the non-AIDS-PJP group potentially had a more fulminant course, more diffuse ground glass opacities, and fewer cystic lesions. The mortality rate decreased in the AIDS-PJP group after the advent of antiretroviral therapy; however, the mortality rate remained high in both groups. A laboratory diagnosis was usually nonspecific; CD4+ T-cell < 200 cells/mL or < 14% favored AIDS-PJP. Serum 1,3-β-D-glucan (BDG) had a high diagnostic odds ratio. Combining BDG and lactic dehydrogenase improved the diagnosis of AIDS-PJP. Histopathological staining and polymerase chain reactions could not discriminate infection from colonization when the result was positive. The use of antibiotics, prophylaxis, and adjunctive corticosteroids was controversial.

Conclusions: Early diagnosis and treatment can be achieved through vigilance, thereby improving the survival rate for PJP in immunocompromised patients.

**Key words:** human immunodeficiency virus; acquired immunodeficiency syndrome; immunocompromised host; *Pneumocystis jirovecii* pneumonia; mortality.


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**Introduction**

*Pneumocystis jirovecii* (PJ) pneumonia (PJP) is an opportunistic fungal infection that is associated with a high mortality rate in immunocompromised patients, including those with acquired immunodeficiency syndrome (AIDS) and those without AIDS (non-AIDS). The non-AIDS group includes patients with innate or acquired immunodepression such as those receiving long-term or high-dose corticosteroids or immune suppression treatment (monoclonal antibody therapy) for autoimmune diseases, those with solid-organ or hematologic malignancies receiving hematopoietic stem cell transplantation, and those with bone marrow or solid-organ transplantations [1,2]. Good syndrome [3], DiGeorge syndrome and common variable immunodeficiency [4], severe combined immunodeficiency [5], and protein-calorie malnutrition [6] are also associated with PJP.

In the case of PJP, clinical studies have shown that the clinical course of non-AIDS-PJP is potentially fulminant, and that the prognosis can be poor if the diagnosis of PJP is delayed, thereby resulting in poor outcomes [1,2]. Therefore, we conducted this review of studies of immunocompromised patients with and without AIDS with PJP. We used the PubMed database to search for studies until December 2017. The aim of this review was to raise the awareness of clinicians and intensivists so that they can make an early diagnosis of...
PJP by comparing the differences in clinical manifestations and pathogenesis of hypoxemia between patients with AIDS and non-AIDS-related PJP. We also discuss the challenges of making a diagnosis and the treatment of PJP.

Methodology

Search Strategy

We conducted a systematic review of studies of immunocompromised patients with and without AIDS with PJP. Data collected from the studies included patient demographics, methods of diagnosis, treatment details, duration of treatment, microbiologic response, presence of respiratory failure, cause of death related pneumocystis, and mortality. We used the PubMed database to search for studies using the following combinations of search items: pneumocystis AND (classical article OR clinical study OR clinical trial OR controlled clinical trial OR editorial OR journal article OR guideline OR letter OR meta-analysis OR review OR scientific integrity review OR systematic OR validation studies) AND (free full text AND full text) AND (humans) AND (English) AND (Medline) AND studies published from January, 1970 to December, 2017. A total of 5913 articles were identified. Of these, a total 487 items were included based on the following criteria.

Inclusion and exclusion criteria

The inclusion criteria for the review were: 1) all classical articles, clinical studies, clinical trials, journal articles, meta-analyses, multicenter studies, observational studies, scientific integrity reviews, systematic reviews, randomized controlled trials or practice guidelines; 2) studies evaluating AIDS or non-AIDS patients with the diagnosis of PJP; 3) studies in which patients were treated with PJ therapy; 4) studies in which microbiologic response was measured; and 5) studies which reported the presence of respiratory failure, cause of death related to pneumocystis, and mortality. The exclusion criteria were studies published in the form of a letter, comment, editorial, case report, proceedings, and personal communications, or studies without quantitative primary outcomes. We reviewed and eliminated 440 articles, and retained 48 articles (Figure 1). Of the 48 articles, we screened the references listed in the review papers to find further relevant studies. Another 12 references were selected. A total of 60 publications were identified (Figure 1).

Results

Organism and transmission route

The PJ organism, previously known as Pneumocystis carinii, was thought to be a primary infection occurring in young children. PJP occurred due to a reactivation of a latent infection when the host’s immune system was compromised [7]. The primary route of PJ transmission has yet to be determined conclusively [8]. It is also possible that PJ infection can occur due to airborne transmission from the respiratory tract of other mammals and humans [7,9]. A study stated that PJ isolates were found in the air surrounding PJP patients and from the environment of hospitals where PJ patients were admitted [9]. Several outbreaks of PJP have been reported among organ transplant recipients or non-AIDS immunocompromised patients [8]. Interhuman transmission of PJ may lead to nosocomial outbreak infections of varying prevalence and the spread of sulfa drug-resistant strains [7].
**Epidemiology and risk factors for Pneumocystis jirovecii pneumonia**

The global incidence of PJP is estimated to be more than 400,000 cases per year [10]. With antiretroviral therapy (ART) and the use of anti-pneumocystis prophylaxis, the incidence of AIDS-PJP significantly declined from 95 to 8.4 per 1000 person-years from 1993 to 2008 [11]. In industrialized countries, the annual incidence of AIDS-PJP decreased from 13.4 cases/1000 AIDS patients to 3.3 cases/1000 AIDS patients (p < 0.001) from 2000 to 2013 [12]. One meta-analysis reported a positive relationship between the gross domestic product and the diagnosis of AIDS-PJP in tropical and middle income countries due to a lack of resources to report such cases in poor countries [13]. The authors also indicated that prophylaxis appeared to reduce the risk of developing PJP in adults [13]. The associated risk factors for AIDS-PJP included CD4+ T-cell count ≤ 200 cells/mL or ≤ 14%, history of oropharyngeal candidiasis, previous episode of PJP, history of unexplained fever, recurrent bacterial pneumonia, unintentional weight loss, and high levels of plasma HIV RNA [14] (Table 1).

With the increasing use of corticosteroids, chemotherapy, and other immunosuppressive treatments, the incidence of non-AIDS-PJP varies widely [15]. An observational cohort study on 293 PJP patients including 154 non-AIDS-PJP patients reported that 32.5% had hematological malignancies, 18.2% had solid tumors, 14.9% had inflammatory diseases, 12.3% had solid organ transplants, and 9.7% had vasculitis. The annual incidence rate was estimated and stratified into three groups: 1) high risk, defined as > 45/100,000 patients with polyarteritis nodosa, granulomatosis with polyangiitis, polymyositis/dermatopolymyositis, acute leukemia, chronic lymphocytic leukemia, or non-Hodgkin lymphoma; 2) intermediate risk, defined as 25-45/100,000 patients with Waldenström macroglobulinemia, multiple myeloma, or central nervous system cancer; and 3) low risk, defined as < 25/100,000 patients with other solid tumors, inflammatory diseases, or Hodgkin lymphoma [15]. This stratification may be used to guide anti-pneumocystis prophylaxis for non-AIDS-PJP [15].

**Pathogenesis of infection and hypoxemia**

Both groups had similar clinical manifestations and radiological features but different courses and outcomes. The life cycle of PJ remains elusive [16], but it was presumed to play a particularly critical role in the pathogenesis in one clinical study [17]. This is may be due to the different pathogenesis of infection and hypoxemia.

**Infection**

A large number of neutrophils was noted in the non-AIDS-PJP group, which may have been caused by trophic forms of PJ, in which the capability to bind type I alveolar cells is strong enough to cause overwhelming alveolar inflammation [18]. There were few PJ cysts inside the alveoli [17] because there was not enough time for the cysts to grow. In contrast, there were fewer neutrophils in the alveoli of the patients with AIDS-PJP.

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**Table 1. Comparisons of Pneumocystis jirovecii pneumonia with regards to the epidemiology, risk factors, clinical characteristics, and pathogenesis between the patients with and without AIDS.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>AIDS</th>
<th>Non-AIDS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, per 1000 person-years</td>
<td>Decline from 95 to 8.4; Decline 3.4 to 3.3 in the industrialized countries</td>
<td>45-25</td>
<td>[11], [12], [15]</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>Fever, respiratory symptoms (dry cough, dyspnea), gradual, insidious progression</td>
<td>Similar clinical manifestations, fulminant course</td>
<td>[1], [2], [16], [20], [22], [23]</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Significant Pneumocystis cyst formation within the alveoli of the lung and fewer neutrophils recovered in BAL fluid</td>
<td>Few Pneumocystis cysts and abundant neutrophils, reflecting more severe lung inflammation</td>
<td>[16-19]</td>
</tr>
<tr>
<td>Risk factors</td>
<td>CD4 lymphocyte count ≤ 200 cells/mL or ≤ 14%, history of oropharyngeal candidiasis, previous episode of PJP, history of unexplained fever, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV viral load levels</td>
<td>CD4 lymphocyte counts variety, long-term or high-dose corticosteroids use, immune suppression treatment for autoimmune disease, solid or hematologic malignancies, BMT or SOT, also seen in Good syndrome, DiGeorge syndrome, common variable immunodeficiency, severe combined immunodeficiency, and Protein-calorie malnutrition</td>
<td>[1-6], [14], [15]</td>
</tr>
</tbody>
</table>

BAL: Bronchoalveolar lavage; BMT: bone marrow transplantations; HIV: human immunodeficiency virus; PJP: Pneumocystis jirovecii Pneumonia; SOT: solid-organ transplantations.
so that the alveolar inflammation was not so fulminant, thereby allowing cysts to grow over time [17].

**Hypoxemia**

Several studies reported that hypoxemia was induced by true intrapulmonary shunting after alveolar inflammation [18,19]. Since the infection caused different levels of pulmonary inflammation between the non-AIDS and AIDS patients [17-19], it was not surprising that the patients with non-AIDS-PJP had more severe hypoxemia than those with AIDS-PJP. Respiratory failure ensued within 5-7 days of symptom onset [18], thereby requiring a higher oxygen flow and more frequent invasive mechanical ventilation [17]. In the patients with AIDS, hypoxemia progressed slowly at approximately 3 weeks after symptom onset [19], and mechanical ventilation was required less frequently, and thus more people survived [19]. Further studies are needed to confirm these pathophysiological assumptions.

**Clinical manifestations**

The constitutional and respiratory symptoms and signs and findings of chest radiography (CXR) and computed tomography (CT) were nonspecific and similar in the early stage between the two groups [1,2,19]. However, there were some clues that tended to favor one over the other (Figure 2).

**Symptoms**

The symptoms of PJP ranged from a subtle onset of progressive dyspnea, nonproductive cough, low-grade fever, and loss of body weight to acute onset of dyspnea and pleuritic chest pain [2,19]. Bienvenu et al. reported that the most common symptoms in both patients with AIDS-PJP and non-AIDS-PJP were dyspnea (66%), fever (65%), and cough (55%) [2]. Approximately one third of these patients presented with these three symptoms, one third presented with two symptoms, and one third had one symptom. Of note, approximately one tenth of the patients did not develop any of the three typical symptoms [2]. The frequency of fever was similar between the two groups; however, the AIDS-PJP group developed a more gradual onset of dry cough and dyspnea [2], while the non-AIDS-PJP group presented with a more fulminant course and atypical manifestations [1,16,20]. The time from symptom onset to seeking medical consultation was 21 days for the patients with AIDS and 5 days for those without AIDS, with times to a diagnosis of PJP of 30 and 7 days, respectively [1]. The time delay to initiate treatment for PJP was 2 days [95% confidence interval (CI), 0-6] and 1 day [95% CI, 0-2], respectively [1] (Table 1).

**Signs**

The signs associated with PJP were also nonspecific in both groups, and may have included fever, tachypnea, and inspiratory crackles. Of note, chest physical examinations were unremarkable in half of the patients [19]. Oropharyngeal candidiasis was a common co-infection and indicated the immunodeficiency status and the risk of developing PJP, thereby indicating the need to start primary prophylaxis for PJP [14,21]. There were some unusual extrapulmonary features including retinitis, digital necrosis, and space occupying lesions of the liver, spleen, kidney, and brain [22]. The incidence of

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**Figure 2.** Flowchart of clinical characteristics, diagnosis, management, and outcome of *Pneumocystis jiroveci* pneumonia in the immunocompromised patients.

extrapulmonary features was < 2.5% in the AIDS-PJP group and even lower in the non-AIDS-PJP group [22,23].

**Radiological features**

**Chest radiography**

The patterns of CXR were similar for PJP in both groups [1,2]. The typical CXR pattern was bilateral symmetric perihilar interstitial infiltrates or extensive ground glass opacity (GGO) [23,24]. As the disease progressed, the lesions emanated from the hila to the periphery forming a butterfly pattern. The other presentations included alveolar consolidation, asymmetrical infiltrates, finely granular, reticular, and military lesions, cavities, intrathoracic adenopathy, pleural effusions, and pneumothorax [25]. Nevertheless, PJP often spared apical regions except in the cases of prophylactic pentamidine inhalation [22]. A typical pattern of extensive GGO and a presentation of oropharyngeal candidiasis and/or CD4+ T-cell count ≤ 250 cells/mL or ≤ 14% should raise the suspicion of AIDS-PJP [21]. Comparing the CXR in the two groups, the AIDS-PJP group had a more diffuse pattern, large-sized ground glass nodules (5-10 mm), and intrathoracic adenopathy [26]. Of note, a normal CXR did not eliminate the diagnosis of PJP, as it was noted in approximately 40% of the AIDS-PJP group in the early stage [24]. This may be related to a temporal effect.

**Chest computed tomography**

In general, chest high-resolution computed tomography (HRCT) is the most reliable diagnostic tool in detecting and differentiating intestinal or diffuse parenchymal lung diseases in immunocompromised hosts [27,28]. In the AIDS-PJP group, HRCT typically demonstrated the characteristic GGOs [25]. The atypical manifestations included sub-pleural nodules, focal condensation, cavitations, and marked pleural effusions [1]. The incidence of atypical chest CT findings was rare (5%), and the number of cases who were eventually confirmed to have co-infection with bacteria was even lower (1%) with other opportunistic microorganisms. Hence, atypical radiographic findings indicate the need for advanced diagnostic investigations and the concomitant administration of broad-spectrum antimicrobials [1,29]. Nevertheless, HRCT had a high negative predictive value, thereby excluding PJP should the findings be normal, equivocal, or nonspecific [29].

In the non-AIDS-PJP group, GGOs were more centrally distributed while relatively sparing the periphery in 43% (n = 36) of the patients, apical predominance in 86% (n = 71) [27], a mosaic pattern in 57% (n = 48), parenchymal consolidations in 17% (n = 14), and fine reticulation and traction bronchiectasis in only 6% of the patients (n = 5). Compared with the AIDS-PJP group, the non-AIDS-PJP group had more frequent diffuse GGO lesions (86% versus 44%, p = 0.02) and less frequent cystic lesions (3% versus 56%, p = 0.015) [30]. This may also have been related to a temporal effect. In the non-AIDS group, the severity of PJP could be assessed by HRCT, thereby predicting survival [28].

**Laboratory diagnosis**

**CD4+ T-cell count**

Immune status as assessed by CD4+ T-cell count could also serve as a clue for the suspicion of PJP in the patients with AIDS, but not in those without AIDS [1,16]. A CD4+ T-cell count < 200 cells/mL indicated the potential development and progression of PJP [16,21]. Therefore, the CD4+ T-cell count may guide clinicians as to whether to use or discontinue PJP prophylaxis.

**Histopathology staining methods**

Since PJ organisms are not cultivatable, a definitive diagnosis relies on positive staining for PJ using conventional staining methods such as the Grocott-Grocott test, toluidine blue stain, or a direct immunofluorescence assay (DFA) from induced sputum, bronchoalveolar lavage (BAL) fluid, or lung biopsy specimens [1]. These staining methods for PJP are more suitable for patients with AIDS than those without AIDS due to the number of PJ cysts in the alveoli [17]. However, these staining methods cannot discriminate infection from colonization when the result is positive [20].

**Polymerase chain reaction (PCR)**

The first study to use a real-time PCR assay to diagnose PJP used a semi-quantitative PCR, and the results showed that it could distinguish colonization, sub-clinical infection, and PJP, and the authors suggested that PJP could be excluded if the PCR results were negative, and that this could be used instead of DFA [31]. PCR-based methods had a higher sensitivity than conventional staining methods and were therefore good tools to exclude PJ in BAL fluid and induced sputum. However, they were still unable to discriminate infection from colonization when the results were positive [32]. Therefore, these methods appear to be more suitable for patients without AIDS than those with AIDS, as the number of PJ cysts in the alveoli is small.
Another study reported that a positive real-time PCR result may indicate the development of long-term emphysema [7]. Quantitative real-time PCR (qPCR) assays were very sensitive to detect PJ in BAL fluid [32], and they were able to distinguish between infection and colonization [32]. However, the definition of the threshold value of fungal load for the diagnosis of PJP was problematic, and the accuracy of qPCR was affected by underlying diseases [32]. Moreover, the timing of the collection of sputum or BAL fluid affected the accuracy of the PCR test. Samples collected during or after anti-pneumocystis therapy may have caused false negative results. Hence, samples should be collected in a timely manner [33].

**Serum 1,3-β-D-glucan (BDG)**

Serum BDG assays appeared to be a promising alternative approach to diagnose PJP [34-37], and they could be used as a screening tool for PJP to avoid unnecessary invasive procedures such as BAL in patients with AIDS [34,36]. Two meta-analyses of the use of BDG to diagnose PJP in patients with and without AIDS reported that the average sensitivity and specificity were 95%-96% and 84%-86%, respectively, with a diagnostic odds ratio of 102.3, positive/negative likelihood ratios of 6.9 and 0.06, respectively, and the area under the summary receiver operating characteristic curve of 0.96 [35,36]. However, it should be noted that BDG is: (1) a common cell-wall component of many fungi including Candida, Aspergillus, and Pneumocystis (except for Zygomycetes), so it can be difficult to discriminate between fungal species [38]; (2) confounded by the concurrent use of intravenous antimicrobials such as ampicillin-sulbactam, cefazolin, cefotaxime, cefepime, trimethoprim-sulfamethoxazole (TMP-SMX), colistin, and ertapenem [38]; and (3) also confounded by cross-reacting with Pseudomonas aeruginosa or bacterial bloodstream co-infections [39].

**Lactic dehydrogenase (LDH)**

Serum LDH was often reported to be elevated, but a normal LDH level did not rule out the diagnosis [7]. Zaman and White reported a level > 450 U/L could predict PJP, a normal LDH value could exclude the diagnosis, and a progressive increase in the level of LDH during treatment could predict a poor prognosis but that was also nonspecific [40]. However, combining BDG and LDH could further improve the diagnosis of AIDS-PJP. One study demonstrated that a BDG level > 400 pg/mL plus an LDH level > 350 U/L and a clinical presentation of PJP could improve the diagnostic rate of AIDS-PJP (92.8% sensitivity, 83.9% specificity, 92.8% positive predictive value, 83.9% negative predictive value, 5.764/0.086 positive/negative likelihood ratios, p < 0.001) [37]. In addition, Grover et al. reported that dyspnea and an LDH level ≥ 220 U/L could predict PJ in patients with AIDS with a sensitivity and specificity of 94% and 78%, respectively [41]. However, further studies are needed to investigate the use of serum LDH in the diagnosis of non-AIDS-PJP.

**Other laboratory findings**

Laboratory findings including high C-reactive protein, low albumin, and high blood urea nitrogen levels were common in PJP, but none could differentiate AIDS from non-AIDS [42]. Hypoxemia was the most characteristic laboratory finding [17-20], and ranged from mild to severe with room air breathing (mild: PaO_2 predicted value ≥ 70 mm Hg or alveoloarterial O2 gradient (A-aDO2) < 35 mm Hg, moderate: PaO2 < 70 mm Hg or A-aDO2 ≥ 35 and < 45 mm Hg, and severe: PaO2 < 70 mm Hg or A-aDO2 ≥ 45 mm Hg) [21]. Oxygen desaturation with exercise was also common but non-specific [21].

**Mortality**

The overall mortality rate ranged from 4% to 60% [1,2,42-45]. The mortality rate in the AIDS-PJP group improved after the advent of ART [43,44]. In a recent study of 544 patients with PJP, the overall in-hospital mortality rates were 4% for AIDS patients and 27% for non-AIDS patients (p < 0.0001) [1]. However, in the intensive care unit, the mortality rate of PJP remained higher in both groups (AIDS 17% versus non-AIDS 48%) [45]. The main causes of mortality in both groups were acute respiratory failure, using mechanical ventilation, and/or the development of pneumothorax [1,42,43]. In the AIDS-PJP group, pneumothorax was thought to occur because PJ had enough time to grow in the sub-pleural spaces and was thus difficult to eradicate by treatment [46]. In contrast, the most common causes of death in the patients with non-AIDS-PJP were hypoxemia and microbial co-infection with shock (odds ratio 3.09 [95% CI 1.44-6.68], p = 0.004) [1].

The factors related to mortality were non-AIDS patients, higher Simplified Acute Physiology Score, use of mechanical ventilation, and the development of pneumothorax [45]. The early detection of pneumothorax and appropriate treatment of the disease could reduce PJP-associated complications and
outcomes [26]. Using multivariate analyses, a high A-aDO2, bacteremia, preexisting lung disease, and elevated blood urea nitrogen were associated with mortality [42]. It was suggested that to improve the outcomes of the non-AIDS-PJP patients, clinicians could use invasive diagnostic techniques during the early stage to identify the pathogens [33].

**Treatment**

**Trimethoprim-sulfamethoxazole (TMP-SMX)**

TMP-SMX was used as a first-line treatment for PJP in patients with AIDS and non-AIDS [19,21]. Despite the indications being well established for patients with AIDS [21], most of the data for patients without AIDS were derived from the experience with patients with AIDS (Table 2). Hence, there was no consensus on the indications, duration, and discontinuation of primary prophylaxis for non-AIDS-PJP patients. Some concerns regarding anti-pneumocystis were also raised as below.

**Table 2. Comparison of Pneumocystis jirovecii pneumonia in treatment guideline recommendations between the patients with and without AIDS.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>AIDS</th>
<th>Non-AIDS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to initiation</td>
<td>Early after admission</td>
<td>Delayed initiation</td>
<td>[1]</td>
</tr>
<tr>
<td><strong>Guideline Preferring therapy</strong></td>
<td></td>
<td>Preferred therapy based on AIDS guidelines</td>
<td>[16,18-21,47,57]</td>
</tr>
<tr>
<td><strong>Guideline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose, mg/kg/day</td>
<td>15–20, IV every 6–8 hours</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Modified dose*</td>
<td>≤ 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, days</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>** exchanged**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alternative therapy, more adverse effects</strong></td>
<td>4, IV infused over ≥ 60 minutes</td>
<td>Alternative therapy, based on AIDS guidelines</td>
<td>[16,18-21,48,52,53,57]</td>
</tr>
<tr>
<td><strong>Preferred therapy based on AIDS guidelines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose, mg/kg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Echinocandins</strong></td>
<td></td>
<td>Case reports as salvage therapy only, failure of salvage also reported</td>
<td>[49-51]</td>
</tr>
<tr>
<td>Echinocandins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microbial co-infections,</strong></td>
<td>80/223 (35.8%)</td>
<td>121/331 (36.5%)</td>
<td>[1]</td>
</tr>
<tr>
<td>Bacterial infection, %</td>
<td>18.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemoprophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Guideline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>First-choice</td>
<td>First-choice</td>
<td>[16,18-21,47]</td>
</tr>
<tr>
<td>Indications</td>
<td>CD4+ T-cell count &lt; 200/mL or oropharyngeal candidiasis</td>
<td>No consensus</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>TMP-SMX, 1 DS, or 1 SS PO daily, or 1 DS PO three times weekly^</td>
<td>Undecided regarding the immunosuppressive conditions§</td>
<td>[16,18-21,47,53,54,57]</td>
</tr>
<tr>
<td>Duration</td>
<td>Decided by CD4+ T-cell count§</td>
<td>No consensus</td>
<td></td>
</tr>
<tr>
<td>Benefit</td>
<td>Increase survival</td>
<td>Limited data</td>
<td></td>
</tr>
<tr>
<td><strong>Adjunctive corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td>Moderate to severe disease§</td>
<td>No randomized studies</td>
<td>[19,21]</td>
</tr>
<tr>
<td>Dose</td>
<td>Start 40 mg of prednisone or equivalent twice daily</td>
<td>high-dose steroid therapy ≥ 1 mg/kg/day</td>
<td>[19,21]</td>
</tr>
<tr>
<td>Outcome</td>
<td>Increase survival</td>
<td></td>
<td>[54-57]</td>
</tr>
<tr>
<td>Duration, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No consensus</strong></td>
<td></td>
<td></td>
<td>[54-57]</td>
</tr>
</tbody>
</table>

TMP-SMX can be administered intravenously for patients with severe illnesses and gastrointestinal dysfunction. However, the use of TMP/SMX in the treatment or prophylaxis for AIDS-PJP was reported to cause adverse effects including severe asthenia (8%), severe abdominal pain (20%), nausea/vomiting (11.5%), severe rash (16%; including Stevens-Johnson syndrome), fever (30%–40%), anemia (31%), leukopenia (21.8-59%), hepatitis (16.4%), acute psychosis (11.9-13.3%), hyperkalemia (21.1%), hyponatremia (70.7%), thrombocytopenia (7%), azotemia (1-15%) and acute pancreatitis (3%) [21,47,48]. Although a daily dose of TMP/SMX of 15-20/75-100 mg/kg was recommended by Lee *et al.*, this caused 11.9% of 135 patients with AIDS to develop acute psychosis [47]. They therefore recommended a lower daily TMP dose of 12 mg/kg or lower [47]. Life-threatening immune reconstitution inflammatory syndrome was also noted after PJP in AIDS patients, and the U.S. Department of Health and Human Services
guidelines recommended that ART should be initiated within 2 weeks of a diagnosis of PJP [21].

Other alternatives
Salvage therapy with echinocandins was also reported in PJP patients with and without AIDS [49-51] after encountering the significant adverse effects of TMP-SMX and intravenous pentamidine [47,48,52]. PJP does not respond to standard antifungal treatment such as theazole family and amphotericin B because of the lack of ergosterol biosynthesis in PJ. In contrast, echinocandins were reported to inhibit BDG [49], and caspofungin was reported to improve overall mortality in patients with AIDS-PJP [49]. However, some studies reported failure of salvage therapy using echinocandins to improve survival among non-AIDS patients [50,51].
Pentamidine administered parenterally was as effective as TMP-SMX, however severe adverse effects including tremors, rash, leucopenia, thrombocytopenia, interstitial nephritis, impaired renal function, hyperkalemia, torsade de pointes, prolonged rate corrected QT interval, and acute pancreatitis may limit its use [48,52,53]. Other treatment regimens included clindamycin-primaquine, atovaquone, and dapsone-TMP [21]; however, most lacked clinical trials to compare their efficacy with TMP-SMX for the treatment of patients with AIDS-PJP [21].

Adjunctive corticosteroid therapy (ACT)
Indications for ACT for the patients with AIDS included those with moderate to severe PJP [21], and it was reported to potentially be beneficial for adult AIDS-PJP patients with substantial hypoxemia [54]. The recommended initial dose of ACT was 80 mg daily of oral prednisone divided into two doses on day 1 through 5, 40 mg of prednisone daily on day 6 through 10, and 20 mg of prednisone daily on day 11 through 21 [19,21]. The recommended dose of intravenous methylprednisolone was equal to 75% of the prednisone dose. However, Gallant et al. reported that this could increase the risk of oropharyngeal candidiasis among the patients with AIDS-PJP [55]. The authors also reported that there were no significant differences in the incidence of other opportunistic infections, including cytomegalovirus disease, Mycobacterium avium complex, cryptococcal meningitis, toxoplasmosis, Kaposi's sarcoma, herpes simplex and herpes zoster between the patients who did and did not receive steroid treatment [55]. Moreover, ACT did not increase the risk of mortality in the patients with AIDS [55].

Relatively few studies reported the use of corticosteroids for non-AIDS-PJP [56,57]. Guidelines for the treatment of solid-organ transplantation recipients with PJP recommend an ACT protocol that may improve survival, such as 40-60 mg of prednisone or equivalent twice daily within 72 hours of initiating antimicrobial therapy for 5-7 days, followed by tapering over a period of at least 7-14 days [57]. High-dose ACT was reported to have a detrimental effect on survival for both the patients with AIDS-PJP and non-AIDS-PJP [56].

Prophylaxis
Trimethoprim-sulfamethoxazole
TMP-SMX was used as the first-line prophylaxis regimen for PJP in patients with and without AIDS [19,21]. This prophylaxis regimen is well established for AIDS patients [21], however, most of the data for non-AIDS patients were extrapolated from experience with those with AIDS. Prophylaxis with TMP-SMX could reduce the occurrence of PJP among non–AIDS patients.

Huang et al. reported that the widespread and long-term prophylaxis with TMP-SMX led to the development of sulfua drug-resistant PJ [58]. In addition, drug-resistant PJ may result in the failure of standard therapy and prophylaxis, and may cause interhuman transmission [7,32]. Interhuman transmission and severity of PJP were reported to be related to specific PJ genotypes [59,60]. Susceptibility testing for PJ would seem to be pertinent to counter this issue, however, this is not possible in routine practice as PJ is not cultivatable in vitro [7].

Aerosolized Pentamidine
Intravenous pentamidine treatment for AIDS-PJP was reported to be more toxic than TMP-SMX [48,52,53]. Compared with TMP-SMX, aerosolized pentamidine was reported to have a better tolerance rate and survival rate (11% versus 7.4%) [53]. However, aerosolized pentamidine was not suggested as first-line treatment for AIDS-PJP due to more frequent relapses [21,53], although it could be an alternative choice for primary and secondary prophylaxis despite causing respiratory adverse effects (bronchospasm, cough or dyspnea). Of note, prophylaxis with aerosolized pentamidine for PJ was reported to potentially cause atypical presentations and make the diagnosis difficult [24]. The recommended dose was 300 mg monthly via a Respigard II™ nebulizer (manufactured by Marquest, Englewood, Colorado) [21]. For the non-AIDS-PJP patients, aerosolized pentamidine may also be an alternative prophylactic option [48,57]. Other options include dapsone,
dapsone/pyrimethamine/leucovorin, atovaquone, or atovaquone/pyrimethamine/leucovorin for primary or secondary prophylaxis in AIDS or non-AIDS-PJP patients with PJP (Table 2) [21, 57].

**Conclusion**

Comparing the two groups of patients, the clinical course of PJP is potentially more acute and the frequency of PJP seems to be higher in immunocompromised patients without AIDS. Once acquired, the patients have greater fulminant progression, possibly due to a stronger immune reaction. This results in more severe hypoxemia, more frequent use of mechanical ventilation, and a higher mortality rate. The dilemma of diagnosis is differentiating between active infection and colonization of PJ. At present, neither conventional staining nor PCR-based methods can resolve this problem. Staining method is not sensitive enough to detect colonization as the fungal load is low. The best treatment strategy for PJP has yet to be determined in immunocompromised patients without AIDS, however, early initiation of therapy and early invasive investigation seem appropriate. For patients with AIDS, prophylaxis and early treatment with an optimal dose of TMP-SMX for PJP and adjunctive corticosteroid therapy for moderate to severe PJP may achieve a better prognosis. Invasive procedure (BAL-qPCR-based therapeutic strategies) may help identify the pathogens earlier thereby offering additional benefits in the management of non-AIDS subjects.

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