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# PCP prophylaxis; Weighing the adverse effects

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## Abstract

A 54 year old female with Granulomatosis with Polyangiitis (GPA) presented with shortness of breath. The patient had been on Rituxan infusions and prednisone and was not on PCP prophylaxis. Bilateral ground-glass opacities were seen on chest CT and Bronchoalveolar lavage with silver stain was indicative of pneumocystis infection. She developed septic shock and Acute Respiratory Distress Syndrome. Despite aggressive therapy, she continued to deteriorate and expired shortly after.

**Discussion:** Pneumocystis Jiroveci colonization has been detected in 16-29% of patients with autoimmune disease. The risk factors include age over 60, chronic pulmonary disease, smoking, low absolute lymphocyte and CD4 cell counts, low serum immunoglobulins and corticosteroid use. Onset of the disease is acute and life-threatening, with mortality rates exceeding 30%. Rituximab is an anti-CD20 antibody and has been demonstrated to induce susceptibility to Pneumocystis infection in vivo mouse model by depleting CD20. Medications that can be used for prophylaxis include Bactrim, Dapsone, Dapsone plus Pyrimethamine plus Leucovorin, Atovaquone and Pentamidine. Although prophylaxis is effective in reducing mortality, the risk for PCP must be greater than 3.5% to outweigh the side effects.

**Conclusion:** The European League Against Rheumatism (EULAR) suggested chemoprophylaxis for GPA patients who were receiving immunosuppressive agents. The patient presented in this case report would have warranted PCP prophylaxis. Recent research is focused on developing vaccine against PCP. A monoclonal antibody to 4F11 has been found in mice that elicit immunity to PCP. Hopefully, in the near future there will be better prophylaxis options which are safe and effective.

## Keywords

granulomatosis with polyangiitis; pneumocystis pneumonia; prophylaxis; immunosuppressive therapy

## Abbreviations

GPA: Granulomatosis with polyangiitis; PCP: Pneumocystis pneumonia; CKD: Chronic kidney disease; CT: Computerized tomography; BAL: Bronchoalveolar lavage; ARDS: Acute respiratory distress syndrome; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation

## Introduction

The patient is a 54 year old female with past medical history of Granulomatosis with Polyangiitis (GPA) and Chronic Kidney Disease (CKD) who presented to the hospital with shortness of breath. The patient had been on rituximab infusions for 2 months and prednisone therapy for 10 weeks for treatment

of GPA. She was originally on prednisone 60mg daily and this was decreased to 20 mg daily due to generalized weakness. She was not taking trimethoprim-sulfamethoxazole for PCP prophylaxis during this time due to sulfa-drug allergy. Over the course of the 10 weeks, she had developed episodes of worsening shortness of breath. Her symptoms progressed from minimally affecting her daily activities to causing her significant distress. The patient reported these symptoms to her nephrologist, who then recommended she have a Computerized Tomography (CT) scan done. The non-contrast CT showed bilateral ground-glass opacities and she was advised to come to the emergency room. In light of her immunocompromised state, she was admitted to the Medical Intensive Care Unit (MICU) and started on broad spectrum intravenous (IV) antibiotics with meropenem and azithromycin to cover for atypical pneumonia. The patient underwent Bronchoalveolar Lavage (BAL) with silver stain which was indicative of pneumocystis infection. She developed septic shock and Acute Respiratory Distress Syndrome (ARDS). She was electively intubated and desensitization to sulfa was done based on recommendations from infectious disease specialists. While the patient was being desensitized to trimethoprim-sulfamethoxazole, vasopressor support (levophed and vasopressin) along with broad spectrum antibiotics (meropenem, clindamycin, primaquine, and micafungin) were continued. She had worsening electrolyte abnormalities and development of refractory acidosis for which she was started on Continuous Renal Replacement Therapy (CRRT). Despite aggressive vasopressor support, stress dose steroids, antibiotics, and CRRT she continued to deteriorate. Extracorporeal Membrane Oxygenation (ECMO) was discussed with cardiothoracic surgery; it was unlikely to provide significant benefit or prevent further decompensation. After extensive discussion, the patient's family decided that the patient would not have wanted to continue further aggressive measures in this situation. The patient was placed on comfort measures and expired the next day.

## Discussion

*Pneumocystis Jiroveci* is an opportunistic fungal infection which is transmitted through airborne route. Asymptomatic carriers of Pneumocystis may be infected transiently or throughout their lives [2]. Colonization has been detected in 16-29% of patients with autoimmune disease, and the risk factors include age over 60, chronic pulmonary disease, smoking, low absolute lymphocyte count, low CD4 cell count, low serum immunoglobulins and the use of corticosteroids. Of these factors, age has been shown to be the strongest contributor. Nonetheless, the association between colonization of P. jiroveci and pneumocystic disease is not strong [7]. Its presence in the lungs usually does not lead to disease however it can lead to *Pneumocystis* pneumonia in patients with impaired immunity [1]. In immunocompromised individuals it is the leading cause of morbidity and mortality [7]. Onset of the disease is acute and life-threatening, with mortality rates exceeding 30% [7].

The patients at risk for the disease include patients with Acquired Immune Deficiency Syndrome (AIDS), malignancies receiving cytotoxic chemotherapies, organ transplant recipients, or those taking immunosuppressive therapy. In patients not infected with Human Immunodeficiency Virus (HIV), corticosteroids are the leading cause of PCP pneumonia in immunosuppressed patients. Specifically, in patients with GPA, methotrexate, high dose prednisolone and cyclophosphamide have been associated with increased risk for PCP. It has been shown that patients receiving greater than 20mg/day for eight weeks or more are at risk [4,7]. Studies also show that anti-TNF α agents and methotrexate are associated with the disease [4,7]. Currently there are no strict guidelines on PCP prophylaxis in

immunocompromised patients without HIV. The decision of if and when to start a patient on prophylactic therapy is often based on an individual's risk factors and the clinician's judgment. As PCP is usually noted to develop within four to twelve weeks of beginning immunosuppressive therapy, many clinicians choose to start prophylaxis prior to or at the time immunosuppressive therapy is initiated [8]. The patient in our case report was diagnosed with GPA and was started on rituximab and high dose prednisone. Rituximab is an anti-CD20 antibody. Elsegeiny et al. developed in vivo mouse model by depleting CD20 which induced susceptibility to pneumocystis infection. B cells play an integral role in immunity to pneumocystis. It has been shown that CD20+ B cells are required to prime CD4+ T-cells against pneumocystis [2]. CD20 is also expressed in 6% of T cells [6]. Multiple murine model studies in recent years have shown that when B-cell deficient mice were infected with pneumocystis, it resulted in decreased number of activated T cells in the lungs during early PCP. Studies also showed that B cells were necessary for the generation of $CD4^+$ memory T cells in response to *Pneumocystis* infection. It can therefore be concluded that in any disease processes where B cells are depleted or targeted, PCP prophylaxis would be warranted as well [9].

The patient in the case report was an appropriate candidate for PCP prophylaxis. She was not placed on trimethoprim-sulfamethoxazole, which is the most popular agent for prophylaxis, due to a sulfa drug allergy. However alternative drugs that could have been used for prophylaxis include dapsone, dapsone plus pyrimethamine plus leucovorin, atovaquone and pentamidine. Dapsone has been associated with prophylaxis failure in transplant populations and aerosolized pentamidine results in worse survival rates in bone transplant patients [4]. In 1995 Bozzette et al. showed that in HIV patients, the lowest rate of PCP was in the trimethoprim-sulfamethoxazole or high dose dapsone group, while the highest rate was in aerosolized pentamidine group [5]. Trimethoprim-sulfamethoxazole also has significant risks including bone marrow suppression and Steven-Johnson syndrome, which impede unrestricted use for PCP prophylaxis [6]. Nonetheless, there are multiple prophylactic agents and therapy can be tailored to the individual patient's needs and restrictions.

## Conclusion

It is clear that prophylaxis presents with its own adverse effects. Although PCP prophylaxis is effective in reducing mortality, the risk for PCP must be greater than 3.5% to outweigh the side effects of prophylaxis [7]. This risk assessment was made by calculating the relative risk of PCP and number needed to treat in patients on prophylaxis against those on placebo or no intervention in a systematic review and meta-analysis of twelve randomized controlled trials [10]. The European League Against Rheumatism (EULAR) suggested chemoprophylaxis in patients with GPA who were receiving cyclophosphamide or similar immunosuppressive agents [6,7]. As the patient presented in this case report was on rituximab and prednisone, PCP prophylaxis, despite the risk of adverse effects, would have been warranted. Recent research is focused on developing vaccine against PCP. A monoclonal antibody to 4F11 has been found in mice that elicit immunity to PCP. Its target and mechanism is not fully understood [3]. Hopefully, in the near future there will be better prophylaxis options which are safe and effective.

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