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Original Article

Pneumocystis jiroveci pneumonia in Taiwan from 2014 to 2017: Clinical manifestations and outcomes between pediatric and adult patients

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KEYWORDS
Opportunistic infection;
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Abstract *Background: Pneumocystis jiroveci* pneumonia (PJP) is a severe and lethal opportunistic infection in the immunocompromised patients. As the increasing usage of immunosuppressants, the incidence of non-HIV related PJP has increased in recent years. Still, there is little research regarding children with PJP. The aim of this study is to understand PJP more among pediatric population.

Methods: We reviewed the medical records of the patients with PJP in National Taiwan University Hospital from 2014 to 2017. Diagnosis was made if the patient met all of the criteria: presence of relevant pulmonary symptoms and signs, pulmonary infiltrates on images, detection of *Pneumocystis jiroveci* from respiratory specimens via polymerase chain reaction (PCR), and received antibiotics for PJP.

Results: Twenty children and 132 adults were enrolled in this study. The most common underlying diseases among children included malignancy (40%), post-transplantation (30%), and primary immunodeficiency (20%). The major underlying diseases in adults included malignancy (36%), HIV with acquired immunodeficiency syndrome (AIDS) (31%), and autoimmune diseases (24%). There is no significant difference in the clinical manifestations, mortality, and complication between children and adults, but children tended to have less chance of using alternative antibiotics, methylprednisolone and inhaled nitric oxide (NO). The chance of concomitant cytomegalovirus disease was also significantly lower in pediatric patients.

Conclusion: No significant difference was found in the clinical manifestations, mortality, and complication between children and adults, but children tended to have lesser chance of using alternative antibiotics, methylprednisolone and inhaled NO. The chance of associated cytomegalovirus (CMV) disease was also significantly lower in children.

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Introduction

Pneumocystis jiroveci (P. jiroverci) is an extracellular pathogen usually found in the lungs of mammals. Different mammals are infected by different strains of *P. jiroveci*. For example, *P. jiroveci* infects human only whereas *P. carini* is exclusively found in rats.[1] The nucleic acid of *P. jiroveci* is similar to fungi but the morphology and drug susceptibility resembles protozoa. Hence, it was first classified as a protozoa, and finally determined to be a fungus based on its composition until the 1980s.[1]

Immunocompetent hosts are usually infected asymptomatically by the age of four years.[2] However, it is a severe and probably life-threatening infection in immunocompromised patients. Previously, it was well known as an opportunistic infection in patients with acquired immunodeficiency syndrome due to HIV infection. However, as the invention and worldwide usage of antiretroviral therapy and routine PJP prophylaxis in HIV patients, the cases of HIV related PJP diminished.[3] Meanwhile, as the wide spread usage of various immunosuppressive agents in patients with malignancy, autoimmune disease and hematopoietic or solid organ transplant, the incidence of non-HIV related PJP has increased in recent years.

Still, there is limited clinical data regarding the non-HIV related PJP especially in children. The aim of this study is to discover the predisposing underlying diseases, clinical manifestations, and clinical outcomes in PJP among pediatric population. The clinical characteristics between pediatric and adult patients were compared and the risks for mortality were also discussed.

Methods

We retrospectively reviewed the medical records of the patients with Pneumocystis pneumonia in National Taiwan University Hospital from January 2014 to December 2017. Diagnosis of PJP was made if the patient met all of the following criteria: 1. Presence of relevant pulmonary symptoms and signs (including fever, cough, or dyspnea), 2. Bilateral consolidation or ground glass opacity on chest X ray or chest computed tomography scan, 3. Detection of *P. jiroveci* DNA fragment in sputum or bronchoalveolar lavage via quantitative real-time polymerase chain reaction (qPCR), 4. Received relative antibiotics treatment for PJP including trimethoprim—sulfamethoxazole, or echinocandin antifungals like anidulafungin or caspofungin. Patients were excluded if they only had positive PCR result without relevant clinical or radiological manifestations. The concurrent bloodstream infection defined as presenting of bacteria or fungi in blood samples in patients with PJP. The cytomegalovirus (CMV) disease here defined as presence of relative clinical symptoms with documentation of CMV by polymerase chain reaction in respiratory specimens, blood, or tissue from the relevant organs, and receiving appropriate anti-viral therapy.

The respiratory specimens were either from bronchoalveolar lavage fluid or sputum. For patients receiving bronchoscope during hospitalization, bronchoalveolar lavage fluid was obtained; for those who intubated without receiving bronchoscope, sputum samples from endotracheal tube were collected. Induced sputum specimens were sent from patients without intubation. All of the samples were examined by in-house quantitative real-time PCR (qPCR) named BD MAX system (Beckon Dickinson, Diagnostic Systems, Sparks, MD, USA), a fully automated molecular platform, provides fully automated DNA extraction and multiplex qPCR for in vitro detection. It targets *P. jiroveci*-specific genes, which are major surface glycoproteins (MSG).[4] According to the previous research, the sensitivity and specificity of this in-house MSG qPCR assay reached 92.6% and 94.5%, respectively.[4] The previous study also found that patients with *P. jiroveci* colonization had significantly higher median amplification cycle threshold values than patients with true *P. jiroveci* infection (32.0 vs. 25.7, $P = 0.002$).[4] Thus this assay is more sensitive compared to conventional stain, but also provides a clue to differentiate colonization from true infection. In our study, we excluded patients with amplification cycle threshold values greater than 30 to minimize the chance of colonization.

Approval for this study was obtained from the Institutional Review Board of NTUH (IRB number: 201901070RINA).

Statistical analyses

The categorical variables in our study were described as the numbers of patients and the percentage of the total (%), and compared by Pearson's chi-square test. The continuous variables were represented as median and maximum—minimum, and were compared by Mann—Whitney test. Data were analyzed by SPSS for windows version 25. All the tests were 2-sided, and statistically significant were defined as $P < 0.05$.

Results

Underlying diseases of the enrolled patients

From 2014 to 2017, 384 patients were found to have *P. jiroveci* DNA fragment in their sputum or bronchoalveolar lavage by PCR in National Taiwan University Hospital. However, 232 cases were excluded due to lack of clinical,

radiological manifestations of PJP, or PCR amplification cycle threshold values greater than 30. The remaining 152 respiratory specimens included 17 bronchoalveolar lavage fluid, and 135 sputum samples. Among the 152 patients, 20 cases were children, and 132 cases were adults (Fig. 1). The most common underlying diseases among pediatric patients were malignancy ($N = 8$, 40%), post-transplant ($N = 6$, 30%), and primary immunodeficiency ($N = 4$, 20%). The major underlying diseases in adult patients included malignancy ($N = 48$, 36%), HIV infection with acquired immunodeficiency syndrome ($N = 41$, 31%), and autoimmune disease ($N = 32$, 24%). The flowchart of patient selection, enrollment and underlying diseases are shown in Fig. 1.

Characteristics in pediatric patients

Table 1 shows the clinical characteristics of pediatric patients. The most common underlying diseases among pediatric patients were hematology-oncology disease, and leukemia was most common. The second place was post-transplant (1 child received solid organ transplantation and 5 children received stem cell transplantation), and PJP usually occurred over 100 days after transplant. The third most common disease was primary immunodeficiency ($N = 4$, 20%). Besides, autoimmune disease ($N = 2$, 10%) and previous pulmonary disease ($N = 2$, 10%) were also included. About the previous medication use prior to this infection, 50% of children ($N = 10$) had corticosteroids and 30% of children ($N = 6$) had chemotherapy. The minimal dose and duration of corticosteroid was 1 mg/kg/day for 4 weeks in one primary immunodeficiency patient. 25% of children had PJP prophylaxis (trimethoprim–sulfamethoxazole, TMP–SMX) within 3 months before PJP onset ($N = 5$, 25%), but none of them acquired PJP under antibiotic prophylaxis (Table 1).

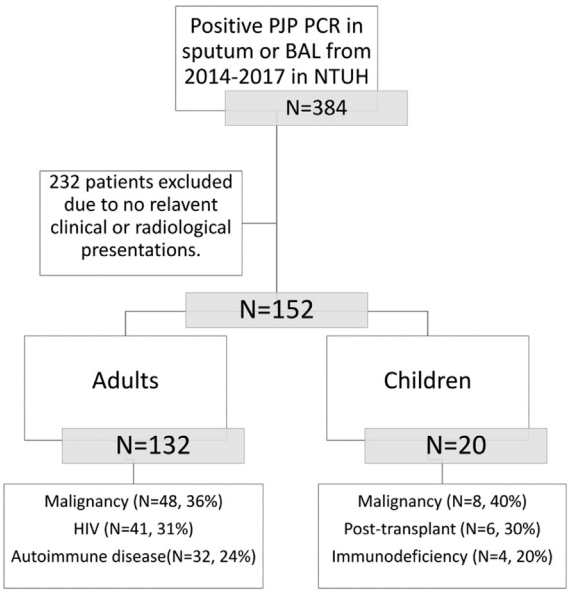

Figure 1. Flowchart of patient selection in *Pneumocystis jiroveci* pneumonia. PJP, *Pneumocystis jiroveci* pneumonia; PCR, polymerase chain reaction; BAL, bronchoalveolar lavage; NTUH, National Taiwan University Hospital.

The most common clinical manifestation of pneumocystis pneumonia in pediatric patients including fever ($N = 19$, 95%), dyspnea ($N = 18$, 90%), cough ($N = 15$, 75%), and desaturation (the median SpO2 is 90%). The median absolute lymphocyte count is 923/uL. The radiological presentation of pneumocystis pneumonia in children included bilateral consolidation ($N = 10$, 50%) and interstitial pattern ($N = 10$, 50%). Over half of the children with pneumocystis pneumonia required intensive care ($N = 14$, 70%), and mechanical ventilator support ($N = 13$, 65%). Half of the pediatric patients progressed to acute respiratory distress syndrome ($N = 10$, 50%), and most of them had moderate severity based on oxygen index. 15% ($N = 3$) of children needed Extracorporeal membrane oxygenation (ECMO) support. 20% ($N = 4$) of the children had adverse events when receiving sulfamethoxazole–-trimethoprim, the most common adverse event is hyponatremia ($N = 2$, 10%), following by hyperkalemia ($N = 1$, 5%), vomiting ($N = 1$, 5%) and hepatitis ($N = 1$, 5%) (Table 1).

There were 25% of pediatric patients had concurrent bloodstream infection ($N = 5$), and 10% of children had concomitant cytomegalovirus infection ($N = 2$).

The all-cause mortality is 25% ($N = 5$), most of them died due to hypoxemic respiratory failure ($N = 5$, 25%). The complication included acute kidney injury ($N = 4$, 20%), pneumothorax ($N = 2$, 20%) and gastrointestinal bleeding ($N = 2$, 10%) (Table 1).

Comparison between pediatric and adult patients

The median age of children was 12 years old (ranged from two months old to 18 years old), and 55 years old in adults (ranged from 22 years old to 87 years old). Both pediatric and adult groups were male predominant, 70% in the adult group and 65% in the pediatric group, as Table 2 shows. The dosage of patients using corticosteroid and chemotherapy before PJP showed no significant difference between children and adults. However, the proportion of patients receiving PJP prophylaxis within three months before PJP was significant higher in the pediatric group than the adult group ($N = 5$, 25% in children, $N = 10$, 7.6% in adults).

There is no significant difference between children and adults in the clinical manifestations, proportion of patients receiving intensive care (including ICU admission, intubation, mechanical ventilation), and extra-corporeal membrane oxygenation (ECMO) support. However, the pediatric group tended to have lower serum CRP level and higher value of PaO2/FiO2 ratio, and lower PEEP of ventilator setting (Table 2).

Besides, more adult patients had adverse event when receiving sulfamethoxazole–trimethoprim ($N = 58$, 44% in adult; $N = 4$, 20% in children, $P = 0.05$), and adult patients had more chance of using alternative anti-PJP antibiotics ($N = 53$, 40% in adult; $N = 3$, 15% in children, $P = 0.01$), and more received iNO ($N = 32$, 24% in adult; $N = 0$, 0% in children, $P = 0.01$) and corticosteroid as adjunctive therapy ($N = 96$, 73% in adult; $N = 11$, 55% in children, $P = 0.03$) (Table 2). The chance of associated CMV disease was also significantly higher in adult patients than pediatric patients ($N = 38$, 29% in adult; $N = 2$, 10% in children, $P = 0.05$). The mortality and complication rate between pediatric and adult patients revealed no significant difference (Table 2).

Table 1 Characteristics of pediatric patients with *P. jiroveci* pneumonia.

	Pediatrics ($N = 20$)
Patient information	
Age (y)	12 (0.17—18)
Male	13 (65%)
Female	7 (35%)
Underlying disease	
Hematology-oncology disease	8 (40%)
Leukemia	6 (30%)
Lymphoma	1 (5%)
Solid organ tumor	1 (5%)
Primary immunodeficiency	4 (20%)
Post-transplant	6 (30%)
Solid organ transplantation	1 (5%)
0—30 days after transplantation	0 (0%)
30—100 days after transplantation	0 (0%)
>100 days after transplantation	1 (5%)
Stem cell transplantation	5 (25%)
0—30 days after transplantation	1 (5%)
30—100 days after transplantation	0 (0%)
>100 days after transplantation	4 (20%)
Autoimmune disease	2 (10%)
Previous pulmonary disease	2 (10%)
Previous medication use	
Steroid	10 (50%)
Minimal dose; duration	1 mg/kg/day; 4wk
Chemotherapy	6 (30%)
Other immunosuppressant	5 (25%)
Prophylaxis within 3 months before PJP	5 (25%)
Duration of S/S before antibiotics (day)	6 (1—31)
Clinical manifestation	
Fever	19 (95%)
Dyspnea	18 (90%)
Cough	15 (75%)
SpO2 (%)	90% (70—98%)
Initial lab data	
WBC (/uL)	9800 (160—69,650)
Absolute lymphocyte count (/uL)	923 (2—7644)
Hb (g/dL)	10.7 (5.8—17.2)
CRP (mg/dL)	4.1 (0.02—25.4)
Albumin (g/dL)	3.0 (2.0—4.6)
Cr (mg/dL)	0.4 (0.2—2.3)
ALT (U/L)	24 (5—198)
pH	7.41 (7.19—7.51)
PaO2 (mmHg)	62.6 (30/1—157.9)
PaCO2 (mmHg)	32.1 (20.4—78.8)
PaO2/FiO2	116 (65—350)
Oxygen index	12.1 (7.5—29.3)
Image presentation	
Bilateral consolidation	10 (50%)
Interstitial pattern	10 (50%)
Hospital course	
ICU admission	14 (70%)
ICU length of stay (day)	22 (6—73)
Mechanical ventilation	13 (65%)
Duration of mechanical ventilation (day)	14 (4—73)
PEEP (mmHg)	6 (3—9)
ARDS	10 (50%)
ARDS severity (oxygen index)	
Mild	2 (10%)
Moderate	7 (35%)
severe	1 (5%)
Treatment	
Total medication duration (day)	22 (8—43)
AE of trimethoprim/sulfamethoxazole (TMP/SMX)	4 (20%)
Vomiting	1 (5%)
Hyperkalemia	1 (5%)
Hyponatremia	2 (10%)
Hepatitis	1 (5%)
Use of alternative anti-PJP medication	3 (15%)
Use of steroid as adjunctive therapy	11 (55%)
ECMO	3 (15%)
Co-infection	
Bloodstream infection	5 (25%)
CMV disease	2 (10%)
Complication	6 (30%)
Pneumothorax	2 (10%)
Acute kidney injury	4 (20%)
GI bleeding	2 (10%)
Mortality	
All-cause mortality	5 (25%)
Mortality due to hypoxemia	4 (20%)
Mortality due to septic shock	2 (10%)

Data were presented with *N* (%) or median (minimum—maximum) unless otherwise specified.
PJP denotes *Pneumocystis jiroveci* pneumonia; S/S, symptoms/signs; ICU, intensive care unit; PEEP, positive end expiratory pressure; ARDS, acute respiratory distress syndrome; AE, adverse event; ECMO, extracorporeal membrane oxygenation; CMV, cytomegalovirus.

Comparison between survivors and fatal patients

The mortality rate of the patients with the underlying disease of malignancy was 54% (29/54), and of autoimmune disease was 48% (21/44), whereas the rate in HIV patients was 12% (5/41) as Table 3 shows.

Compared with the survivor group, the mortality group had lower initial absolute lymphocyte count (ALC = 460/uL in the mortality group vs. ALC = 776/uL in the survivor group, $P < 0.01$), lower Hb level (9.9 g/dL in the mortality group vs. 11.3 g/dL in the survivor group, $P < 0.01$), and lower serum albumin level (2.7 g/dL in the mortality group vs. 3.0 g/dL in the survivor group, $P < 0.01$) than the survivor group. Besides, the mortality group also had higher

Table 2 Comparison between pediatric and adult patients with *P. jiroveci* pneumonia.

	Adults ($N = 132$)	Children ($N = 20$)	*P* value
Patient information			
Age (y)	55 (22–87)	12 (0.17–18)	**<0.01**
Male	93 (70%)	13 (65%)	0.62
Underlying disease			
Malignancy	48 (36%)	8 (40%)	0.75
Autoimmune	32 (24%)	2 (10%)	0.15
Primary immunodeficiency	0 (0%)	4 (20%)	**<0.01**
HIV	41 (31%)	0 (0%)	**<0.01**
Post-transplant	13 (9%)	6 (30%)	**0.01**
Solid organ transplantation	8 (6%)	1 (5%)	
Stem cell transplantation	5 (3%)	5 (25%)	
Previous medication use			
Steroid	50 (38%)	10 (50%)	0.45
Chemotherapy	30 (23%)	6 (30%)	0.59
Prophylaxis within 3 months before PJP	10 (8%)	5 (25%)	**0.02**
Duration of S/S before antibiotics	7 (0–75)	6 (1–31)	0.69
Clinical manifestation			
Fever	109 (83%)	19 (95%)	0.15
Cough	87 (66%)	15 (75%)	0.58
Dyspnea	118 (89%)	18 (90%)	0.9
Initial lab data			
WBC (/uL)	6880 (40–29,380)	9800 (160–69,650)	0.22
Absolute lymphocyte count (/uL)	559 (0–6108)	923 (2–7644)	0.28
CRP (mg/dL)	8.7 (0.2–40)	4.1 (0.02–25.4)	**0.03**
Cr (mg/dL)	0.9 (0.3–11.5)	0.4 (0.2–2.3)	**<0.01**
ALT (U/L)	23 (3–613)	25 (5–198)	0.39
Hospital course			
ICU admission	74 (56%)	14 (70%)	0.27
Mechanical ventilation	68 (52%)	13 (65%)	0.29
ARDS	64 (48%)	10 (50%)	0.66
PaO2/FiO2	78 (23–284)	116 (65–350)	**0.03**
PEEP	8 (3–16)	6 (3–9)	**<0.01**
Treatment			
AE of TMP/SMX	58 (44%)	4 (20%)	**0.05**
Use of alternative anti-PJP medication	53 (40%)	3 (15%)	**0.01**
Use of steroid	96 (73%)	11 (55%)	**0.03**
iNO	32 (24%)	0 (0%)	**0.01**
ECMO	6 (5%)	3 (15%)	0.07
Co-infection			
CMV disease	38 (29%)	2 (10%)	**0.05**
Bloodstream infection	36 (27%)	5 (25%)	0.83
Mortality	51 (39%)	5 (25%)	0.19
Complication	24 (18%)	6 (30%)	0.25

Data were presented with *N* (%) or median (minimum–maximum) unless otherwise specified.
PJP denotes *Pneumocystis jiroveci* pneumonia; S/S, symptoms/signs; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; PEEP, positive end expiratory pressure; AE, adverse event; TMP/SMX, trimethoprim/sulfamethoxazole; iNO, inhaled nitric oxide, ECMO, extracorporeal membrane oxygenation; CMV, cytomegalovirus.

percentage of patients receiving alternative anti-PJP medication (50% in the mortality group vs. 30% in the survivor group, $P = 0.01$), steroid as adjunctive therapy (90% in the mortality group vs. 60% in the survivor group, $P < 0.01$), and concomitant CMV disease (38% in the mortality group vs. 19% in the survivor group; $P < 0.01$). Table 3 shows difference between the mortality group and the survivor group.

Discussion

In our study, the three most common underlying diseases among pediatric patients were hematology-oncology disease, post-transplant, and primary immunodeficiency. The underlying diseases of our pediatric patients are similar to previous studies in Taiwan and Korea.[5,6] Infection of *P.*

Table 3 Comparison of survivor and mortality in pneumocystis pneumonia.

	Survivor ($N = 94$)	Death ($N = 58$)	P value
Underlying disease			**<0.01**
Malignancy	25 (46%)	29 (54%)	
Autoimmune disease	23 (52%)	21 (48%)	
HIV	36 (88%)	5 (12%)	
Post-transplant	13 (65%)	7 (33%)	
Duration of S/S before antibiotics	7 (0–75)	4 (0–60)	**0.01**
Initial lab data			
WBC (/uL)	6870 (70–37,360)	7510(40–69,650)	0.86
ALC (u/L)	776 (2–7644)	460 (0–3375)	**<0.01**
Hb (g/dL)	11.3 (6.2–16.4)	9.9 (5.8–17.2)	**<0.01**
CRP (mg/dL)	5.7 (0.02–40)	10.4 (0.28–40)	**0.02**
Albumin (g/dL)	3.0 (1.9–4.6)	2.7 (2.0–3.8)	**<0.01**
Hospital course			
ICU admission	36 (38%)	51 (88%)	**<0.01**
Mechanical ventilation	29 (31%)	51 (88%)	**<0.01**
PEEP (mmHg)	5 (3–16)	8 (3–14)	**0.03**
ARDS	26 (28%)	48 (83%)	**<0.01**
Treatment			
Use of alternative anti-PJP drug	28 (30%)	29 (50%)	**0.01**
Use of steroid	56 (60%)	53 (90%)	**<0.01**
ECMO	1 (1%)	8 (14%)	**<0.01**
iNO	5 (5%)	27(47%)	**<0.01**
Co-infection			
CMV disease	18 (19%)	22 (38%)	**<0.01**
Bloodstream infection	22 (23%)	19 (32%)	0.25
Complication	7 (7%)	23 (40%)	**<0.01**

Data were presented with N (%) or median (minimum–maximum) unless otherwise specified.
PJP denotes *Pneumocystis jiroveci* pneumonia; S/S, symptoms/signs; ICU, intensive care unit; PEEP, positive end expiratory pressure; ARDS, acute respiratory distress syndrome; iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation; CMV, cytomegalovirus.

jiroveci is mainly due to impaired cell-mediated immunity. Hence, malignancy, solid organ or hematopoietic stem cell transplantation, and prolong corticosteroid use may lead to T-cell suppression and subsequent *P. jiroveci* infection.

In patients with malignancy, the risk of PJP is related to several factors, including the underlying malignancy, disease status (in remission or relapse), duration of neutropenia, prior exposure to chemotherapy, and the intensity of immunosuppressive therapy.[7,8] Current literature reviews have suggested that prophylaxis is not necessary for children receiving standard chemotherapy for solid tumors if the duration of neutropenia is shorter than 7 days.[9] However, prophylaxis is strongly suggested for all children being treated for hematologic malignancies, such as lymphoma or leukemia.[9] There is no consensus about the duration of PJP prophylaxis in pediatric patients receiving chemotherapy. Some suggested that prophylaxis should be continued until three months after the end of chemotherapy,[9,10] others recommended that prophylaxis should be kept until the lymphocyte count reached normal range.[9,10] In our study, all of the children with malignancy acquired PJP while lymphopenia, thus absolute lymphocyte count may be a reliable indicator other than CD4 count for PJP prophylaxis.

Previously we believed that patients receiving stem cell transplantation predisposed to *P. jiroveci* infection at post-engraftment period (30–100 days after transplant) since the predominant defect in host defenses at this period is cell mediated immunity.[2] However, in our study, the majority (9/10, $N = 90\%$) of PJP happened at late post-transplantation period (>100 days) among both pediatric and adult populations. This is probably due to multiple immunosuppressive therapy for graft-versus-host disease. According to our study and literature reviews, *P. jiroveci* infection should still be taken into consideration for patients receiving transplantation even at late post-transplantation period.[11] Recently more researches have also suggested that PJP prophylaxis should be consider for 3–6 months after transplant for autologous hematopoietic cell recipients; and at least 6 months for allogenic hematopoietic cell recipients.[12] If patients continue to receive immunosuppressive therapy, prophylaxis for PJP should also be extended to over 6 months.[13]

In our study, the minimal dose and duration of corticosteroid usage predisposed to PJP in pediatric patients was prednisolone 1 mg/kg/day for 4 weeks in one primary immunodeficiency children. Corticosteroids have a major effect on the production and distribution of circulating T-helper lymphocytes. It also reduces the production of cytotoxic T-cells and B-cells, suppresses the release of cytokine, and therefore inhibits the function of macrophage, delay clearance of *P. jiroveci*.[14] Currently, we know little about the minimum dose and duration of corticosteroids that may predispose patients to *P. jiroveci* infection.

Some suggested that patients receiving prednisolone 30 mg or the equivalent for longer than 12 weeks require PJP prophylaxis,[15] other studies suggest that prednisolone equivalent of 20 mg or more daily for four or more weeks is long enough to cause *P. jiroveci* infection.[16] It is difficult to establish a guideline for PJP prophylaxis in children with long-term corticosteroids use because there are some specific underlying diseases predisposing to PJP infection even under lower dose of corticosteroids, including acute lymphoblastic leukemia, chronic lymphoblastic leukemia, and non-Hodgkin's lymphoma.[14] Still, based on the literature review and our study, physician should raise the awareness of PJP and consider giving PJP prophylaxis when immunocompromised children receiving corticosteroid dose equivalent to more than 1 mg/kg/day (or 20 mg/day) over four weeks.

According to our study, although the pediatric and adult patients with PJP had no significant difference in clinical manifestation, laboratory data and mortality, adult patients tended to have lower PaO2/FiO2 ratio, higher ventilator setting (base on PEEP), more inhaled NO and extracorporeal membrane oxygenation (ECMO) requirement in severe cases. There is no publishing data regarding the benefits of inhaled nitric oxide in patients with pneumocystis pneumonia, and most of the patients in our study receiving inhaled NO as an adjunctive therapy for acute respiratory distress syndrome. Unfortunately, some of the studies revealed that inhaled NO could only improve the oxygenation for a short period of time but failed to decrease the mortality rate in patients with acute respiratory distress syndrome.[17] Among the 32 patients received inhaled NO in our study, 27 patients died eventually (27/32, 84%), which was consistent to previous study result.

Besides, adult patients had significantly higher percentage of cases presented with adverse events when receiving sulfamethoxazole—trimethoprim which required to shift to second line antibiotics. The chance of associated CMV disease is also higher among adult group. Currently there is no published data regarding the difference between these two groups due to lack of sufficient pediatric cases. More research is required to demonstrate the difference between children and adults in the future.

In our study, the mortality rate of PJP in patients with malignancy and autoimmune disease is higher than the patients with HIV (53% in malignancy and 48% in autoimmune disease, compared to 12% in HIV patients). Previous published studies revealed that the clinical severity of *P. jiroveci* pneumonia depends mainly on two major factors, including the amount of *P. jiroveci* in lung tissue and the inflammatory reaction it generates.[18,19] Patients with HIV/AIDS have more *P. jiroveci* at lung tissue but less inflammatory reaction and fewer neutrophils in the lung. Fewer neutrophils cause less impairment on gas exchange and lung tissue damage. Thus in the patients with absence of adaptive immunity, the infection by *P. jiroveci* seldom caused obvious changes in lung histology and function.[20] In contrast, in patients with adequate functional lymphocytes, the inflammatory response will cause massive and rapid cellular infiltrate, lung compliance reduction, and hypoxemia.[21,22] This can explain why the *P. jiroveci* pneumonia is more severe in patients with autoimmune diseases and malignancy than the patients with HIV/AIDS.

In our study, the mortality group tended to have higher percentage of patients infected with CMV disease compared with survival group. There are two hypotheses. In animal model, CMV infection will suppress the function of antigen-presenting cells and helper T-cells, which results in delay clearance of *P. jiroveci* in lung tissue and more severe pulmonary parenchyma damage.[23] On the other hand, CMV reactivation and CMV disease is believed to be associated with severe immune suppression which may lead to subsequent complicated infection.[24] These two reasons can explain why the mortality group in our study had significantly higher prevalence of CMV disease compared with the survival group.

Our research has several limitations. First, the clinical data were from one tertiary center in Taiwan, and the pediatric case number was small, so it may not be able to represent the whole clinical picture of the patients with PJP. However, most of the patients with PJP had underlying diseases of malignancy, post-transplant and autoimmune disease, which were mostly treated in medical center, so the chance of patient selection bias is minimal. Second, the respiratory specimen was examined by real-time polymerase chance reaction without histochemical stain, which may not differentiate respiratory tract colonization from true infection. But the patients without clinical or radiological manifestations, and patients with PCR amplification cycle threshold values greater than 30 were all excluded from our study, so the possibility of respiratory tract colonization in our study population was low.

Last, the data was collected retrospectively, so the treatment duration and medical strategy varied according to different physicians, it may also influence the outcome of the patients.

Conclusion

There is no significant difference between children and adult with PJP in clinical manifestation and outcomes, but children tended to have less adverse events when using sulfamethoxazole—trimethoprim, and lesser chance of using alternative antibiotics, methylprednisolone and inhaled NO in treatment. The chance of associated CMV disease was also significantly lower in children. Immunocompromised children receiving prednisolone more than 20 mg/day (or 1 mg/kg/day) for over one month should be highly aware of PJP and PJP prophylaxis may be considered. The patients with malignancy, autoimmune disease, low absolute lymphocyte count, low albumin level, concomitant CMV disease were high risk for mortality in pneumocystis pneumonia.

Conflicts of interest

All the authors have no conflicts of interest to disclose.

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