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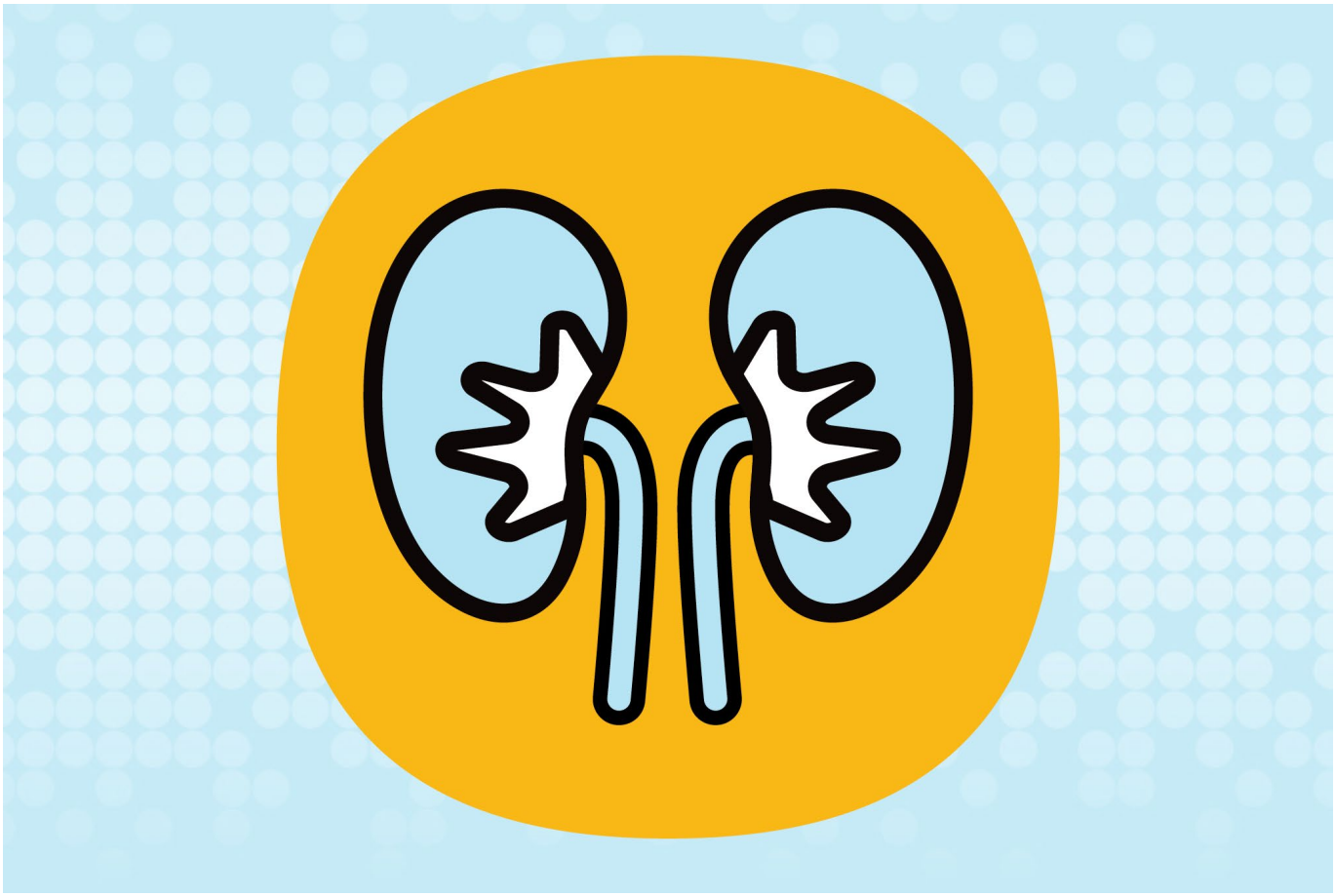

PCP Prophylaxis Recommendations

For adult glomerulonephritis patients

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Summary of Recommendations

Description

Pneumocystis *jiroveci* pneumonia (formerly known as Pnemocystis *carinii*) is an opportunistic infection of the lung caused by the fungus pneumocystis jirovecii.

Throughout this document the term *Pneumocystis jirovecii* will be used when referring to the specific human infecting fungus and the acronym PCP will be used when referring to the infection caused by this species (*Pneumocystis* pneumonia).

General Recommendations

Please refer to the Appendix for a background document summarizing evidence and rationale.

1. Discuss the risk of PCP with patients starting on immunosuppressive therapy.

2. Weigh the benefits versus risks of prophylaxis for PCP with consideration given to the type of immunosuppressive regimen, glomerulonephritis diagnosis, morbidity and/or mortality associated with PCP and the adverse effect profile of the prophylactic regimen. In patients receiving active immunosuppressive treatment who are high risk of infection, PCP prophylaxis is recommended (See Table 1 for drug-specific recommendations).

Table 1: PCP Prophylaxis Recommendations for GN patients on Immunosuppressive Therapy

Immunosuppressive Therapy	ORN PCP Prophylaxis Suggestions [Comments]	Evidence Base
Cyclophosphamide	Consider prophylaxis in all patients and continue for at least 3 months after stopping cyclophosphamide.[1]	Extrapolated from vasculitis guidelines.[2] Case-control study of patients with rheumatic disease.[3] [ANCA-associated vasculitis patients are among the highest risk for PCP.[2] Case-control study of patients with rheumatic disease.[3]

Immunosuppressive Therapy	ORN PCP Prophylaxis Suggestions [Comments]	Evidence Base
		There is weak evidence to support prophylaxis for SLE patients given lower risk of PCP. Suggest clinician consider no prophylaxis,[3,3,4]
Rituximab	Consider prophylaxis for all patients and continue for at least 6 months after receipt of rituximab or until repletion of B cells.[5] Patients receiving maintenance rituximab should remain on prophylaxis.	Extrapolated from vasculitis guidelines.[2] Duration of prophylaxis based on a retrospective cross-sectional study.[6]
Prednisone	May consider initiating prophylaxis when prednisone dose >30mg/day (or equivalent) with planned duration of >4 weeks.[3] Discontinue prophylaxis when doses are <15mg/day.[3]	Case-control study of patients with rheumatic disease.3
Triple immunosuppression	Consider initiating prophylaxis in patients on triple immunosuppressive therapy (i.e. calcineurin inhibitor plus mycophenolate mofetil/sodium or azathioprine plus low dose prednisone).	Extrapolation from kidney transplant guidelines.[6,7]

3. The first line agent for PCP prophylaxis is sulfamethoxazole (SMX)/trimethoprim (TMP) with the usual prophylactic dose of 1 single strength tablet (SMX:400mg/TMP:80mg) once daily OR 1 double strength tablet (SMX:800mg/TMP:160mg) three times per week. Renal dosage adjustment to half the usual dose is required for CrCl 15-30mL/min (i.e. 1 single strength tablet three times per week).[8,9] For CrCl <15mL/min the product monograph recommends to avoid use, however, other references suggest using half the usual dose.[9,10] It is recommended to have close monitoring of serum creatinine and electrolytes.

4. In patients where SMX/TMP cannot be used due to issues with safety or tolerability, alternative second line prophylactic agents include dapsone 100mg once daily or atovaquone 1500mg once daily.

Background

Definition

Pneumocystis jirovecii is a yeast-like fungus. This organism was formerly called *Pneumocystis carinii*. The nomenclature changed in 2001 such that *Pneumocystis carinii* now only applies to the *Pneumocystis* species that is found in rats.[1]

When the name of *Pneumocystis* pneumonia (PCP) changed from *P. carinii* pneumonia to *P. jirovecii* pneumonia, it was at first felt that "PJP" should replace "PCP". However, because the term PCP was already used among physicians that managed patients with *Pneumocystis* infection, it was rationalized that the term PCP could continue to be used, as it could stand for **P**neumo**C**ystis (jirovecii) **P**neumonia.[1]

Throughout this document the term Pneumocystis jirovecii will be used when referring to the specific human infecting fungus and the acronym PCP will be used when referring to the infection caused by this species (*Pneumocystis* pneumonia).

Introduction

Pneumocystis jirovecii is a ubiquitous, species-specific fungus. Infection with Pneumocystis jirovecii is common and occurs at an early age. Serologic surveys have shown nearly universal seropositivity to Pneumocystis by two years of age and more than 80% of children having developed antibodies against it by 4 years.[10] Primary infection is probably largely asymptomatic.11 Colonization with Pneumocystis jirovecii is common, occurs in more than 50% of the general adult population, and is assumed to represent re-infections through person-to-person transmission or environmental re-exposures rather than re-activation. [12,13]

Immunocompetent hosts clear this organism without obvious clinical consequences via innate cell-mediated immunity. Symptomatic, tissue invasive disease is rare and limited to immunocompromised individuals who are at risk of developing interstitial Pneumocystis pneumonia (PCP).

In the past, the occurrence of PCP has mainly been in patients with human immunodeficiency virus infection (HIV) before immune reconstitution. But the incidence of PCP in immunocompromised patients without HIV is increasing.[14] Host defenses against PCP have largely been attributed to CD4+ lymphocytes, however, animal studies have also indicated a role for B lymphocytes and antibody defense in this infection.[6]

Considerations for PCP Prophylaxis in Glomerulonephritis

The requirement for PCP prophylaxis is based on a risk-benefit assessment taking into consideration several important issues: (1) the incidence of PCP in the specific population (disease and/or immunosuppressive regimen); (2) the morbidity and/or mortality associated with PCP; and (3) the adverse effect profile of the chosen prophylactic regimen.

Incidence and Risk Factors for PCP in Glomerulonephritis

Patients at risk of PCP include cancer patients receiving chemotherapy, bone marrow and solid organ transplant recipients, and other patients treated with corticosteroids or other immune suppressive medications. The incidence of PCP in glomerulonephritis patients is not well defined or described in the literature.

The incidence and risk factors likely varies depending on the type of glomerulonephritis.

Park et al. conducted a cohort study examining the efficacy and safety of sulfamethoxazole/trimethoprim (SMX/TMP) for prophylaxis of PCP.[3] Patients with rheumatic diseases treated with high dose steroids (prednisone ≥30mg/day) for more than 4 consecutive weeks between January 2004 to December 2015 were included in the study. During the observation period of 1474.4 person-years there were 30 PCP cases in 30 patients with an incidence of 2.37/100 person years. When stratified by underlying disease, the incidence of PCP was highest in those with ANCA-associated vasculitis at 12.14 per 100 person-years. Systemic lupus erythematosus (SLE) had the lowest incidence at 2.42 per 100 person-years. The mean equivalent dose of prednisone at the time of PCP diagnosis was 31mg with half of the cases occurring with the dose was >30mg/day. There were 12 cases when the dose was 15-30mg per day and only 3 when the dose was <15mg/day. Gupta et al. conducted a literature review to determine the incidence of PCP in patients with systemic lupus erythematosus (SLE) on cyclophosphamide therapy.[4] The authors identified 18 original manuscripts from 1987 to 2006 which addressed infections in SLE patients over 18 years of age treated with immunosuppressive agents. From these papers the investigators estimated the incidence of PCP in SLE patients who received cyclophosphamide. Of these 18 manuscripts, 10 were retrospective observational case series, 2 were retrospective case control studies, and 6 were prospective randomized controlled studies. There were 121 cases of PCP were identified in 76,156 SLE patients treated with cyclophosphamide giving a frequency of 15.88 per 10,000 (0.1588%) patients. Other studies have found similarly low rates of PCP in the SLE population.[15,16,17]

Lertnawapan et al. conducted a case control study of SLE patients to identify the risk factors which would warrant PCP prophylaxis. The study found that PCP infected SLE patients had higher disease activity, higher dose of prednisolone treatment, more likelihood of renal involvement and lower lymphocyte count as well as lower CD4+ count than those with no PCP infection.[18]

Corticosteroids

A 2014 Cochrane systematic review assessed the effectiveness of PCP prophylaxis among non-HIV immunocompromised patients and found a PCP event rate of 6.2% in the control groups of the 13 included trials. Prophylaxis with SMX/TMP was found to be highly effective providing an 85% reduction in PCP and thus the authors suggest that prophylaxis be considered in patients with a similar or higher baseline risk.[11]

The most commonly identifiable risk factor for PCP is corticosteroid use, and other immunosuppressive drugs may also play a role. Yale et al. conducted a retrospective study of 116 cases of pneumocystis pneumonia in non-HIV infected patients. The major common exposure was steroid treatment in the month preceding presentation (90.5% of patients). The median prednisone dose was equivalent to 30mg for a median of 12 weeks before presentation.[19]

Yang et al. investigated risk factors for PCP infection in glomerulonephritis patients receiving immunosuppressants in Taipei Veterans General Hospital.[20] During this observational study from August 2009 to July 2010 a total of 73 glomerulonephritis patients under immunosuppressant agents were enrolled. PCP prophylaxis was not given to these patients. During the observation period, 7 patients developed PCP infection. Logistic regression analysis was performed to identify predictors of PCP infection. Factors found to have an increased odds ratio included higher blood urea nitrogen, higher serum creatinine, lower hemoglobin, lower

absolute lymphocyte count at immunosuppressant initiation and higher chronicity indices of kidney pathology (global glomerulosclerosis, interstitial fibrosis, and tubular atrophy). Corticosteroid dose was borderline significant in predicting PCP infection. Age, underlying diabetes and dosage of immunosuppressants did not significantly predict risk for PCP development.

Most recently the Testing Trial, which randomized patients with IgA nephropathy 1:1 to oral methylprednisolone (0.6-0.8 mg/kg/d; maximum, 48 mg/d) (n = 136) or matching placebo (n = 126) for 2 months, with subsequent weaning over 4 to 6 months, was halted prematurely do to the excess of serious adverse events, including life threatening infections.[21]

Rituximab

Rituximab is a monoclonal antibody that binds to the CD20 antigen on B lymphocytes which may be an important line of defense against PCP. Martin-Garrido et al. conducted a retrospective review of patients who received rituximab and developed PCP at the Mayo Clinic during the period from 1998 to 2011.[6] Over this period 30 patients developed PCP during treatment with rituximab, 29 of which had not received PCP prophylaxis while being B-cell depleted after receiving rituximab. In 90% of cases the underlying disease was hematologic malignancies. Three patients (10%) had no underlying malignancy (1-rheumatoid arthritis/Sjogren/bronchiolitis obliterans, 1-granulomatosis with polyangitis (Wegener), 1-idiopathic thrombocytopenic purpura) and developed PCP in the setting of rituximab without concomitant chemotherapy or significant glucocorticoid exposure.

Triple Immunosuppression

Triple immunosuppression increases the overall net state of immunosuppression which is a main contributor to risk of PCP rather than any specific immunosuppressive agent.[8] Given the lack of evidence and guidelines for PCP prophylaxis for glomerulonephritis patients, it may be reasonable to extrapolate transplant guideline recommendations to glomerulonephritis patients receiving triple therapy. Guidelines for solid organ transplant recommend routine PCP prophylaxis for all patients for a period of at least 6 – 12 months post-transplant and longer durations are advocated.[1]

Morbidity and Mortality Associated with PCP in Glomerulonephritis

In non-HIV patients PCP typically presents with an abrupt onset of respiratory failure. The mortality rate among non - HIV patients is 30% to 60%, with a greater risk of death amongst cancer patients in part related to delays in diagnosis.[14] In a retrospective study of Pneumocystis infections at Beth Israel Deaconess Medical Center, admissions to the intensive care unit, mechanical ventilation and mortality rates were 10%, 7% and 10% among HIV patients versus 69%, 66% and 39% among non-HIV patients.[22]

Prophylaxis Efficacy and Safety

Prophylaxis Regimens

Pneumocystis jirovecii, despite its classification as a fungus, is susceptible to several antibacterial and antiparasitic drugs that can be used to treat or prevent PCP amongst high-risk patients.

The agent most commonly used agent for prophylaxis is SMX/TMP. Other agents that have activity against *Pneumocystis jirovecii* include dapsone, atovaquone and pentamidine.

Efficacy & Safety

A 2014 Cochrane systematic review assessed the effectiveness of PCP prophylaxis among non-HIV immunocompromised patients and found SMX/TMP to be highly effective, providing an 85% relative reduction in CP (RR 0.15, 95% CI 0.04 to 0.62) without significant heterogeneity. All-cause mortality was not significantly reduced with prophylaxis (RR 0.71, 95% CI 0.28 to 1.8) but since there were fewer PCP infections, PCP-related mortality was reduced by 83% (RR 0.17, 95% CI 0.03 to 0.94).[11]

All the agents used for prophylaxis can cause side effects that may counterbalance the benefits of PCP prevention. SMX/TMP is considered the first line agent for PCP prophylaxis but does have a several potential adverse effects. Hyperkalemia is a common adverse effect as trimethoprim inhibits potassium elimination in the distal nephron. In a randomized controlled trial of outpatients taking trimethoprim/sulfamethoxazole, 6% of patients experienced hyperkalemia with a potassium level >5.5mmol/L and 81.5% of patients experienced an increase in serum potassium. Known risk factors for developing hyperkalemia while on trimethoprim/sulfamethoxazole include diabetes, renal insufficiency, older age, and treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and spironolactone.[23] SMX/TMP can also cause allergic reactions and more serious hypersensitivity reactions. Simple exanthems and fixed drug eruptions occurring in about 3% of hospital inpatients taking the drug. Classic drug hypersensitivity syndromes are rarer but can be serious, manifesting with a triad of fever, exanthems and varying degrees of internal organ involvement.[23] These adverse effects must be considered when deciding whether or not to give prophylaxis with this agent.

Drug	Dose	Place in Therapy/Efficacy	Side Effects/ Precautions [Drug Interactions]	Monitoring/Comments	Cost/dose* & Coverage
Sulfamethoxazole/ Trimethoprim/ (SMX/TMP) SS: 400/80mg DS: 800/160mg	Single-strength (SS) tablet (400 mg/80 mg) once daily OR 1 Double-strength (DS) tablet (800 mg/160 mg) 3x/week Renal adjustment:9,10 CrCl >30mL/min: usual dose; CrCl 15-30mL/min: half the usual dose (i.e. 1 Single-strength tablet 3x/week) CrCl <15mL/min: half the usual dose (i.e. 1 Single-strength tablet 3x/week)	1st line agent	GI intolerance; cholestatic hepatitis; renal failure and hyperkalemia; rash, pruritus, and photosensitivity; serum sickness and drug fever; Stevens-Johnson syndrome; bone marrow suppression Pregnancy: Avoid in 1st trimester (neural tube & CV defects), avoid after 32 weeks (hemolytic anemia & kernicterus) [Sulfonylureas –combination can result in hypoglycemia]	CBC, differential, BUN, creatinine, and electrolytes	SS: $0.11/dose DS: $0.15/dose ODB general benefit
Dapsone 100mg tablet	100 mg once daily No renal dose adjustment9	May be less effective than SMX/TMP Fewer adverse reactions than SMX/TMP but may have cross-allergy if allergic to SMX/TMP	Hemolytic anemia and/or blood dyscrasia, especially with G6PD deficiency, thrombocytopenia, neutropenia, liver dysfunction, rash, gastrointestinal intolerance, and allergic reactions.	Consider screening & avoid if G6PD deficient	$1.41/dose ODB general benefit
Atovaquone 750mg/5mL suspension	1500mg (2 tsp) once daily No renal dose adjustment9	Similar efficacy compared to dapsone or aerosol pentamidine Fewer adverse reactions than SMX/TMP but is very expensive	GI intolerance due to diarrhea; rash headache, nausea, diarrhea, rash, and fever. These are generally mild to moderate.	Must be taken with meals to ensure optimal absorption of the drug	$5.68/dose ODB general benefit
Aerosolized pentamidine	300 mg nebulized once monthly	May be less effective than SMX/TMP.	Nephrotoxicity (25–50%); hypoglycemia and hyperglycemia; GI		$145 per 300mg vial**

	Option for patients intolerant of SMX/TMP and dapsone; once monthly administration	intolerance; hypotension; bone marrow suppression; electrolyte abnormalities	Not an ODB general benefit Not eligible via EAP

*Cost/dose based on ODB reimbursement rates as of July 2019 (excludes additional costs such as dispensing fees and co-payments/deductibles); ** Hospital wholesale price as of July 2019

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