

Pneumocystis jirovecii pneumonia prophylaxis in a 42-year-old woman on immunosuppressive therapy

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A 42-year-old woman, with a 2-year history of dermatomyositis controlled with prednisone (5 mg once daily), presents to her family physician 1 week after a flare that required admission to hospital. The patient's symptoms include proximal muscle weakness and dyspnea secondary to interstitial lung disease. High-dose prednisone (60 mg orally daily) is started, with plans for prolonged taper. Her family physician questions whether she needs prophylaxis for *Pneumocystis jirovecii* pneumonia.

Is this patient at risk of *Pneumocystis jirovecii* pneumonia?

Pneumocystis jirovecii pneumonia is an opportunistic fungal infection.^{1,2} Impaired cell-mediated immunity is the predominant risk factor; a link best established in patients with HIV and CD4 counts of less than 200 cells/mm³.³ However, increasing rates of *Pneumocystis jirovecii* pneumonia in patients without HIV (Box 1) highlight the role of non-HIV-mediated immunosuppression.¹⁻⁵ Glucocorticoid therapy impairs cell-mediated immunity by reducing CD4 lymphocytes and attenuating signaling in inflammatory cascades.^{3,6} Although corticosteroids confer the greatest risk when combined with a high-risk underlying condition (i.e., hematologic malignant disease) or additional immunosuppressive agents, monotherapy has also been associated with *Pneumocystis jirovecii* pneumonia.³ In a prospective cohort study involving patients with rheumatologic diseases who were taking prednisone (≥ 30 mg daily for at least 4 wk), 1-year incidence of *Pneumocystis jirovecii* pneumonia was 2.37 cases per 100 person-years.⁷ Higher doses of prednisone (≥ 60 mg), concomitant cyclophosphamide pulse therapy, increased age and baseline lymphopenia exacerbated this risk.⁷ A retrospective analysis involving patients without HIV found that *Pneumocystis jirovecii* pneumonia can occur at corticosteroid doses as low as 16 mg/day and durations of 8 weeks or less.³ This patient's history of dermatomyositis and recent flare requiring high-dose prednisone increases her risk of *Pneumocystis jirovecii* pneumonia.

How would *Pneumocystis jirovecii* pneumonia present clinically in this patient?

Although clinical presentations may be varied and nonspecific, typical symptoms in this patient would include acute dyspnea, cough and fever over days.⁸ This contrasts with the indolent onset of symptoms over several days to weeks observed in those with HIV.⁸ A 2014 prospective study in France reported that patients with *Pneumocystis jirovecii* pneumonia who were HIV negative had fewer reported symptoms at time of presentation (contributing to delays in diagnosis), were started on treatment later, and had higher rates of mechanical ventilation and death than patients who were HIV positive.⁸

Clinicians should maintain a high index of suspicion for *Pneumocystis jirovecii* pneumonia in patients with non-HIV-mediated immunosuppression, as diagnostic confirmation can be challenging. Surrogate markers are not useful; tests for lactate dehydrogenase levels have 63% sensitivity in patients who are HIV negative compared with greater than 90% in those who are HIV positive.⁹ Although computed tomography of the chest will show bilateral ground-glass opacities in both populations, diagnostic confirmation requires direct visualization of the organism.⁴ Detection methods, such as bronchoalveolar lavage, have lower sensitivity in patients who are HIV negative owing to a lower burden of organisms.⁴

Should this patient receive prophylaxis for *Pneumocystis jirovecii* pneumonia?

The decision to start prophylaxis in this patient is nuanced, warranting careful consideration of benefits and risks; however, it is supported by evidence.⁷ Prophylaxis is recommended when the risk of *Pneumocystis jirovecii* pneumonia is greater than 3.5%.⁵ The strongest evidence for prophylaxis in HIV-negative populations exists for solid organ or hematopoietic stem cell transplantation, solid tumours on T-cell-depleting agents, hematologic malignant disease, primary immune deficiencies, vasculitides and autoimmune conditions treated with tumour-necrosis-factor- α inhibitors (Box 1).^{1,2,4,5}

Box 1: Indications for prophylaxis for *Pneumocystis jirovecii* pneumonia in patients who are immunocompromised and HIV negative

Patient population	Indication for prophylaxis
Solid organ transplantation	For 6–12 mo after transplantation*
Hematopoietic stem cell transplantation	Autologous stem cell transplant <ul style="list-style-type: none"> • For 3–6 mo
	Allogeneic stem cell transplant <ul style="list-style-type: none"> • For at least 6 mo • Longer duration may be required with chronic GVHD or ongoing immunosuppressive therapy
Hematologic malignant disease	Glucocorticoids† equivalent to prednisone ≥ 20 mg/d for ≥ 4 wk
	Acute lymphoblastic leukemia receiving chemotherapy
	Alemtuzumab <ul style="list-style-type: none"> • During therapy and for at least 2 mo after cessation (and until CD4 count > 200 cells/mm³)
Solid tumour	T-cell depleting agents (e.g., fludarabine or cladribine) <ul style="list-style-type: none"> • Until CD4 count > 200 cells/mm³
	Glucocorticoids† equivalent to prednisone ≥ 20 mg/d for 4 wk
Autoimmune diseases and vasculitis	Temozolomide and radiation therapy <ul style="list-style-type: none"> • Until CD4 count > 200 cells/mm³
	Rheumatoid arthritis receiving TNF- α inhibitors <ul style="list-style-type: none"> • If also receiving glucocorticoids† or other immunosuppressive agents
	Inflammatory bowel disease receiving TNF- α inhibitors <ul style="list-style-type: none"> • If also receiving glucocorticoids† or other immunosuppressive agents
	Granulomatous polyangiitis receiving cyclophosphamide
	Vasculitis associated with ANCA <ul style="list-style-type: none"> • Receiving cyclophosphamide and glucocorticoids†
	Other vasculitis <ul style="list-style-type: none"> • Receiving glucocorticoids† and a 2nd immunosuppressive agent
	Connective tissue disease <ul style="list-style-type: none"> • Receiving glucocorticoids† equivalent to prednisone ≥ 20 mg/d for ≥ 4 wk
Primary immune deficiency	Severe combined immune deficiency
	Idiopathic CD4 lymphocytopenia X-linked hyper-IgM syndrome
Glucocorticoid therapy (other)†	Prednisone equivalent ≥ 20 mg/d for ≥ 4 wk plus one of: <ul style="list-style-type: none"> • Additional immunosuppressive agents • Steroid-sparing antirheumatic drugs • Underlying immunosuppressive condition
Other populations (where prophylaxis may be considered)	
Glucocorticoid therapy†	Prednisone equivalent ≥ 20 mg/d for ≥ 4 wk <ul style="list-style-type: none"> • With or without underlying lung disease
Note: ANCA = antineutrophil cytoplasmic antibody, GVHD = graft versus host disease, IgM = immunoglobulin M, TNF = tumour necrosis factor. *Duration varies with organ transplanted and requirement for other immunosuppressive agents (kidney transplant recipients may receive a shorter duration of prophylaxis). †Glucocorticoids (prednisone equivalent of ≥ 20 mg/d for ≥ 4 wk; some experts suggest ≥ 16 –20 mg/d).	

Two meta-analyses that compared prophylaxis using trimethoprim-sulfamethoxazole (TMP-SMX) with placebo or no prophylaxis in high-risk patients with hematologic malignant disease or transplantation reported numbers-needed-to-treat (NNT) as low as 15 and 19 to prevent 1 case of *Pneumocystis jirovecii* pneumonia; the overall rate of adverse events was 3.1%, with no difference between groups.^{1,5}

Among connective tissue diseases, incidence of *Pneumocystis jirovecii* pneumonia is highest in the presence of granulomatosis with polyangiitis (8%–12%), polyarteritis nodosa (6.5%) and dermatomyositis/polymyositis (2.7%).⁴ Although the isolated risk of *Pneumocystis jirovecii* pneumonia with inflammatory myopathies falls below 3.5%, these conditions are associated with T-cell lymphopenia¹⁰ and often require glucocorticoid therapy; concomitant interstitial lung disease exacerbates this risk.¹¹ In a cohort study involving 1092 patients with rheumatologic diseases who were taking moderate- to high-dose steroids, some patients were treated with TMP-SMX prophylaxis according to the judgment of the treating physicians.⁷ Prophylaxis with TMP-SMX reduced 1-year incidence of *Pneumocystis jirovecii* pneumonia by 93% and associated mortality by 92%.⁷ The NNT to prevent 1 case of *Pneumocystis jirovecii* pneumonia was 52; serious adverse drug reactions were uncommon (number-needed-to-harm = 131).⁷ In the absence of consensus guidelines, existing literature favours prophylaxis in this patient with dermatomyositis and interstitial lung disease that requires prolonged high-dose steroids.

What are the options for *Pneumocystis jirovecii* pneumonia prophylaxis?

The preferred agent is TMP-SMX.² Dosing regimens include 1 double-strength tablet 3 times per week or 1 single-strength tablet daily, with no difference in efficacy or toxicity.¹ Adverse reactions include rash, myelosuppression, and liver and renal toxicities.^{1,7} Alternative options include dapsone, atovaquone and aerosolized pentamidine based on limited evidence and largely extrapolated from the HIV literature.^{2,4}

Case revisited

This patient has multiple risk factors for *Pneumocystis jirovecii* pneumonia, including underlying rheumatologic disease that requires long-term, high-dose glucocorticoids. She is at risk of severe infection and poor outcomes if *Pneumocystis jirovecii* pneumonia develops, particularly with concurrent interstitial lung disease. Based on available evidence, the benefits of prophylaxis outweigh the risks of harm. In consultation with rheumatology, she started prophylaxis with TMP-SMX and monitoring for adverse events.

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The clinical scenario is fictional.

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