Introduction

Historically, premature and malnourished infants were those who were at risk of Pneumocystis jirovecii pneumonia (PJP) in Europe following World War II. The at-risk population shifted to those with hematological malignancies in the 1960s and 1970s, while in the 1980s, PJP increased dramatically with the emergence of the HIV epidemic. Nowadays, PJP in HIV patients can be adequately controlled by maintaining the CD4 count and using routine prophylaxis. In 2000 and later, PJP among immunosuppressed patients, especially renal transplant recipients, has increased compared to PJP in HIV patients. Many outbreaks of PJP in renal transplant recipients have been described recently. Whether or not a kidney transplant center has experienced an outbreak, preparation for a PJP outbreak is nevertheless required in order to save the many as yet uninfected recipients and those patients who already have PJP.

History

Pneumocystis organisms were first incorrectly reported in 1909 as the protozoan Trypanosoma cruzi, which is found in Chagas disease. Pneumocystis carinii was reported from a rat sample in 1910 by Dr. Carini as another protozoan that was different from T. cruzi, and it was subsequently described as a new protozoan in the International Code of Zoological Nomenclature (ICZN) in 1912. During the 1940s, it may have been a possible cause of pneumonia in human beings, and in 1952, it was recognized as a pathogen of Pneumocystis pneumonia by the Czech researcher, Dr. Jirovec. Whereas P. carinii originated from the rat, P. jiroveci from human beings was described as a new protozoan in the ICZN in 1976. In 1988, however, DNA analysis demonstrated that P. jiroveci is actually a fungus.

The reasons that P. jiroveci was recognized as a protozoan are as follows: (1) fungi are similar to protozoa morphologically; (2) P. jiroveci demonstrated sensitivity to the antiprotozoal agent, TMP-SMX; (3) P. jiroveci was resistant to many antifungal agents; and (4) it was not possible to culture P. jiroveci in vitro, though it can be cultured from the recent report.

In 1999, it was reclassified as a fungus and described in the International Code of Botanical Nomenclature (ICBN), and in 2005, it was modified to P. jiroveci by the ICBN. In 2012, the ICBN became the International Code of Nomenclature for algae, fungi, and plants, and P. jirovecii was classified...
under the Ascomycota group according to the new code. Since *P. carinii* was derived from rats, the term *Pneumocystis carinii* pneumonia (PCP) is no longer used for human beings. As such, the name for *Pneumocystis*-related pneumonia in human beings was changed to PJP.

**Epidemiology in Kidney Transplantation**

Owing to the use of highly active antiretroviral therapy and primary PJP prophylaxis (which is dependent on the CD4 count), PJP with HIV has become a controllable disease and resulted in a decrease in the number of cases. On the other hand, a decrease in the number of cases of PJP in non-HIV patients has increased with the recent enhancements in immunosuppressive therapy. French data spanning from 1990 to 2010 showed that, of the cases of PJP without HIV, polyarteritis nodosa, granulomatosis with polyangiitis, and polymyositis/dermatopolymyositis were the concomitant diseases with the top three highest incidence rates, although hematological malignancies such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, and acute leukemia were also part of the high-risk group (>45 cases per 100,000 patient-years). Among transplant recipients, estimates of incidence rates vary from 13.7 for heart transplant recipients to 44.6 per 100,000 patient-years for kidney transplant recipients. From data in England, the difference in rates between two time periods (2000–2005 and 2006–2010) was most marked among patients who had undergone solid organ transplantation (SOT), 47% of whom had undergone kidney transplantation (KT), compared to other immune deficiencies such as chronic lung diseases, renal failure, hematologic malignancy, other hematologic disorders, systemic connective tissue disorders, inflammatory diseases, and receipt of immunosuppressive or chemotherapeutic drugs. Therefore, the management of PJP in KT is becoming more and more important. Despite antimicrobial prophylaxis, which has reduced the incidence of PJP, clusters of late infections have been reported among kidney transplant recipients worldwide. An outbreak that begins from main clusters is most frequently observed in kidney transplant recipients. It may be related to the high number of kidney transplant recipients worldwide, their immunosuppression status, and their compliance with regular follow-up within hospital settings, combined with the consequent high rate of encounters and potential transmission of the fungus.

Not only patients with PJP but also colonized patients may be potential infectious sources of *P. jirovecii*. Pathogen

Even with recently developed techniques, it is still not possible to culture *Pneumocystis in vitro*. Although the life cycle of *P. jirovecii* remains poorly defined, the *Pneumocystis* life cycle is known to have four stages, namely, the trophic form, sporocyst, cyst (includes eight spores), and spore. *Pneumocystis* organisms in different mammals are quite different, and strains from one host animal do not infect other animal species. *P. jirovecii* can only survive in the respiratory organ of human beings. The infective form that travels from individual to individual by the airborne route has not been elucidated. Although *Pneumocystis* DNA has been detected in air, no environmental form has been isolated. In the lungs of hosts with pneumocystosis, trophic forms are the most abundant of all *Pneumocystis* life cycle stages, representing 90%–95% of the total population, while mature cysts are detected in the bronchial lumen. Mature cysts are certainly the best equipped to retain infectivity during transient host-to-host air travel, which may help explain how direct patient–patient transmission occurs or how reservoirs in infected patients form, and since cysts can survive outside the human host for some time, which may explain how transmission from the environment occurs.

There is little information regarding isolation of *P. jirovecii* cysts in ambient air, but in our study, we detected *P. jirovecii* DNA from the outpatient consulting rooms, and the genotype was the same as *P. jirovecii* DNA of PJP that was diagnosed in the same room two months before. We cannot explain this without cysts.

**Genotype**

*Pneumocystis*-specific DNA sequences were first cloned from an experimental rat model in 1990 and this enabled typing methods. The target genes are the mitochondrial large subunit rRNA (mt LSU rRNA), dihydropteroate synthase (DHPS), and internal transcribed spacer regions (ITS1, ITS2). Typing based on mt LSU rRNA or DHPS can only identify four types of *P. jirovecii*. More recently, a four-locus scheme that includes ITS1, 26S, mt26S, and beta-tubulin has emerged, and this method can identify more than 35 different genotypes. *P. jirovecii* can be classified into more than 130 types by using a combination of ITS1 and ITS2, and this is suitable for the determination of nosocomial infections. Recent studies have proposed the short tandem repeat-based molecular typing analysis, which is a quick, cheap, and reliable approach to genotype *P. jirovecii* in hospital settings and is sensitive enough to detect minor genotypes.

**Transmission route of *P. jirovecii***

Pneumocystis is a common childhood respiratory infection. B lymphocytes participate in the immune response. By four years of age, two-thirds of normal children who have been exposed to the respiratory-aerosol route are found to have antibodies to *P. jirovecii*. B-cells are also important for the costimulation of T-cells in response to the organism. T-cells then activate alveolar macrophages, which is the major cell type responsible for the clearance of *P. jirovecii* from the lungs. It was previously thought that PJP may have occurred from the reactivation of chronic colonization, but reinfection with different genotypes probably occurs as frequently as reactivation of endogenous organisms.

There are three ways of acquiring PJP. The first is transmission from a PJP patient to an immunocompromised host, after
which the patient develops new PJP soon after such contact. This is the most likely mode of acquiring new infections.\textsuperscript{41} Immunocompromised patients also can be a reservoir without developing PJP.

The second is from environmental exposure.\textsuperscript{27,42–44} As mentioned earlier, we detected \emph{P. jirovecii} DNA from the outpatient consulting rooms, and the genotype was the same as \emph{P. jirovecii} DNA of PJP that was diagnosed in the same room two months before.\textsuperscript{7}

\emph{P. jirovecii} in the air exhaled by infected patients may be in the cyst form, because \emph{P. jirovecii} can only survive in the respiratory organ of human beings. Cysts can survive outside the human host for some time. An alternative hypothesis is that this organism may be capable of multiplying in an environmental niche and may not be totally dependent on human beings.\textsuperscript{27} Immunocompromised hosts can develop new PJP or colonization by inhaling this cyst. The third is from asymptomatic carriers.\textsuperscript{45} Immunocompromised patients infected by PJP patients or from environmental exposure can easily become a reservoir for infection; this has been proven in mice.\textsuperscript{46,47} There is a possibility that the same phenomenon occurs in human beings. Coughing or sneezing by reservoir patients can induce new PJP in other immunocompromised hosts. Several studies have suggested that asymptomatic carriers may have contributed to the spread of infection in an outbreak of PJP among kidney transplant recipients or rheumatoid arthritis patients.\textsuperscript{6,48} \emph{P. jirovecii} species were exhaled by colonized patients and therefore proposed that such carriers can participate in nosocomial transmission of this organism via the airborne route.\textsuperscript{49}

Immunocompetent hosts can clear reinfection by different genotypes without obvious clinical consequences in themselves, but the transient reservoir in their bronchial lumen might allow the transmission of this organism to other immunocompetent or immunocompromised hosts.

Immunocompromised patients develop the disease as a consequence of reinfection and possibly reactivation.\textsuperscript{50} Whether asymptomatic carriers can clear their colonization or develop PJP is dependent on their immunosuppression. For modern immunosuppression in KTs, the estimated median incubation period of PJP is 53 days (range 7–188 days).\textsuperscript{7}

**Risk Factors**

The most significant risk factors for PJP in non-HIV patients are glucocorticoid use and defects in cell-mediated immunity.\textsuperscript{51–53} In retrospective studies of non-HIV PJP, the median dose of prednisone used was 30 mg/day, but some patients received as little as 16 mg/day. The median duration of glucocorticoid therapy before the development of PJP was 12 weeks, but some developed before eight weeks.\textsuperscript{52} If the kidney transplant recipients do not use steroid avoidance or withdrawal protocols, the dose of prednisone is gradually decreased to \textasciitilde5 mg/day as a maintenance dose over three months. Thus, only during the maintenance phase, the use of glucocorticoid may not be a significant risk factor for the kidney transplant recipient.

In addition to glucocorticoids, the combined use of calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), or sirolimus (mostly triple therapy) is needed to maintain graft function. These immunosuppressive agents are also risk factors for PJP.\textsuperscript{23,54–57} The incidence of rejection increases the risk of PJP.\textsuperscript{58,59} In a case–control study, treatment of one, two, and three rejections was associated with 2-, 5-, and 10-fold increases in the incidence of PJP, respectively.\textsuperscript{58} Although rituximab, an anti-CD20 antibody, is used as induction therapy in ABO- and HLA-incompatible KTts, as a therapy for antibody-mediated rejection, or as a treatment for posttransplantation recurrence of focal segmental glomerulosclerosis, its use is also a risk factor for PJP.\textsuperscript{60,61} The risk of PJP is determined by the net state of immunosuppression.\textsuperscript{52,62} While the risk of HIV PJP increases when the CD4-positive T-cell count is <200 cells/\textmu L, there is no valuable index for assessing the risk of non–HIV PJP.\textsuperscript{64}

In addition, there are also other nonimmunological risk factors. Cytomegalovirus (CMV) infection may be an independent risk factor for PJP,\textsuperscript{63,66} while aging (>55 years at the time of transplantation) is also a risk factor.\textsuperscript{66} Primary TMP-SMX prophylaxis failure may occur in association with some of these risk factors.\textsuperscript{67} Furthermore, close contact to a PJP cluster, which sometimes causes PJP outbreaks, is a risk factor for transplant recipients.\textsuperscript{7,68} Asymptomatic carriage plays a role in the transmission of \emph{P. jirovecii} and may pose a risk in the development of PJP.\textsuperscript{40,45}

**Clinical Manifestations**

Diarrhea, vomiting, flu-like prodromes, and dry cough without dyspnea are all known symptoms that may precede the classical presentation. PJP in HIV patients is slowly progressive in onset, and fever, nonproductive cough, and dyspnea are common.\textsuperscript{69} In contrast, PJP in non–HIV patients is sometimes void of these symptoms, because immunosuppressive agents suppress these clinical findings. For transplant recipients at outpatient visits who are suspected of having PJP, it is useful to monitor oxygenation by pulse oximetry after walking for a while. Oxygen saturation will be reduced if the recipient suffers from PJP. Over a few days, PJP finally develops to become the symptomatic disease state with severe dyspnea and hypoxemia.

While the serum level of lactate dehydrogenase (LDH) is significantly higher in PJP patients, the C-reactive protein (CRP) is not elevated.\textsuperscript{70} Thus, PJP in transplant recipients are sometimes misdiagnosed as a common cold in the early stages because of the low CRP level and suppressed fever.

**Diagnosis**

In addition to clinical symptoms and imaging (X-ray and high-resolution computed tomography [HRCT] scans), Diff-Quik (DQ; a method for staining bronchoalveolar lavage fluid [BALF]), polymerase chain reaction (PCR) or loop-mediated isothermal amplification (LAMP) method from BALF, and...
serum (1–3)-beta-D-glucan (BDG) are useful for diagnosing non-HIV PJP.

**Microbiological diagnosis. Staining.** It is not possible to culture *P. jirovecii in vitro.* Identification of *P. jirovecii* from oral wash, sputum, BALF, or lung tissue is needed for the definitive diagnosis of PJP. Sensitivity for diagnosing PJP is reduced significantly with the use of oral wash and sputum. Transbronchoscopic or surgical lung biopsy is rarely needed. Therefore, if the patient’s respiratory status is good, bronchoscopy with BALF should be performed for all suspected transplant recipients.

During infection, the amount of trophic forms is ten times more dominant than that of the cyst form. However, trophic forms are small (1–4 μm in diameter) compared to the larger cysts (8 μm in diameter), and can only be stained by DQ, a modified Wright-Giemsa stain, or by an immunoenzyme assay. DQ is inexpensive and takes only several minutes to prepare. It can also detect both trophic and cyst forms, but this stain requires a high level of technical expertise. Cysts can be stained with Grocott silver, which is more rapid than Gomori methenamine silver, cresyl echt violet, toluidine blue O, or calcofluor-white. These staining techniques do not detect the trophic forms. Compared to DQ, these stains do not require special skills for the finding of cysts. If a laboratory does not have sufficient technical expertise for performing DQ, the Grocott silver stain can be useful for identifying *P. jirovecii*. However, the most commonly used Grocott silver stain is not suitable for making rapid diagnoses. PJP is associated with significantly lower numbers of *P. jirovecii* and substantially higher numbers of neutrophils in the lavage fluid samples of non-HIV patients compared to that of HIV patients. It is therefore very difficult to identify *P. jirovecii* with staining of samples from non-HIV PJP patients. Even if the trophic or cyst forms cannot be detected, non-HIV PJP cannot be ruled out. Immunofluorescent staining techniques are also available, which could provide increased specificity and sensitivity.

**Genetic testing (PCR and LAMP).** PCR with oral-wash, sputum, and BALF samples has a high sensitivity and specificity for the detection of the organism, but lacks sensitivity in diagnosing PJP because of the fact that PCR cannot differentiate colonization from infection. In the diagnosis of PJP in HIV patients, PCR sensitivity was 72%–100% and specificity was 86%–100%. In the diagnosis of PJP in non-HIV patients, sensitivity was 87.2% and specificity was 92.2%, with a positive predictive value (PPV) of 51.5% and a negative predictive value (NPV) of 98.7%. However, PCR is helpful in excluding PJP in HIV-negative patients. Clinical judgment is essential in cases of negative staining and positive PCR. Treatment for PJP should be initiated if clinical suspicion is high, and PCR may be useful in such patients. By using quantitative real-time PCR other than the aforementioned conventional PCR method, several studies have shown that the copy number of a specific *P. jirovecii* gene is significantly higher in patients with PJP than in colonized patients, thereby differentiating colonization from infection. But this is far from being a standardized testing method as there are many target genes and no cutoff value for the copy number.

Recently, a new specific DNA amplification technique called LAMP was developed. In non-HIV PJP patients, *Pneumocystis* LAMP showed higher sensitivity (95.4%) and PPV (91.3%) than conventional PCR showed in the diagnosis of PJP. Advantages of the LAMP method are that it is faster and easier than the PCR-based method.

**Serological diagnosis. Beta-D-glucan.** BDG is a major component of many fungal cell walls, excluding Zygomycetes and *Cryptococcus neoformans*. The measurement of BDG in sera was first established in 1995 in Japan, and then in 2004 in the USA and has been recommended as one of the indirect mycological criteria for the diagnosis of invasive fungal infection (IFI). It was first reported that BDG was in the cyst wall of *Pneumocystis* in 1989, which affected how *Pneumocystis* was later found to be a fungus. As a practical serological marker, BDG was first found to be detectable in the sera of patients with PJP in 1996.

There are three measurements with different cutoff values, which are the Fungitell, Fungitec G test MK, and Wako. The plasma cutoff values for MK and Wako are 20 and 11 pg/mL, respectively. These data were established with aspergillosis or candidiasis as the IFI and did not include PJP. The diagnostic cutoff values for BDG in PJP that was diagnosed by the identification of *P. jirovecii* in BALF were 31.1 pg/mL (in both HIV PJP and non-HIV PJP patients) and 23.2 pg/mL (HIV PJP). From a recent meta-analysis, the sensitivity and specificity of BDG were 94.8% and 86.3%, respectively. These data did not depend on HIV infection, so it indicates that serum BDG may be a helpful marker for the diagnosis of non-HIV PJP. Given this excellent sensitivity, PJP can be ruled out if the BDG is negative.

Of the various serum markers tested, it has also been reported that the serum BDG level is the best test for PJP diagnosis. While its specificity is very good, it is important to consider the factors associated with false-positive results if the BDG result is positive, such as the use of intravenous (IV) amoxicillin–clavulanic acid, treatment with immunological preparations (albumins or globulins), use of cellulose membranes and filters made from cellulose in hemodialysis, and use of cotton gauze swabs/packs/pads and sponges during surgery. It is also important to exclude other IFI coinfections. BDG does not correlate with disease severity and may not be suitable for monitoring the response to treatment.

**Imaging.** A typical radiographic feature of PJP is the presence of bilateral peripheral interstitial infiltrates. HRCT scans are more sensitive than chest radiography and may show ground glass opacities with sparing of the lung periphery, although these abnormalities are nonspecific.
Treatment

**Antipneumocystis agents.** TMP-SMX is the first choice for the treatment of PJP in non-HIV as well as HIV patients.\(^\text{54,107}\) No agent has been shown to have outcomes superior to TMP-SMX. It has excellent oral bioavailability, but if the general condition is poor, IV administration is used to achieve comparable serum levels as oral (PO) administration. The standard dose of TMP-SMX is TMP 15–20 mg/kg/day + SMX 75–100 mg/kg/day IV in divided doses every six to eight hours, according to the renal function, and adequate hydration should be maintained. Because TMP inhibits excretion of creatinine in the renal tubule, elevated serum creatinine levels have been observed.\(^\text{108}\) During the administration of standard-dose TMP-SMX, cell counts, creatinine, and potassium should be monitored. Although increases in serum potassium and gastrointestinal disorders are seen clinically for some transplant recipients with PJP, most recipients can use TMP-SMX.

Twenty-one days of treatment with TMP 15–20 mg/kg/day + SMX 75–100 mg/kg/day for HIV PJP have not been evaluated by randomized controlled trials (RCTs). Because *P. jirovecii* cannot be cultured, the minimum inhibitory concentration (MIC) against it is not known. One retrospective study suggests that TMP 10 mg/kg/day + SMX 50 mg/kg/day for HIV PJP has comparable efficacy to treatment with the low dose.\(^\text{109}\)

Atovaquone is a second-line agent, although it is used only for mild-to-moderate PJP. As absorption of atovaquone decreases under fasting conditions or with diarrhea, administration after meals is needed. Therefore, it is difficult to use in severe cases of PJP that require care in the intensive care unit (ICU). IV pentamidine is a third-line agent, but it is also highly toxic. Its side effects include pancreatitis, hypoglycemia, hyperglycemia, bone marrow suppression, renal failure, and electrolyte disturbances.\(^\text{107}\)

The optimal duration of therapy for PJP in HIV-negative patients has not been fully studied. Owing to the low number of organisms and fast clinical progression, antimicrobial therapy is needed for at least 14 days. Therapy for severe PJP may be required for 21 days, as is the case for HIV patients.\(^\text{110}\) There are no data that verify whether immunosuppression should be continued, reduced, or stopped during the treatment of PJP. However, as a general measure, reduction should be encouraged.\(^\text{111}\)

**Glucocorticoids.** Adjunctive glucocorticoids are recommended in HIV patients with moderate or severe PJP.\(^\text{110}\) Prednisone 40 mg is administered PO twice daily for five days, followed by 40 mg PO once daily for five days, and then 20 mg PO once daily for 11 days. On the other hand, no clear evidence regarding efficacy has been shown for adjunctive glucocorticoid therapy in the treatment of PJP in non-HIV patients. Retrospective studies with adjunctive glucocorticoid use in non-HIV PJP showed either a benefit\(^\text{112–114}\) or no impact.\(^\text{114–117}\) Furthermore, the dose, duration, and timing of steroids have not been fully studied in cases of transplantation.

Recently published guidelines of the American Society of Transplantation (AST) suggest that prednisone 40–60 mg should be administered PO twice daily and tapered after five to seven days over a period of one to two weeks.\(^\text{107}\) While this is a high initial dose, it is tapered early to avoid over-immunosuppression. Given the fulminant course and poor prognosis of non-HIV PJP, adjunctive glucocorticoid therapy might be required. Prospective investigations on the role of adjunctive glucocorticoid therapy in non-HIV patients are needed.\(^\text{118}\)

Glucocorticoids are best administered within 72 hours in the setting of hypoxia (\(\text{PaO}_2\) <70 mmHg). In HIV patients, glucocorticoids should be administered along with TMP-SMX.

Non-HIV PJP should be treated as soon as possible in all suspected recipients without a definitive diagnosis, since the onset is abrupt and prognosis is poor. In most cases, TMP-SMX and adjunctive glucocorticoids are administered first followed by bronchoscopy. In the hospital, pulse therapy of methylprednisolone sodium succinate injection (500 mg for three consecutive days) is performed for severe PJP requiring ICU care.

**Reduction of immunosuppression.** The overall net state of immunosuppression is the main contributor to PJP, and reduction in immunosuppression is a common initial approach to PJP management.\(^\text{62,63}\) But the optimal strategy for immunosuppression reduction is uncertain. We discontinue MMF as antimetabolite for 14–21 days with adjunctive glucocorticoids. When PJP patients requiring ICU care need saving their lives rather than maintaining grafts function, we discontinue temporarily both MMF and CNIs with pulse therapy of methylprednisolone sodium succinate injection.

**Prophylaxis**

TMP-SMX is also the first drug of choice for PJP prophylaxis in SOT.\(^\text{119}\) TMP-SMX prophylaxis also prevents infections involving *Toxoplasma* and *Listeria* species, which are respiratory, urinary, and GI pathogens. Therefore, TMP-SMX reduces urinary tract infections and possibly GI and respiratory infections in transplant patients. Side effects, which are often dose-related, are less common with the prophylactic dose. Trimethoprim inhibits potassium and creatinine secretion in the renal tubules, resulting in hyperkalemia and an elevation in serum creatinine.\(^\text{107}\) These laboratory abnormalities are emphasized when graft function deteriorates. Breakthrough PJP infection with TMP-SMX prophylaxis is rare.

The second treatment option is dapsone,\(^\text{107}\) while atovaquone (1500 mg PO qd) and aerosolized pentamidine (300 mg administered through aerosolized nebulizer q four weeks) are other options for prophylaxis. But this recommendation is based on HIV-positive patients.\(^\text{120}\) The dose of TMP-SMX can be 80 mg TMP/400 mg SMX daily or 160 mg TMP/800 mg SMX PO (single or double strength) daily or
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The transmission of PJP is inversely correlated with the intensity of the survival of PJP patients without HIV infection. An early diagnosis and treatment within three days are crucial for the outcome of PJP is inversely correlated with the intensity of the survival of PJP patients without HIV infection. An early diagnosis and treatment within three days are crucial for the outcome of PJP, combined bacteremia, increased BUN, and preexisting lung disease are all independent factors of a poor prognosis in non-HIV PJP. Because of the rapid progression in clinical worsening, early diagnosis and treatment are required. Starting treatment within seven days after onset is important because intubation and mechanical ventilation may be avoided. Furthermore, diagnosis and treatment within three days are crucial for the survival of PJP patients without HIV infection. The outcome of PJP is inversely correlated with the intensity of immunosuppression. Mortality is 6.6% in HIV patients and 39% in non-HIV patients. Mortality is high (32%–33%) in PJP complicated with connective tissue disease where the immunological status may not be as severely impaired as in transplant recipients or HIV patients.

Infection Control when an Outbreak has Occurred

It is important to control PJP when it occurs as a nosocomial infection. In particular, since there is a larger number of kidney transplant recipients compared to other types of organ transplantations, kidney transplant recipients have a greater chance of sharing time and space in outpatient clinics. There are three important things that PJP patients, other recipients, and medical staff can do during an outbreak, as described below.

- **Treat PJP patients so as not to transmit P. jirovecii to others (other recipients and medical staff).** In the outpatient setting. Among outpatients, those with a suspected or confirmed PJP diagnosis should wear a mask as soon as possible when sharing a waiting room with other transplant recipients. Close contact should be avoided. PJP therapy should be started as soon as possible in recipients for two reasons. First, PJP in transplant recipients present with an abrupt onset of respiratory distress, unlike the clinical course in HIV patients, and late diagnosis and treatment may increase the risk of respiratory failure and death. If PJP patients in need of hospitalization need to wait for a hospital bed, corticosteroids should be administered along with TMP-SMX at least once in the outpatient setting. Second, a delay in diagnosis and treatment may lead to an increase in the number of other PJP patients as a result of direct transmission. Even if a direct transmission does not occur, a delay in diagnosis and treatment may lead to an increase in reservoir patients, who may pose a risk of a later PJP or may transmit the infection to other recipients.

- **For hospitalized PJP patients.** The transmission of P. jirovecii can be the highest from before the onset of clinical symptoms of PJP until the end of the first week of antipneumocystis therapy. Hospitalized patients with PJP should be managed with standard precautions. Certain authorities recommend that they should not be placed in the same room as immunocompromised patients, including other transplant recipients. However, this recommendation is based on animal studies and anecdotal human experience, and data to support this recommendation as a standard practice are lacking. In the absence of an isolation bed, prophylaxis with TMP-SMX for all hospitalized immunocompromised patients in the same ward should be considered before the admission of PJP patients.

- **Protect other transplant recipients from P. jirovecii transmission in the outpatient setting.** For all transplant recipients that share a waiting room with a PJP patient, starting transient prophylaxis may be the major form in colonization) are not sensitive to TMP-SMX. However, these doses were not determined by RCTs, and to date, no universal consensus exists on the optimal duration of prophylaxis. For example, the European Renal Transplant Guidelines recommend PJP prophylaxis for at least four months after transplantation, whereas the AST recommends 6–12 months. Meanwhile, the Kidney Disease Improving Global Outcomes guideline recommends three to six months after transplantation. The duration of PJP prophylaxis depends on each transplant center. From a survey of US renal transplant centers, 84% of centers use PJP prophylaxis while 16% do not. The duration of prophylaxis also varies widely, with 43% of centers using prophylaxis for six months or less and 22% maintaining prophylaxis for longer than a year. In Japan, some centers do not use PJP prophylaxis, although on the other hand, some large centers that have experienced the painful experience of an outbreak use lifelong PJP prophylaxis in their lung and small bowel transplant recipients. There is no accepted answer, and a unit subject to an epidemic needs to be quick and effective if they are to avoid deaths and graft losses. In addition, lifelong prophylaxis may be indicated for all transplant recipients with a history of prior PJP infection (Grade III; Opinions of respected authorities). It is impossible to prevent colonization with TMP-SMX and furthermore, TMP-SMX cannot clear P. jirovecii colonization. Though these critical points are only supported by clinical data, use of pneumocystis prophylaxis was not related to the risk of colonization in PJP of KT and HIV.

Colonization of P. jirovecii is detected in 18.6% of kidney transplant recipients. Colonization can be cleared by suppressed macrophages caused by immunosuppression. TMP-SMX is an antiparasitic agent and not an antifungal agent. While trophic forms (the most abundant of all Pneumocystis life cycle stages) are sensitive to TMP-SMX, cysts (which may be the major form in colonization) are not sensitive to TMP-SMX.

Outcome

The outcome of PJP in non-HIV patients is generally poorer than that in HIV patients. The most likely explanation is that the host inflammatory response is assumed to be more intense in non-HIV patients with PJP despite the lower number of organisms present, thereby contributing to severe lung injury. BALF neutrophilia, high D(A-a)O₂, combined bacteremia, increased BUN, and preexisting lung disease are all independent factors of a poor prognosis in non-HIV PJP. Because of the rapid progression in clinical worsening, early diagnosis and treatment are required. Starting treatment within seven days after onset is important because intubation and mechanical ventilation may be avoided. Furthermore, diagnosis and treatment within three days are crucial for the survival of PJP patients without HIV infection. The outcome of PJP is inversely correlated with the intensity of immunosuppression. Mortality is 6.6% in HIV patients and 39% in non-HIV patients. Mortality is high (32%–33%) in PJP complicated with connective tissue disease where the immunological status may not be as severely impaired as in transplant recipients or HIV patients.

PJP infection leads to increased graft and patient loss in renal transplantation. Mortality in the absence of TMP-SMX prophylaxis is 5%–33% in the current immunosuppressive era of renal transplantation.

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- **For hospitalized PJP patients.** The transmission of P. jirovecii can be the highest from before the onset of clinical symptoms of PJP until the end of the first week of antipneumocystis therapy. Hospitalized patients with PJP should be managed with standard precautions. Certain authorities recommend that they should not be placed in the same room as immunocompromised patients, including other transplant recipients. However, this recommendation is based on animal studies and anecdotal human experience, and data to support this recommendation as a standard practice are lacking. In the absence of an isolation bed, prophylaxis with TMP-SMX for all hospitalized immunocompromised patients in the same ward should be considered before the admission of PJP patients.

- **Protect other transplant recipients from P. jirovecii transmission in the outpatient setting.** For all transplant recipients that share a waiting room with a PJP patient, starting transient
prophylaxis with TMP-SMX for six months may be effective to avoid repeated outbreaks by infectious asymptomatic carriers. To control a PJP outbreak, all recipients should be treated at the same time with transient prophylaxis using TMP-SMX. Some have compliance to P. jiroveci prophylaxis. Although TMP-SMX cannot clear colonization, it can control the onset of PJP derived from colonization.\textsuperscript{24,124} The estimated median incubation period from the transmission of P. jiroveci to the onset of PJP is 53 days (range 7–188 days),\textsuperscript{4} which means that colonization might be cleared by suppressed macrophages in about six months. The outbreak of PJP as well as any subsequent sporadic PJP can be terminated with six months of TMP-SMX prophylaxis in all recipients without compliance. Transplant recipients that cannot use TMP-SMX because of pregnancy may need to wear a mask in the hospital and visit outpatient clinic at a time with the fewest visits by other transplant recipients.

**Education of medical staff in transplant centers.** Medical staff such as doctors, nurses, and medical clerks who are infected by PJP patients or from environmental exposure can act as a transient reservoir. Coughing or sneezing by reservoir individuals can lead to the development of new PJP in transplant recipients, although this has only been shown in mice.\textsuperscript{46,67} Nevertheless, medical staff who have close contact with recipients when conducting conversations may need a mask so as not to become a reservoir.

PJPs in transplant recipients are sometimes misdiagnosed as a common cold in the early stages because of the low CRP level and suppressed fever. Because of the cold-like symptoms, the patient might only consult the nurse by phone rather than a doctor. Symptoms of PJP in kidney transplant recipients should be well known to nurses or medical clerks in addition to doctors so that PJPs are not missed, especially during an outbreak. Nurses or medical clerks who receive the first call from suspected PJP transplant recipients should recommend the patients to visit the hospital with a mask and avoid waiting in the usual room or outpatient clinic visit time (isolation by time and space).

**Conclusion and Perspective**

Recent progress in immunosuppressive agents has resulted in long-term allograft survival and patient survival. At the same time, however, there have also been unwanted consequences from immunosuppression. The CD4 T-cell count is a useful marker that can be used to classify the risk of developing PJP in HIV patients,\textsuperscript{158} while on the other hand, there are no useful markers for monitoring the immunological status of kidney transplant recipients.

While TMP-SMX is the first choice for PJP prophylaxis, it is impossible to prevent colonization with TMP-SMX\textsuperscript{6,124} and furthermore, TMP-SMX cannot clear cysts that are dominant in colonization.\textsuperscript{24} However, it can control the development of PJP by preventing its onset. Suppression of macrophages by high-level immunosuppression may lead to reduced eradication rate of colonization. In addition, because of the large number of kidney transplant recipients, there are unfortunately a lot of opportunities for recipients to be exposed to each other at the same time and space. Once a PJP cluster enters these populations that are under uniform immunosuppression, a PJP outbreak may occur easily.

To control a PJP outbreak, there are three quick actions, including by PJP patients, other recipients, and medical staff of transplant centers. Breakthrough PJP infection with TMP-SMX prophylaxis is rare. Though the cost of PJP prophylaxis and drug resistance is low, hyperkalemia is the concern of lifelong prophylaxis in kidney transplant recipients when graft function deteriorates. Furthermore, the dose of TMP-SMX for PJP prophylaxis has not been determined by RCTs. In the future, even in kidney transplant recipients, lifelong prophylaxis with a lower dose of TMP-SMX as PJP prophylaxis may be required. Since P. jiroveci can be cultured from the recent report,\textsuperscript{14} the MIC of TMP-SMX against P. jiroveci may become clear. This finding also enables microbiological studies on how P. jiroveci form in colonized recipients or in environment and how long P. jiroveci can survive outside the human host.

**Author Contributions**

Conceived the concepts: NG. Wrote the first draft of the manuscript: NG. Developed the structure and arguments for the paper: NG. Contributed to the development of the results and conclusions: KF, MO, TY, MT, TH, SN, YW. Made critical revisions: NG. All authors reviewed and approved of the final manuscript.

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