

## Pneumocystis Pneumonia in Inflammatory Bowel Disease: The Costs of Immunosuppression

Ersilia M. DeFilippis<sup>1,2\*</sup> and Ellen J. Scherl<sup>1,2</sup>

<sup>1</sup>Jill Roberts Center for Inflammatory Bowel Disease, Division of Gastroenterology and Hepatology, USA

<sup>2</sup>Weill Cornell Medical Center-New York Presbyterian Hospital, 1315 York Avenue, New York, NY 10021, USA

\*Corresponding author: Ersilia M. DeFilippis, 1315 York Avenue, Mezzanine Level, New York, NY 10021, USA, Tel: 212-746-5077; Fax: 212-746-8144; E-mail: emdefilippis@partners.org

Rec date: Oct 26, 2015, Acc date: Nov 4, 2015, Pub date: Nov 11, 2015

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### Abstract

Patients with inflammatory bowel disease (IBD) are subject to a spectrum of immunosuppressive agents including corticosteroids, immunomodulators, and biological therapies. Despite the benefits of these therapies and their ability to induce remission, they increase the risk of infectious complications with various organisms including *Pneumocystis jiroveci* pneumonia (PCP), which is associated with significant morbidity and mortality. Although PCP infection is typically associated with HIV-infected populations, the risk is increased in patients with IBD. Inflammatory autoimmune diseases like IBD account for as high as 20% of PCP infection in HIV-negative patients with greater than 50% mortality. Despite this, there are no clear guidelines for PCP prophylaxis in IBD. PCP should be considered in the differential when an IBD patient on immunosuppression presents with fever and respiratory symptoms. Here we review the existing literature regarding PCP risk in inflammatory bowel disease, the role of tumor necrosis alpha-inhibitors, and considerations for prophylaxis.

**Keywords:** Opportunistic infections; Inflammatory bowel disease; Immunosuppression; Pneumonia

### Introduction

Patients with inflammatory bowel disease (IBD) are subject to a spectrum of immunosuppressive agents including corticosteroids, immunomodulators, and biologic therapies [1,2]. Despite the benefits of these therapies, they increase the risk of infection by intracellular pathogens, granulomatous infections, mycobacteria, histoplasmosis and others including *Pneumocystis jiroveci* (PCP) [3].

*Pneumocystis jiroveci* pneumonia (also known as pneumocystis carinii pneumonia) is an atypical unicellular fungus that produces local inflammatory reactions and alveolar infiltrates in the lung [4]. These lead to widened alveolar-arterial oxygen gradient and impaired gas exchange [1]. The infection is associated with significant morbidity and mortality. Symptoms may be non-specific leading to difficulties in diagnosis. Typical radiographic features include bilateral perihilar interstitial infiltrates. When chest radiographs are normal, high-resolution computed tomography (CT) of the chest may show ground-glass opacities or cystic lesions (Figure 1) [5,6]. It is considered an opportunistic infection since the organism takes advantage of a weakened immune system and would typically cause mild illness or no disease in the immunocompetent host [7]. The treatment of choice is trimethoprim-sulfamethoxazole (TMP-SMX). In patients who are sulfa-allergic or intolerant, second line therapies include primaquine, pentamidine, and dapsone [8].



**Figure 1:** Ground-glass opacities seen on computed tomography (CT) of the chest in a patient with Crohn's disease on triple immunosuppression later found to have *Pneumocystis carinii* pneumonia.

Although PCP is typically associated with human immunodeficiency virus (HIV)-infected populations, a range of patient populations and medications have been associated with increased risk of PCP [9]. Other non-HIV populations at risk include solid-organ transplant recipients, connective tissue and rheumatological disorders, hematologic and solid malignancies, and IBD [10-21]. Inflammatory autoimmune diseases like IBD account for as high as 20% of PCP infection in HIV-negative patients with greater than 50% mortality [3].

In HIV patients, PCP presents as a slow and indolent process characterized by fever, cough, and pulmonary infiltrates [4]. In non-HIV populations, patients with PCP infection typically present with abrupt onset of respiratory insufficiency that may correlate with a

tapered dosage of immunosuppressant agents [5]. One study found that patients with HIV had symptoms for 37.8 days on average before diagnosis compared to 7.6 days in non-HIV patients [8]. The non-HIV patients have more neutrophils and fewer pneumocystis organisms in their lungs as well as higher C-reactive protein and lower beta-D glucan levels [8]. Mortality in patients without AIDS may be 30 to 60 percent [5]. Given the lower number of organisms in their lungs, sputum induction may have less diagnostic yield. Therefore, if the initial specimen is negative, bronchoscopy with bronchoalveolar lavage should be performed [5]. The use of simultaneous serum beta-D glucan and respiratory sample polymerase chain reaction (PCR) testing for PJP may help with diagnosis [8].

The remainder of this review will focus on the risk of PCP in IBD, the role of tumor necrosis factor alpha inhibitors and new biologics, and considerations for prophylaxis.

### **Increased Risk of PCP in Inflammatory Bowel Disease**

PCP has been reported in IBD patients on various medication regimens including cyclosporine, tacrolimus, infliximab, adalimumab, and azathioprine [3,22-39]. In one cohort study, patients with IBD were found to have significantly increased risk of PCP compared to the general population with an adjusted hazards ratio of 2.96 [4]. The annual incidence of PCP was 10.6 cases per 100,000 in the IBD population compared to 3 cases per 100,000 in the non-IBD population [4]. The risk appeared greater in the IBD patients with Crohn's disease (CD) compared to those with ulcerative colitis [4].

The risk of infection depends on the host as well as the specific therapies, including whether a patient is on dual or even triple immunosuppression. One study from the Mayo Clinic examined risk factors for opportunistic infections in IBD patients [40]. They found that age greater than 50 was a significant risk factor as well as Crohn's colitis as compared to isolated Crohn's ileitis [40]. Additional risk factors for PCP infection include concomitant use of corticosteroids for greater than 8 weeks, advanced age greater than 65 years, lung disease, leucopenia, or hypoalbuminemia [3,4,41]. Likewise, in patients on monotherapy with azathioprine or 6-mercaptopurine, their risk of infection is increased 2-3 fold compared to the general population [40]. If these patients are also on corticosteroids, this risk increases to 15-fold [40].

### **Corticosteroids**

Corticosteroids are a major risk factor for development of PCP and infection more generally [4,42,43]. Over fifty percent of the affected individuals in the above cohort study were on corticosteroids alone or in combination with other medication. Fifty percent had been hospitalized in the previous 60 days [4]. In one study by Yale and Limper of PCP in non-HIV patients, they found that regardless of the underlying condition, corticosteroids had been administered systemically in 105 of 116 patients within 1 month before the diagnosis of *P. carinii* pneumonia [44]. The median daily corticosteroid dose was equivalent to 30 mg of prednisone; however, 25% of patients had received as little as 16 mg of prednisone daily. *P. carinii* pneumonia developed after 8 weeks or less of corticosteroid therapy in 25% of these patients [44].

Many patients with IBD are treated with corticosteroids for acute disease flares. This may paradoxically mask the symptoms of PCP in these populations since high-dose steroids (greater than 60 mg of prednisone) are used in the management of severe PCP infection with

hypoxia [1]. Therefore, physicians must be acutely aware of complaints of dyspnea in this population of patients.

### **Cyclosporine and Tacrolimus**

Cyclosporine and tacrolimus have been the backbone of treatment for organ rejection in transplant patients. However, both have also been used in ulcerative colitis patients (UC) who are unresponsive to intravenous steroids [23,32]. Cases of fatal PCP as complications of these therapies have been reported, two patients receiving tacrolimus and one receiving cyclosporine [23,32]. In one case, the patient developed respiratory insufficiency requiring mechanical ventilation only 23 days after initiating tacrolimus therapy [23]. IBD patients treated with high dose cyclosporine for acute UC flares receive a dose roughly comparable to that used initially in renal transplant patients (4 mg/kg/day) [32]. It is standard practice for renal transplant patients to receive prophylaxis against PCP for three to six months after transplantation, however, the same is not currently true for IBD patients.

### **Tumor Necrosis Factor and Host Response to PCP**

The host response to pneumocystis infection specifically involves many of the cytokines and molecules that are inhibited by inflammatory bowel disease therapies including TNF alpha. TNF-alpha helps recruit neutrophils, lymphocytes, and monocytes as well as production of other chemokines like interleukin-8 and interferon gamma [45,46]. When this factor is blocked by therapies like infliximab and adalimumab, clearance of pneumocystis is delayed. Anti-TNF therapy may also decrease CD4 lymphocytes, the same cell population that makes HIV-infected patients susceptible to PCP infection [47].

Tumor necrosis factor alpha (TNF-alpha) inhibitors, such as infliximab, are used for IBD patients with moderate-to-severe disease [48]. Often these patients have been refractory to other immunomodulatory therapy. Infliximab is associated with various opportunistic infections, most commonly histoplasmosis [40]. One study in patients with rheumatoid arthritis found that patients treated with 10 mg/kg of infliximab were three times more likely to have infection compared to the placebo group [40,49].

Infliximab was approved for use in CD in 1998. Three years after, the first reported cases of PCP in patients on infliximab were reported in the literature [8]. Subsequent reports were reported over the following years. Although the studies which led to FDA approval of infliximab for IBD did not report PCP, Kaur and Mahl published a study of 84 cases of PCP associated with infliximab that were reported to the Adverse Event Reporting System (AERS) of the FDA between 1998 and 2003 [47]. Typically, the interval identified between the first infusion or dose and the start of infection is between 9 and 14 weeks [15,47]. Cases of PCP have also been reported in patients receiving adalimumab [3,50]. There are currently no published cases of PCP in association with certolizumab therapy.

Overall, studies in the United States and Japan have differing estimates of incidence of PCP in patients on TNF-alpha inhibitors [15,51-55]. These studies are largely based on studies of patients with rheumatoid arthritis. They report incidence of pneumocystis ranging from 1 to 8.8 cases per 1000 person-years [8,15,51-54,56,57]. This data is currently lacking in IBD-only populations. These discrepancies in results have made it difficult to support broad recommendations for prophylaxis.

## The Role of Vedolizumab

Vedolizumab is a newer biologic agent available for patients with UC and CD who have failed or not responded to anti-TNF therapy [58,59]. Vedolizumab is a humanized monoclonal antibody that recognizes the alpha-4 beta-7 integrin molecule, selectively blocking gut lymphocyte trafficking [58]. Given that the drug is specific to the migration of leukocytes into the gut, it is thought to be safer than other options. In the GEMINI trials of vedolizumab in UC, serious infections were not more common in the study group than with placebo [58]. However, in patients with CD, serious infections occurred in 5.5% of the vedolizumab group compared to 3.0% of the placebo group [59]. Nevertheless, it has been postulated that the specificity of the drug may be safer than other therapies, including the anti-TNF medications which may have more global effects. In PCP specifically, tumor necrosis factor plays a role in clearing the infection. Thus, this pathway may not be affected in anti-integrin therapy.

Loftus et al. studied infection rates in patients treated with vedolizumab alone compared to those on concomitant corticosteroids and/or immunosuppressants using the GEMINI data [60]. The authors found that the percentages of those with infectious adverse events and infectious serious adverse events were similar among the groups, regardless of concomitant steroids or immunomodulatory therapy [60]. More long-term data is needed to determine the safety of vedolizumab and its associated risk of PCP.

## The Question of Prophylaxis

There are no consistent guidelines or consensus regarding the need for prophylaxis for PCP in the IBD. According to the European Crohn's and Colitis Organization (ECCO), patients with IBD on triple immunosuppression where one agent is a calcineurin inhibitor or anti-TNF-alpha therapy should receive standard prophylaxis with trimethoprim/sulfamethoxazole [7]. However, there is no consensus in patients with dual immunosuppression [7]. Furthermore, some consider administration of prednisolone at more than 16 mg/day over 8 weeks or 20 mg/day over 4 weeks as an indication for prophylaxis (Table 1) [30].

Prior PCP infection
Triple immunosuppression where one agent is calcineurin inhibitor or TNF-alpha inhibitor
Prednisolone > 16 mg/day over 8 weeks or 20 mg/day over 4 weeks

**Table 1:** Indications for Prophylaxis against *Pneumocystis jirovecii*. TNF: tumor necrosis factor.

Long et al. performed a retrospective cohort study examining over 100,000 patients with IBD [4]. They determined the number needed to treat of 3750 to prevent one case of PCP, which must be balanced by the side effects of prophylaxis including Stevens Johnson's syndrome, aplastic anemia. These authors suggest considering prophylaxis on an individual basis where the benefits of prophylaxis outweigh the risks [4].

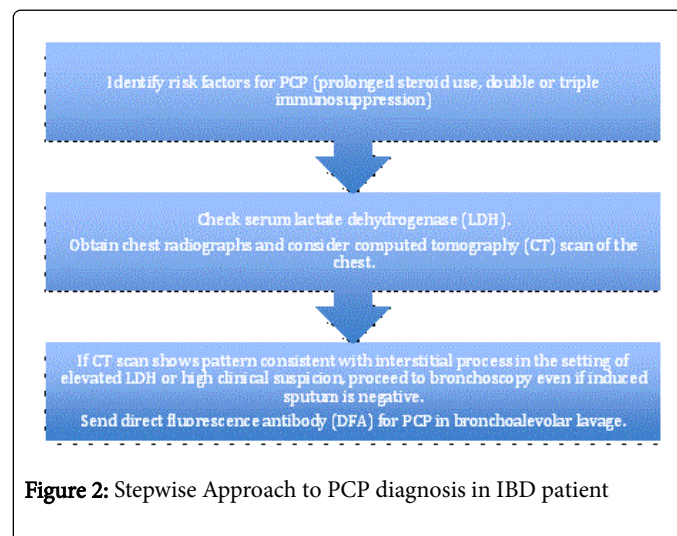
The lack of official guidelines appears to influence the decision to prescribe PCP prophylaxis in IBD patients. Okafor et al. studied practice patterns among gastroenterologists for PCP prophylaxis [61]. Eighty percent of respondents had patients who had developed the infection on immunosuppressive therapy yet only 11% reported

initiating prophylaxis, largely for patients on triple immunosuppressive therapy [61]. Furthermore, those gastroenterologists with patients who had developed PCP were 7.4 times more likely to prescribe prophylaxis [61].

Some have suggested that one means of identifying the most at-risk patients could involve testing for colonization by *P. jirovecii* [62]. Oral washes are a specific and sensitive procedure for detecting colonization through the use of polymerase chain reaction (PCR) [62]. However, existing data is limited and further trials are needed to determine the role of this in prevention of PCP in IBD patients.

## Conclusion

Pneumocystis carinii pneumonia is not a wholly uncommon infection in patients with IBD and has significant associated morbidity and mortality. PCP should be considered in the differential diagnosis in IBD patients on infliximab as well as other immunosuppressants who present with respiratory symptoms [22]. An algorithmic approach to the diagnosis of PCP is presented in Figure 2.



**Figure 2:** Stepwise Approach to PCP diagnosis in IBD patient

Bronchoalveolar lavage should be performed rapidly in patients with IBD presenting with fever and pulmonary infiltrates even if induced sputum samples are negative. Furthermore, prophylaxis should be strongly considered in patients receiving combination therapy with corticosteroids, especially in those of older age. The absolute risk of opportunistic infection in IBD patients and the potential benefit of preventive strategies remainS to be determined. As more and more biologic therapies become available for this patient population, one must constantly weigh the risks and benefits of immunosuppression especially when multiple agents are required for treatment. More research is required in order to form more definitive guidelines for PCP prophylaxis in order to reduce morbidity and mortality associated with this disease.

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