

Review

Pneumocystis jirovecii infection: an emerging threat to patients with rheumatoid arthritis

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Abstract

Accompanying the increased use of biologic and non-biologic antirheumatic agents, patients with RA have been exposed to an increased risk of *Pneumocystis jirovecii* infection, which causes acute fulminant *P. jirovecii* pneumonia (PCP). Mortality in this population is higher than in HIV-infected individuals. Several guidelines and recommendations for HIV-infected individuals are available; however, such guidelines for RA patients remain less clear. Between 2006 and 2008 we encountered a clustering event of *P. jirovecii* infection among RA outpatients. Through our experience with this outbreak and a review of the recent medical literature regarding asymptomatic colonization and its clinical significance, transmission modes of infection and prophylaxis of PCP, we have learned the following lessons: PCP outbreaks among RA patients can occur through person-to-person transmission in outpatient facilities; asymptomatic carriers serve as reservoirs and sources of infection; and short-term prophylaxis for eradication of *P. jirovecii* is effective in controlling PCP outbreaks among RA outpatients.

Key words: *Pneumocystis jirovecii*, rheumatoid arthritis, colonization, transmission, outbreaks, prophylaxis.

Introduction

Over the past decade, the treatment of RA has dramatically changed. Early use of MTX as the first-line DMARD and the emergence of innovative biologic agents targeted at specific molecules and pathways in the immune system have altered the course of RA and improved patient and social outcomes [1, 2]. However, accompanying the increased use of biologic and non-biologic antirheumatic drugs, RA patients have been exposed to an increased risk of *Pneumocystis jirovecii* pneumonia (PCP) [3–6]. CSs, widely used in the treatment of RA, are also implicated as a major predisposing factor for PCP development [7]. RA itself also contributes to increased risk of infection because of its immunomodulatory effects [8].

Pneumocystis jirovecii (formerly known as *Pneumocystis carinii* f. sp. *hominis*) is an important opportunistic fungal pathogen in humans who have depressed

immune function [9, 10]. The onset of PCP in RA patients often presents with abrupt severe oxygenation impairment and this complication is potentially life threatening [11]. Recently we reported a PCP outbreak among RA outpatients [12]. This is the first report indicating the possibility that clustering events of nosocomial *P. jirovecii* infection can occur among such patient groups, although sporadic cases of PCP have been reported. In the years ahead, more RA patients will be treated with immunosuppressive therapy, with increasing therapeutic durations. Therefore rheumatologists should be prepared for an increased risk of PCP outbreaks among RA patients. In this mini-review, we examine the recent literature with the goal of developing a preventative strategy against outbreaks of *P. jirovecii* infection among RA outpatients.

History

Pneumocystis jirovecii was first recognized as a pathogen in premature infants developing an epidemic form of interstitial plasma cell pneumonitis in European countries during the Second World War. In 1952 the Czech pathologists Vanek and Jirovec [13] described *Pneumocystis* as the causative agent of this endemic pneumonia [14]. Since then PCP has only been reported sporadically in premature infants and malnourished young children [15, 16]. In the 1960s PCP started to be recognized as

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an opportunistic pathogen in immunocompromised children with congenital T cell immunodeficiency and in patients with haematological neoplasm such as acute lymphoblastic leukaemia or lymphomas [17, 18]. After the introduction of trimethoprim-sulphamethoxazole (TMP-SMZ) as PCP chemoprophylaxis, however, its incidence markedly decreased [19]. With the emergence of the human immunodeficiency virus (HIV) pandemic, there was a dramatic increase in the incidence of PCP. In the 1980s PCP was the most common opportunistic infection in patients with AIDS, and among them >60% developed PCP during their disease course [20]. In the 1990s the routine use of PCP prophylaxis and the widespread use of highly active anti-retrovirus therapy brought a substantial decline in the incidence of PCP among HIV-infected persons [21, 22]. As a result of the increased number of patients receiving immunosuppressive or cytotoxic therapy for solid tumours and haematological malignancies, organ and bone marrow transplantation, and inflammatory and rheumatic diseases, the clinical significance of PCP has been recognized in HIV-negative immunocompromised individuals [23–28].

Immunosuppressive therapy and PCP

Roles of immunosuppressive therapy in PCP development

Host defence against *P. jirovecii* involves a complex series of interactions between CD4⁺ T lymphocytes, alveolar macrophages, polymorphonuclear cells and various pro-inflammatory mediators released by these cells [29, 30]. Immunosuppressive agents apparently influence such host immune systems. In particular, it is likely that CSs promote PCP development through depletion of CD4⁺ T cells [31]. This therapy has therefore been identified as a risk factor of PCP in HIV-negative patients who have a variety of underlying conditions [7, 25, 32–34]. Even low or moderate doses of CSs can increase the risk of PCP [24, 35–37]. In most cases CSs were being given as pulse therapy with sudden discontinuation or the dose was lowered on diagnosis of PCP [23, 28]. Withdrawal of CSs can lead to reconstitution of the immune system and result in immune-mediated damage to the lungs [38]. Inflammatory responses directed against *P. jirovecii* are essential for clearance of *P. jirovecii* from the body; however, excessive inflammation can cause severe lung injury and impairment of pulmonary function [39]. These findings may be related to the fact that PCP often occurs in HIV-negative rheumatic disease patients with CD4⁺ T cell counts >200/ μ l [11, 12, 34, 37, 40].

Incidence and mortality of PCP in RA patients and those with other rheumatic diseases during immunosuppressive therapy

Recent post-marketing surveillance (PMS) reports by the Japan College of Rheumatology (JCR) indicated a high incidence of PCP in RA patients receiving the anti-TNF- α agents infliximab (0.4% of 5000 patients), etanercept

(0.2% of 7091 patients) and adalimumab (0.3% of 3000 patients) [41–43]. A review of US Food and Drug Administration data between 1998 and 2003 identified 84 cases of PCP following infliximab therapy [44]. Regarding a humanized monoclonal anti-IL-6 receptor antibody tocilizumab, a PMS conducted by the JCR reported that the incidence of PCP is 0.28/100 patient-years [45]. Low-dose MTX can also increase the risk of developing PCP in RA patients [3, 4, 37, 46]. As shown in Table 1, the most recent surveillance by individual pharmaceutical companies in Japan indicates a high number of PCP cases in RA patients during treatment with low-dose MTX (S. Mori, June 2012, personal communication).

In typical cases of untreated or delayed-treatment PCP, progressive alveolar damage leads to death. Despite the availability of medications for treatment, the mortality rate of PCP still remains high. Most studies indicate better survival rates for HIV-positive PCP patients (86–92%) than HIV-negative PCP patients with various underlying conditions (51–80%) [47]. HIV-negative PCP patients appear to rapidly develop fulminate pneumonia with severe oxygenation impairment, diffuse alveolar damage and respiratory failure, whereas PCP in HIV-positive individuals presents as a subacute disease course [23, 25–28, 40, 48–51]. Differences in inflammatory responses of the lungs apparently contribute to such marked differences between the two types of PCP in clinical presentations, outcomes and mortality [29]. High mortality rates have been reported in RA patients and those with other rheumatic diseases who developed PCP during immunosuppressive therapy [11, 32–34, 37, 44, 52]. High numbers of fatal PCP cases during treatment with biologic or non-biologic agents for RA have been reported by pharmaceutical companies in Japan (Table 1).

TABLE 1 Incidence and mortality rate of *P. jirovecii* pneumonia in RA patients during immunosuppressive therapy in Japan

Anti-RA agents	PCP incidence, n (%) ^a	Mortality, n (%) ^a
MTX	236	28 (11.9)
Tacrolimus	14	4 (28.6)
Infliximab	188 (0.3)	19 (10.1)
Etanercept	81 (0.1)	15 (18.5)
Adalimumab	54 (0.3)	10 (18.5)
Golimumab	1 (0.03)	0
Tocilizumab	14 (0.2)	2 (14.3)
Abatacept	9 (0.1)	2 (22.2)

^aPCP incidence and mortality are expressed as numbers of patients who developed PCP during treatment with the respective immunosuppressive agents and who died due to this pneumonia, respectively. Exact numbers of patients who used MTX and tacrolimus were not available. Data were obtained from the most recent surveillance reports by individual pharmaceutical companies in Japan (S. Mori, June 2012, personal communication).

Reactivation from lifelong latency or *de novo* infection?

It has long been debated whether PCP development is due to a reactivation of latent childhood infection or *de novo* acquisition. There is evidence that contact with *P. jirovecii* occurs early in life (primary infection). Pifer *et al.* [53] found that two-thirds of normal children have acquired antibody against this organism by 4 years of age, analogous to other opportunistic infections, indicating early exposure to this organism. Vargas *et al.* [54] also showed that seroconversion developed in 85% of healthy infants by 20 months and *P. jirovecii* DNA was frequently detected during episodes of mild respiratory infection in 32% of normal infants. These findings suggest that sub-clinical *P. jirovecii* infection is highly prevalent in healthy infants. PCP events occurring in adults were therefore considered to be mostly due to a reactivation of latent infection of *P. jirovecii*.

However, this theory has been challenged by recent findings that clustering of specific genotypes is associated with the place of diagnosis (residence) rather than the place of birth [55–57]. Other studies also demonstrated geographic clustering of PCP cases among HIV-infected individuals living in specific zip codes of San Francisco and Cincinnati [58, 59]. These findings have suggested that *P. jirovecii* infections are actively acquired from a common environmental source or person-to-person contact [60]. Several studies have indicated that recurrent episodes of PCP in HIV-infected individuals were caused by *de novo* infection rather than by reactivation of latent infection, because genetically distinct strains were isolated during each episode of PCP [61–64].

Serial examinations of pulmonary specimens indicated that persistent *P. jirovecii* cysts at the end of antimicrobial treatment for acute PCP are gradually cleared from the lungs of HIV-infected patients [65]. Wakefield *et al.* observed asymptomatic carriage of *P. jirovecii* for no longer than 9.5 months in HIV-positive patients after a PCP episode [66]. These findings provide support for the conclusion that, instead of lifelong latency, the relationship between *P. jirovecii* and its host appears to be transient colonization. PCP development seems to result from new infection rather than reactivation of latent childhood infection. Using mouse or rat models, several groups showed that immunocompromised animals naturally acquired *P. carinii* infection as well as developed pneumonia, but with the recovery of the immune system, the hosts completely cleared this organism within relatively short periods (3 weeks to 1 year) [67–69]. The carrier status of *Pneumocystis* organisms in immunocompetent hosts seems a time-limited phenomenon.

Establishing the major route for infection: a common environmental source or interhuman transmission?

Possible infectious sources of *de novo* infection of *P. jirovecii* have not yet been established, but they may

include the environment, asymptomatic carriers and patients with active PCP. Utilizing data from genotyping and contact tracing, several studies of PCP clusters among HIV-infected individuals or immunosuppressive patients from other conditions have suggested that person-to-person transmission may occur but does not constitute the majority route of acquisition [70–72]. Another group reported a PCP episode due to genetically distinct *P. jirovecii* strain in each member of three HIV-infected couples, and therefore ruled out direct transmission within each couple [73]. Wakefield [74] detected *P. jirovecii* DNA in ambient air collected from a number of spore traps, suggesting that *P. jirovecii* is a common component of air spores in a rural area in England. *Pneumocystis jirovecii* DNA has also been identified in air samples obtained from hospital environments, which suggests an environmental risk to susceptible persons [75, 76]. At the same time, this finding may indicate the presence of nosocomial person-to-person transmission via the airborne route (aerosol spread). Choukri *et al.* [77] indicated that detection rates of *P. jirovecii* in air samples decrease with increasing distance from hospitalized patients with PCP and thereby proposed a possible risk of direct airborne transmission of *P. jirovecii* from close contact with PCP patients. In each PCP patient reported in that study, *P. jirovecii* genotypes in surrounding air samples closely matched those in pulmonary specimens, confirming that *P. jirovecii* organisms in the air of hospital rooms were exhaled by PCP patients [78]. Animal models also indicate a direct airborne transmission route of *Pneumocystis* species among immunosuppressed mice, from immunocompetent mice to highly susceptible mice, and among healthy mice [79–81].

Humans do not appear to contract *Pneumocystis* pneumonia from animals. *Pneumocystis* species are transmissible only to the same host species and cross-transmission among different mammalian species has not been documented [82, 83]. Molecular analysis also showed that rats and humans harbour distinct types of *Pneumocystis* species [84]. In addition, the challenging task of continuously culturing this species outside of the host lung has not as yet been successful; namely, *Pneumocystis* cannot propagate outside an infected host [85].

Asymptomatic carriers of *P. jirovecii* as the infectious reservoir

Recent studies have shown the presence of asymptomatic carriers of *P. jirovecii* and their participation in the transmission cycle as an infectious reservoir for susceptible individuals in the community. High rates of prevalence of *P. jirovecii* colonization are reported among HIV-positive individuals who were hospitalized with non-PCP pneumonia (68%) or who died from causes other than PCP (46%) [86, 87]. Of particular note is the fact that carriage of this organism has been described in HIV-negative individuals with immunosuppressive conditions, those with chronic pulmonary disease and even immunocompetent healthy persons.

Healthy individuals

Ponce *et al.* [88] reported a high prevalence (more than half) of mild infection of *P. jirovecii* in the autopsy lungs of the general adult population. The authors have proposed that immunocompetent individuals can develop frequent self-limiting reinfection throughout life after primary infection. Medrano *et al.* [89] also showed evidence that *P. jirovecii* DNA can be detected in the respiratory tract of 20% of healthy adults without underlying pulmonary disease or immunosuppression. This infection was short-lived: the DNA was not detected in >75% of colonized individuals after 6 months of follow-ups. Such colonization has also been demonstrated in older adults (21.5%) and healthy infants (32%) [54, 90]. Totet *et al.* [91] reported shared features of *P. jirovecii* genotypes between immunocompetent infants with a primary infection and immunocompromised adults with PCP. These findings strongly support the idea that the general population is a reservoir and source of *P. jirovecii* infection.

Transmission by contact of health-care workers to PCP patients

Molecular evidence has accumulated that immunocompetent health-care workers are at risk of *P. jirovecii* colonization by occupational close contact with patients who have developed PCP [92, 93]. In addition, several groups observed that *P. jirovecii* persists for limited periods of time in HIV-positive patients who have clinical recuperation after PCP [65, 66]. Thus transmission of this infection through hospital staff may continue for some time after patients' recovery from PCP. Health-care workers may serve as vectors of this infection. In contrast, Lundgren *et al.* [94] have claimed, based on serological and molecular testing, that immunocompetent hospital staff treating PCP patients are not a potentially infectious source of *P. jirovecii* for immunocompromised patients.

Patients with pulmonary disease

Asymptomatic carriage of *P. jirovecii* has been recognized in immunocompetent patients who have primary pulmonary disorders such as chronic obstructive pulmonary disease (COPD), lung cancer, interstitial lung disease, tuberculosis and cystic fibrosis, suggesting that lung tissue injury may favour colonization by this organism [95–102]. CS therapy was an independent risk factor for colonization in patients undergoing diagnostic bronchoscopy and those suspected of bacterial pneumonia [103, 104]. Montes-Cano *et al.* [105] showed the presence of a continuous cycle of colonization and clearance in cystic fibrosis patients during a 1-year follow-up period. Considering that the patients with chronic pulmonary diseases are sputum producers, they may represent a reservoir for *P. jirovecii* with the potential ability of transmission to susceptible hosts. In fact, Rivero *et al.* [106] reported a case of *P. jirovecii* transmission from a grandfather with chronic bronchitis and sputum production to a grandmother and an infant via the airborne route. Morris *et al.* [107] reported a strong association between *P. jirovecii* colonization and severity of airway obstruction in

smokers, suggesting that this organism may play a pathogenic role in COPD progression. Recently we have shown that bronchiolar abnormalities are commonly seen in RA patients, especially those with long-standing RA [108, 109]. In addition, bronchiectasis was the most frequent finding in both patients with early RA and those with long-standing RA [108]. Such modifications of bronchial and bronchiolar structures in the lungs of RA patients may provide a favourable environment for infection and colonization by *P. jirovecii*.

Patients with underlying diseases associated with immunosuppression

Pneumocystis jirovecii can colonize patients who have immunosuppressive conditions [46, 110–113]. Underlying diseases comprise haematological malignancies, solid tumours, inflammatory and rheumatic diseases, and organ transplant recipients. Many of these patients received immunosuppressive drugs and/or long-term CS therapy. Risk factors for colonization have remained controversial in this clinical setting. Nevez *et al.* [114] showed that an increased risk of *P. jirovecii* colonization is significantly associated with a CD4⁺ T cell count <400/μl in HIV-negative patients with underlying disease associated with immunosuppression. Mekinian *et al.* [113] found a high prevalence of *P. jirovecii* colonization (16%) in patients with systemic autoimmune diseases and identified high-dose CS therapy and low total lymphocyte counts as risk factors for colonization. Fritzsche *et al.* [115] showed that patients with autoimmune inflammatory diseases, especially those over the age of 60, have a high prevalence of *P. jirovecii* colonization. They also indicated that 28.5% of those patients are colonized with this organism, without significant influences of CS dose or immunosuppressive co-medication. We found that 10.9% of RA patients have asymptomatic carriage of this organism and the mean age of these carriers is significantly older than non-carrier RA patients. There were no significant differences in lymphocyte counts or prednisolone use [46]. A high rate of colonization (25.6%) was also reported among patients with rheumatic diseases receiving infliximab [116].

PCP outbreaks among renal transplant recipients

An increased number of PCP outbreaks among kidney transplant recipients have been reported worldwide. Through a systemic review of a total of 15 articles published from 1980 onwards, de Boer *et al.* [117] indicated that the settings of PCP outbreaks are all marked by the following three characteristics: no adequate prophylaxis with antibiotics was introduced, frequent person-to-person contact did exist and no measures were taken to isolate PCP patients during their hospitalization. Many studies have presented epidemiological evidence that there were infectious encounters and exposures between patients carrying *P. jirovecii* [118–125]. In addition, genotyping results have shown that each outbreak was caused

by a single or a predominant strain of *P. jirovecii* [119–127]. The findings have suggested that interhuman transmission occurred in hospital environments, including outpatient facilities and inpatient wards. Sassi *et al.* [128] revealed that two geographically distinct clusters of PCP among renal transplant recipients in Europe were due to a single strain of *P. jirovecii*. The findings may be explained either by the existence of a common source of transmission or by differences in virulence of *P. jirovecii* strains.

Between May 2008 and April 2010, Le Gal *et al.* [129] encountered 12 cases of PCP and 6 cases of *P. jirovecii* colonization in organ recipients in their renal transplantation unit. Ten recipients were identified as potential infectious sources of a predominant strain of *P. jirovecii*: three were colonized by this fungus and seven developed PCP. The findings strongly suggest that asymptomatic carriers of *P. jirovecii* play a critical role in its circulation among renal transplant recipients.

An outbreak of *P. jirovecii* infection among RA outpatients

To determine the prevalence of asymptomatic carriage of *P. jirovecii* in RA patients and identify individuals with a high risk of PCP, between March 2005 and October 2009 we performed PCR tests for *P. jirovecii* on respiratory specimens from 132 outpatients with RA [12]. During the first 2 years only one case of PCP was observed and no asymptomatic carriers were found. However, between November 2006 and October 2008 we found nine cases of asymptomatic carriage of this organism. Among these carriers, three had not received any prophylactic antibiotics and developed PCP within 1 month. The other six obtained negative results for *P. jirovecii* DNA after 2–4 weeks of primary prophylaxis with TMP-SMX or pentamidine isethionate (PI) [130]. During this period we encountered an additional five cases of PCP in RA outpatients who had not yet undergone PCR testing.

Tracing of person-to-person transmission

All the members of this cluster, except two, had potentially infectious encounters at the outpatient facility within at least 4 months before the first detection of *P. jirovecii*. Of the two exceptions, one was in the same inpatient ward for joint surgery at the time when a PCP patient was hospitalized for treatment. The other was a PCP patient's spouse. Person-to-person transmission in hospital environments seems to be a frequent event among RA outpatients. No geographic clustering by postal code was noted, suggesting that a regional environmental source outside the hospital was less likely. During the outbreak period, no PCP occurrence was noted among outpatients of other clinical sections who had shared the same waiting room with RA outpatients, suggesting that *P. jirovecii* circulation is limited to the RA patient group.

Clinical presentation

Patients' respiratory symptoms were non-specific and non-severe at diagnosis of PCP, but all cases complained of slight general fatigue. Their chest radiographs were almost normal, but high-resolution CT scans revealed diffuse ground-glass opacities. In addition, oxygen saturation was in the normal range at rest, but it dropped to low levels after motion. As mentioned above, PCP in HIV-negative patients is likely to cause fulminant respiratory failure within the first several days and the mortality rate is higher. We therefore stress that those RA patients receiving immunosuppressive therapy should be followed up for signs and symptoms of PCP development, with a high index of suspicion. PCP should be included in the differential diagnosis of acute-onset diffuse interstitial pneumonia in RA patients receiving immunosuppressive therapy [131].

Outcomes

Within 2 weeks of hospitalization and treatment with TMP-SMX, *P. jirovecii* DNA disappeared in all PCP cases. Since *P. jirovecii* was eradicated from PCP cases and asymptomatic carriers, the DNA of this fungus was not detected during the follow-ups of these patients without any additional prophylactic intervention, even after resuming immunosuppressive therapy for RA. These findings suggest that RA outpatients with asymptomatic carriage can serve as an infectious reservoir for *P. jirovecii*. If PCP prophylaxis had not been introduced for such asymptomatic carriers, this outbreak may have escalated and resulted in wider transmission. Now we recommend PCR tests for all RA patients, especially aged individuals, on their first visit to our facility, because there is the possibility that they may carry a new infection into our patient cohort. Regular PCR testing during immunosuppressive therapy is not recommended because of its high cost.

Control of *P. jirovecii* infection and prevention of PCP outbreaks among RA outpatients

Primary PCP prophylaxis is recommended for HIV-infected individuals with CD4⁺ T cell counts of <200/μl [132, 133]. Renal transplant guidelines have recommended PCP prophylaxis with TMP-SMX for 3–12 months [134–136]. Considering the poor survival rates of PCP cases, prophylaxis of *P. jirovecii* infection should be discussed for RA outpatients who are scheduled to receive immunosuppressive therapy. However, guidelines for the administration of prophylactic antibiotics to such patients remain less clear. Universal routine prophylaxis is impractical because of the inherently long-term nature of anti-RA therapy. Prophylactic agents against PCP often induce severe adverse effects following MTX therapy for RA, such as allergic pancytopenia to TMP-SMX [137]. Development of *Pneumocystis* resistance to prophylaxis has also been reported [138, 139].

Eradication of *P. jirovecii* from asymptomatic carriers

Various reports have suggested that it is necessary to identify those HIV-negative patients whose risk of developing PCP is great enough to warrant prophylaxis in spite of the adverse effects [7, 24, 34–37, 140–145]. However, no quantitative markers clearly correlate with the risk of PCP in patients with rheumatic diseases, as CD4⁺ T cell count does in HIV-infected individuals. If reactivation of latent childhood infection is the predominant mode of PCP development in humans, prophylactic antibiotic usage for patients at high risk is the only method of preventing the disease. If new acquisition of *P. jirovecii* can occur in hospital environments, lifelong prophylaxis may theoretically be required for susceptible individuals. Alternatively, early identification of asymptomatic carriers as sources and reservoirs of infection leads to other strategies for prevention of PCP outbreaks in RA outpatients. Avoiding interhuman contacts between asymptomatic carriers and susceptible RA patients in a medical waiting room is difficult as standard practice. Rather, we should consider measures to eradicate *P. jirovecii* from asymptomatic carriers.

Duration of measures to eradicate *P. jirovecii* outbreaks

In reducing the potential for outbreaks of PCP among RA outpatients, it is important to consider when prophylactic antibiotics can safely be discontinued. In the outbreak observed among our RA outpatients, *P. jirovecii* was eliminated from carriers and PCP patients with a very short-term course (2–4 weeks) of treatment with TMP-SMX or PI [12, 130]. Through this procedure the outbreak was resolved and no new PCP outbreaks were observed in this patient group. Similarly, Saito *et al.* [33] observed that in almost all of their patients with PCP and rheumatic diseases, *P. jirovecii* disappeared within 7–10 days after commencement of TMP-SMX treatment and no recurrence of this pneumonia was observed. Godeau *et al.* [32] also reported that during follow-ups of 22 months on average, no relapse of PCP was seen among survivors who had been treated with TMP-SMX for a mean of 17 days, even though they continued to receive immunosuppressive drugs for rheumatic diseases without secondary prophylaxis. In contrast, Suryaprasad and Stone [146] reported three cases of new PCP development occurring after discontinuation of primary prophylaxis in patients with rheumatic diseases suffering from profound lymphopenia. These cases may result from new acquisition of *P. jirovecii* from unidentified reservoirs. There is always the possibility that patients with rheumatic diseases may be subject to reinfection as long as *P. jirovecii* reservoirs continue to exist in our patient group.

Conclusions

PCP development seems to result from a *de novo* infection rather than from reactivation of a latent childhood infection, and hospital-acquired, person-to-person transmission would appear to be the most likely mode of

acquisition of new infection in RA outpatients. Identification of *P. jirovecii* carriers would lead to the prompt introduction of PCP prophylaxis when rheumatologists consider immunosuppressive therapy for RA. Once a new case of PCP occurs in an outpatient clinic, physicians should take prompt action not only to treat the patient but also to prevent other patients from becoming new reservoirs of *P. jirovecii*. In this case, short-term prophylaxis for all other RA patients visiting this clinic may be effective and even justified in preventing the increased risk of a PCP outbreak. Understanding the potential role of asymptomatic carriers in the circulation of *P. jirovecii* among RA outpatients will allow us to undertake effective action to control *P. jirovecii* infection and to prevent future outbreaks of PCP.

Rheumatology key messages

- Outbreaks of *P. jirovecii* infection can occur among RA outpatients through person-to-person transmission.
- Asymptomatic carriers serve as reservoirs and sources of *P. jirovecii* infection in outpatient facilities.
- Short-term prophylaxis with TMP-SMX is effective in controlling PCP outbreaks among RA outpatients.

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