Pneumocystis jirovecii pneumonia (PJP) primary prophylaxis in adults: Selection of agent and indications

Inclusion: Adults who may require PJP prophylaxis and are not covered by another guideline

Exclusion: Pediatric patients, patients undergoing solid organ transplant, patients with hematologic malignancies, and patients with HIV are beyond the scope of this guidance. They should be managed according to their respective internal protocols (HBC/CAR-T, SOT) or society/national guidance (HIV)

Selection of agent:
Trimethoprim/Sulfamethoxazole (TMP/SMX) is the most effective regimen for PJP prophylaxis and the most well studied. Every effort should be made to use this agent when possible, including interrogation of reported allergies, and even consideration of induction of tolerance (desensitization) for truly allergic, high-risk patients.[i] Distant histories of benign cutaneous reactions may be able to undergo a one-step drug challenge with TMP/SMX.

1st line	Trimethoprim/ Sulfamethoxazole	Most effective Myelosuppression rare at prophylactic doses Can cause a variety of rashes, including rare high risk reactions including SJS Hyperkalemia rare at prophylactic doses	Also provides effective prophylaxis against toxoplasmosis, and nocardia to some degree
2nd line	Atovaquone	Must be taken with a fatty meal Taste an issue for some patients	Some toxoplasmosis protection
	Dapsone	Rule out G6PD deficiency ***required*** prior to treatment initiation Risk of hemolytic anemia and agranulocytosis even in G6PD negative May cross-react with TMP/SMX allergies, consider discussion with allergy	No toxoplasmosis protection unless combined with pyrimethamine (with leucovorin)
Not routinely recommended, discuss with Infectious Diseases	Inhaled Pentamidine	Generally, not recommended due to unreliable efficacy, dependence on inhalation technique, and very difficult to arrange outpatient	No protection against toxoplasmosis

Indications:
Risk for PJP is mediated by defects in cell mediated immunity, although other factors (underlying lung disease, other comorbidities) also play a role. Risks should be considered on a patient-by-patient basis. In general, benefits of prophylaxis are felt to outweigh the risks when a patient's risk of PJP is ~6%.[ii] The list below includes some of the common indications but is not meant to be

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comprehensive. Society guidelines are a valuable resource, when available. If it is unclear whether a patient is indicated for prophylaxis, discuss with infectious diseases consult service (if inpatient) or e-consult infectious diseases (outpatient). Refer to society guidance when available (Rheumatology: EULAR[iii], HIV)

Prophylaxis generally indicated (not a comprehensive list):

- Primary immunodeficiencies affecting cell mediated immunity
- Patients receiving a glucocorticoid dose ≥20mg prednisone equivalent daily for one month or longer with another cause of immunocompromise.
    - Many clinicians will also provide prophylaxis to patients receiving high dose steroids alone, though this indication is less well studied, and risk likely varies based on other underlying risk factors (lymphopenia, rheumatic disease).[iv,v]
- Lymphodepleting monoclonal antibodies (CD-52, anti-CCR4, anti-SLAMF, polatuzumab)
- Bruton tyrosine kinase inhibitors and phosphatidyl 3-kinase inhibitors
- Patients receiving cyclophosphamide, particularly when associated with other immunosuppression (data is limited)

Indications where prophylaxis may be considered in specific patients, but data is limited. Consider individual patient factors (underlying condition, other immunosuppression, underlying lung disease, duration of therapy)

- JAK inhibitors
- Anti CD-20 monoclonal antibodies; in particular, in patients with ANCA vasculitis, this is recommended by ACR[vi]
- Checkpoint inhibitors
- Other high dose immunosuppression
- mTOR kinase inhibitors
- Patients without HIV with CD4 counts <200 cell/mm3, including Sarcoidosis with lymphopenia

Duration of prophylaxis:

Duration of prophylaxis should be individualized and generally is continued until the underlying risk factor is no longer present. High dose steroids and other medications can cause prolonged immunosuppression after discontinuation of the agent, and care should be taken in these cases. Refer to individual prescribing information, disease-state, or service-specific guidelines when available

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[ii] Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD005590. DOI: 10.1002/14651858.CD005590.pub3. Accessed 06 February 2025.

[iii] George E Fragoulis, Mrinalini Dey, Sizheng Zhao, Jan Schoones, Delphine Courvoisier, James Galloway, Kimme L Hyrich, Elena Nikiphorou - Systematic literature review informing the 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases: RMD Open 2022;8:e002726.

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[iv] Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis. 2018 May;77(5):644-649. doi: 10.1136/annrheumdis-2017-211796. Epub 2017 Nov 1. PMID: 29092853; PMCID: PMC5909751.

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[vi] Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, Archer AM, Conn DL, Full KA, Grayson PC, Ibarra MF, Imundo LF, Kim S, Merkel PA, Rhee RL, Seo P, Stone JH, Sule S, Sundel RP, Vitobaldi OI, Warner A, Byram K, Dua AB, Husainat N, James KE, Kalot MA, Lin YC, Springer JM, Turgunbaev M, Villa-Forte A, Turner AS, Mustafa RA. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383. doi: 10.1002/art.41773. Epub 2021 Jul 8. PMID: 34235894.