Prophylaxis for Pneumocystis Pneumonia (PCP) in non-HIV infected patients

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Pneumocystis pneumonia (PCP) is a potentially life-threatening opportunistic infection that occurs in immunocompromised individuals and is caused by Pneumocystis Jiroveci (formerly known as Pneumocystis carinii), a ubiquitous organism that is classified as a fungus, but also shares biologic characteristics with protozoa. P. Jiroveci was first recognized as a pathogen in severely malnourished and premature infants developing an epidemic form of interstitial plasma cell pneumonitis in Central and Eastern European countries during the Second World War. PCP is the most common opportunistic infection in HIV-infected patients and very often the AIDS-defining illness. Apart from seropositive individuals, patients receiving chronic immunosuppressive medication or those who have an altered immune system are considered to be at high risk for PCP. In the absence of appropriate antibiotic therapy, the mortality rate from PCP in non-HIV-infected patients is 90 to 100 percent[1]. PCP rarely occurs in patients without apparent immunodeficiency[2,3]

Patients who are not infected with HIV but are receiving immunosuppressive medications or who have an underlying acquired or inherited immunodeficiency should receive prophylaxis against pneumocystis pneumonia, as it appears to dramatically lower the risk of disease in susceptible populations[4]. There are no published guidelines for PCP prophylaxis among patients with rheumatologic diseases receiving immunosuppressive drugs, but some suggest PCP prophylaxis when they are receiving high-dose immunosuppressive therapy[5,6]. The most significant risk factors for PCP in patients without HIV infection are glucocorticoid use and defects in cell-mediated immunity[7-10].

PCP usually develops within one month of glucocorticoids administration, with a median dose of prednisone 30 mg/day, but some patients develop PCP with as little dose as 16 mg/day. The median duration of glucocorticoid therapy before the development of PCP in a series of 116 patients in Mayo Clinic was 12 weeks, but 25 percent of patients had been receiving glucocorticoids for ≤8 weeks[11].

Risk factors warranting prophylaxis for PCP are listed below:

1. Glucocorticoid dose equivalent to ≥20 mg of prednisone daily for one month or longer plus another cause of immunocompromise[12].
2. Combination of immunosuppressive drugs, such as TNF-α inhibitors plus high dose glucocorticoids or other immunosuppression[13].

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3. Treatment of polymyositis/ dermatomyositis with interstitial pulmonary fibrosis with glucocorticoids[14].
4. Certain primary immunodeficiencies (severe combined immunodeficiency, idiopathic CD4 T-lymphocytopenia, hyper-IgM syndrome)[15,16].
5. Patients with rheumatologic diseases, receiving ≥20 mg of prednisone daily for one month or longer in combination with a second immunosuppressive drug[17,18].
6. Patients with granulomatosis with polyangiitis [Wegener's] receiving methotrexate in combination with high doses of glucocorticoids[17,19].
7. Acute lymphocytic leukemia[12]
8. Allogeneic or autologous hematopoietic stem cell transplantation[12]
9. Solid organ transplantation and antirejection medications[20]
10. Treatment with a purine analog (fludarabine, another T-cell depleting agent)[12].
11. Severe malnutrition (especially protein malnutrition)

Trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line agent used for PCP prophylaxis due to its high efficacy. It can be administered as one double-strength tablet daily or three times a week or as one single-strength tablet daily. In patients who cannot tolerate the use of TMP-SMX there must be an attempt of desensitization. If the patient cannot tolerate TMP-SMX, alternatively can be administered **atovaquone, dapsone** with or without **pyrimethamine, pentamidine, clindamycin plus primaquine or sulfadoxine plus pyrimethamine** (table 1)[21].

Prophylaxis can often be discontinued after the risk factors for the disease, such as significant dose systemic corticosteroid or other immune suppressant agents are no longer present. However, it should be kept in mind that the immunosuppressed state can persist for months after discontinuation of some cytotoxic agents, such as cyclophosphamide.

Caution is needed regarding PCP prophylaxis in patients with **systemic lupus erythematosus** (SLE), since there are data suggesting that sulfonamide-containing antibiotics, including TMP-SMX, can cause exacerbations of SLE, particularly in patients with adverse reactions to these agents. Atovaquone is suggested as an alternative agent[22,23].

REFERENCES

12. Hughes WT, Feldman S, Sanyal SK. Treatment of Pneumocystis carinii pneumonitis with trimethoprim-sulfamethoxazole. Can Med Assoc J 1975; 112:47-50.
13. Jacobs JL, Libby DM, Winters RA, et al. A cluster of Pneumocystis carinii pneumonia in adults without predisposing illnesses. N Engl J Med. 1991;324(4):246-50.
14. Cano S, Capote F, Pereira A, et al. Pneumocystis carinii pneumonia in patients without predisposing illnesses. Acute episode and follow-up of five cases. Chest 1993; 104:376-81.
15. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 2007; 82:1052-9.
16. Ognibene FP, Shelhamer JH, Hoffman GS, et al. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. Am J Respir Crit Care Med 1995; 151:795-9.
17. Suryaprasad A, Stone JH. When is it safe to stop Pneumocystis

TABLE 1. Regimens for PCP prophylaxis

Drug	Dosage	Adverse reactions
TMP-SMX	1 double strength tbl daily **or** 1 double strength tbl three times a week **or** 1 single strength tbl daily	Fever, rash, neutropenia, elevation of transaminases
Sir Atovaquone	1500 mg once daily	Rash gastrointestinal, upset
Dapsone	50 mg twice daily **or** 100 mg daily	Fever, rash, hemolytic anemia, methemoglobinemia
Aerolized pentamidine	300 mg monthly	Cough, wheezing
Intravenous pentamidine	4 mg/kg monthly	Nephrotoxicity, hypercalcemia, hypoglycemia, hypotension, pancreatitis, elevation of transaminases
Clindamycin/ primaquine	600 mg 3-4 times a day/15-30 mg PO	Rash, diarrhea, fever, abdominal pain, hemolytic anemia

jiroveci pneumonia prophylaxis? Insights from three cases complicating autoimmune diseases. Arthritis Rheum 2008; 59:1034-9.
18. Sepkowitz KA, Brown AE, Telzak EE, et al. Pneumocystis carinii pneumonia among patients without AIDS at a cancer hospital. JAMA 1992; 267:832-7.
19. Festic E, Gajic O, Limper AH, Aksamit TR. Acute respiratory failure due to pneumocystis pneumonia in patients without human immunodeficiency virus infection: outcome and associated features. Chest 2005; 128:573-9.
20. Siegel JD, Rhinehart E, Jackson M, et al. 2007 Guideline for isolation precautions: Preventing transmission of infectious agents in healthcare settings, June 2007. http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf.
21. Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000; 49:1-125.
22. Yale SH, Limper AH. Pneumocystis carinii pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc. 1996;71:5-13.
23. Segal BH, Freifeld AG, Baden LR, et al. Prevention and treatment of cancer-related infections. J Natl Compr Canc Netw 2008; 6:122-74.
24. Stiehm, ER, Ochs, HD, Winkelstein, JA. Immunodeficiency disorders: General considerations. In: Immunological Disorders in Infants and Children, 5th ed, Stiehm, ER, Ochs, HD, Winkelstein, JA (Ed), Elsevier Saunders, Philadephia 2004. p.289.
25. Ochs HD, Stiehm ER, Winkelstein JA. Antibody deficiencies. In: Immunological Disorders in Infants and Children, 5th ed, Stiehm, ER, Ochs, HD, Winkelstein, JA (Ed), Elsevier Saunders, Philadelphia 2004. p.357.
26. Kadoya A, Okada J, Iikuni Y, Kondo H. Risk factors for Pneumocystis carinii pneumonia in patients with polymyositis/dermatomyositis or systemic lupus erythematosus. J Rheumatol 1996; 23:1186-8.
27. White ES, Lynch JP. Pharmacological therapy for Wegener's granulomatosis. Drugs 2006; 66:1209-28.
28. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum 1999; 42:2666-73.
29. Thomas C, Limper A. Pneumocystis pneumonia. N Engl J Med 2004;350:2487-98
30. Radisic M, Lattes R, Chapman JF, et al. Risk factors for Pneumocystis carinii pneumonia in kidney transplant recipients: a case-control study. Transpl Infect Dis 2003; 5:84-93.
31. Rodriguez M, Fishman JA. Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. Clin Microbiol Rev 2004; 17:770-82.
32. Thomas CF, Limper AH. Treatment and prevention of Pneumocystis pneumonia in non-HIV-infected patients. Uptodate, Wolters Kluwer Health, 2012.
33. Pope J, Jerome D, Fenlon D, Krizova A, Ouimet J. Frequency of adverse drug reactions in patients with systemic lupus erythematosus. J Rheumatol. 2003;30:480-4.
34. Jeffries M, Bruner G, Glenn S, et al. Sulpha allergy in lupus patients: a clinical perspective. Lupus. 2008;17:202-5