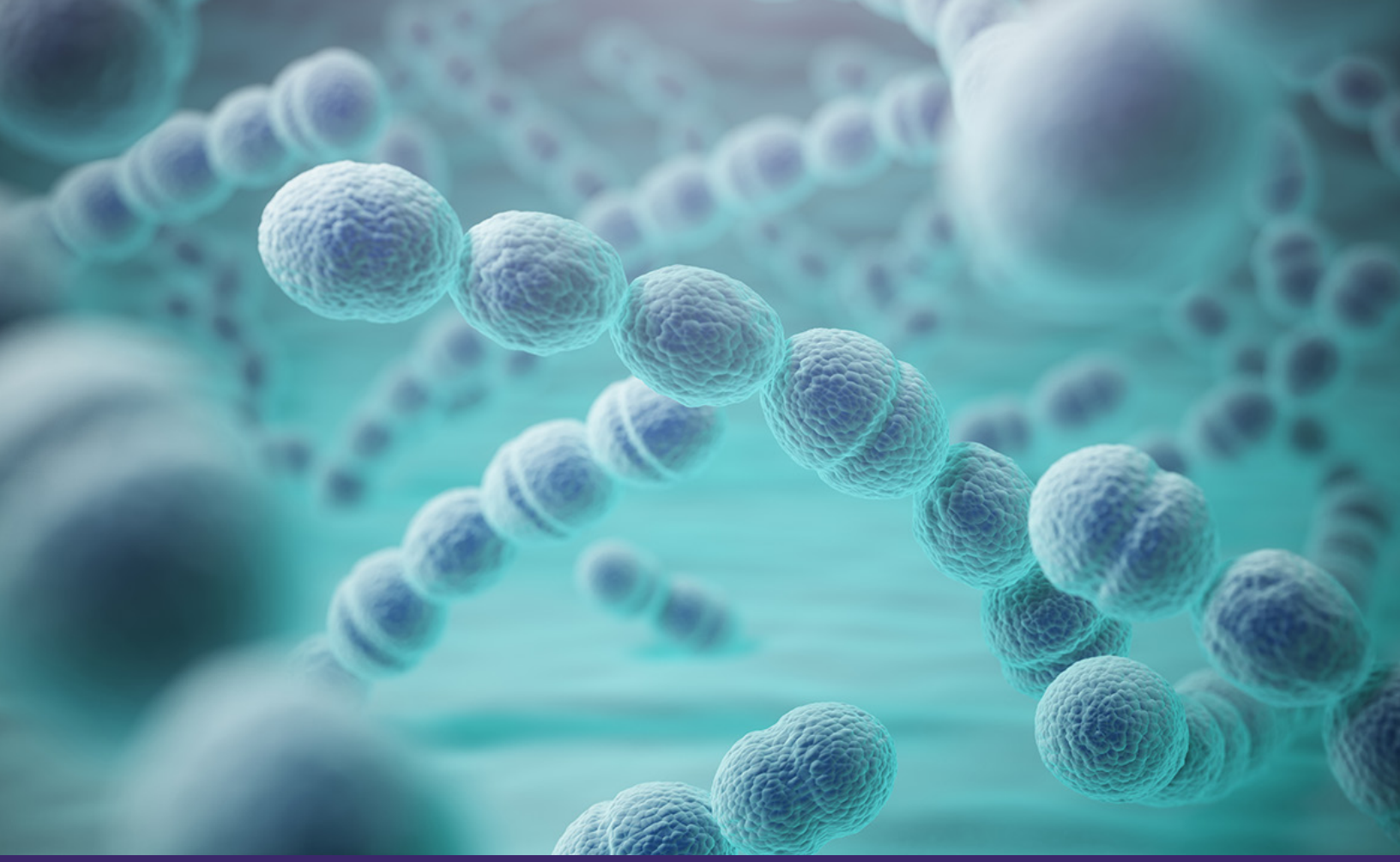

PROVINCIAL STANDARDS & GUIDELINES

BCRenal
Provincial Health Services Authority

Pneumocystis jirovecii Pneumonia Prophylaxis Guidelines in Patients with Glomerulonephritis

June 2021; Updated Dec 2021

Approved by the BC Renal Glomerulonephritis Committee

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PRINTED copies of copies of "*Pneumocystis jirovecii* Pneumonia Prophylaxis Guidelines in Patients with Glomerulonephritis" may not be the most recent version. Check the most recent version on the BC Renal website: www.bcrenal.ca > Health Professionals > Glomerulonephritis.

IMPORTANT INFORMATION

This BC Renal guideline/resource was developed to support equitable, best practice care for patients with chronic kidney disease living in BC. The guideline/resource promotes standardized practices and is intended to assist renal programs in providing care that is reflected in quality patient outcome measurements. Based on the best information available at the time of publication, this guideline/resource relies on evidence and avoids opinion-based statements where possible; refer to www.bcrenalagency.ca for the most recent version.

For information about the use and referencing of BC Renal guidelines/resources, refer to http://bit.ly/28SFr4n.

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1. INTRODUCTION

In the absence of national or international guidelines for the prophylaxis of *Pneumocystis jirovecii* pneumonia (PCP) in patients with glomerulonephritis (GN), the British Columbia (BC) Renal GN Committee commissioned the development of provincial guidelines. These inaugural guidelines aim to standardize the renal clinician's approach to PCP prophylaxis therapy, highlight where clinical studies are required, and set the standard from which practice will improve. A systematic review was undertaken to gather literature, which was interpreted by three renal pharmacists (HW, JM, CL) and a nephrologist (SB) who then distilled the data into treatment recommendations. These guidelines are careful to align with recommendations in the rheumatology and transplant literature, and they state the quality of data that is currently available.

2. BACKGROUND

Pneumocystis jirovecii is a ubiquitous species-specific fungus, in which most people are infected with before the age of 2.[1] It was initially thought that *Pneumocystis jirovecii* remains in a latent stage in the alveoli until the patient becomes immunocompromised, but studies have shown clearance of the organism, with less than 20% of the population having the organism in their lungs at any given time.[2] Thus, person-to-person transmission or environmental reservoirs are important in causing infections. More importantly, not all individuals will develop PCP while they are immunocompromised, as they may not become exposed to *Pneumocystis jirovecii* during this time.

PCP in patients with human immunodeficiency virus (HIV) vs. GN:

There is much more experience and data available for treating/preventing PCP in patients with HIV compared to patients with GN. In addition, a CD4 count < 200 cells/microL has been found to be a reliable threshold to initiate PCP prophylaxis in the HIV population – such clear guidance is not available for patients with GN.

The clinical presentation of PCP is usually subtle in patients with HIV (progressive shortness of breath, nonproductive cough and low-grade fever), with a mortality rate of 10 to 20%. In contrast, in non-HIV patients, more severe lung inflammation and more profound hypoxemia is often described, and mortality rates of approximately 40% are reported.[3] However, as the clinical awareness of PCP in non-HIV patients has increased and as the laboratory diagnosis has improved, it is now common to see PCP of mild to moderate severity presenting in non-HIV patients.

Threshold to initiate PCP prophylaxis in patients with GN:

A 2014 Cochrane meta-analysis recommends that PCP prophylaxis be considered in non-HIV immunocompromised adult or pediatric patients if the risk of PCP is > 6.2%; this was the controlled event rate in the meta-analysis that found PCP prophylaxis to be highly effective [number needed to treat (NNT)=19].[1] 6.2% has since become a commonly cited threshold to initiate PCP prophylaxis in any non-HIV immunocompromised individual even though this threshold was derived from populations of patients with hematologic

malignancies, bone marrow transplant and solid organ transplants.

In our opinion, comparing a patient's risk of PCP to the controlled event rate in a meta-analysis is not the optimal method of making decisions about PCP prophylaxis, as it does not take into account the risks and benefits of prophylaxis. These considerations are particularly important in the context of PCP, a condition with potentially devastating consequences. Risk-benefit analyses and cost-effectiveness analyses are preferred.

When combining all trimethoprim/sulfamethoxazole (TMP/SMX) treatment arms of the studies included in the 2014 Cochrane meta-analysis, severe adverse events requiring permanent discontinuation (including leukopenia, thrombocytopenia, or severe dermatological reactions) occurred in 3.1% of adult patients, corresponding to a number needed to harm (NNH) of 32. Balancing the NNT of 19 to prevent 1 PCP infection against the NNH of 32, it is reasonable to consider trimethoprim-sulfamethoxazole (TMP/SMX) for PCP prophylaxis when the baseline PCP risk exceeds 3.7%. This finding is similar to that of an older, less methodologically sound meta-analysis done in 2007 by Green et al. In this analysis, the NNT and NNH were found to be 15 and 32, respectively. The resultant threshold to initiate TMP/SMX prophylaxis was a baseline PCP risk of 3.5%.[4]

In one study that modeled cost-effectiveness of PCP prophylaxis in patients with Wegner's granulomatosis, it was found that, compared to no prophylaxis, TMP/SMX 160/800 mg three times a week was dominant as long as the incidence of PCP was > 0.2%.[5] The strategy to provide prophylaxis with monthly aerosolized pentamidine if the patient experiences an adverse drug reaction to TMP/SMX was determined to be cost-effective as long as the incidence of PCP was > 2.25%.[5]

PCP prophylaxis with TMP/SMX in patients with systemic lupus erythematosus (SLE):

It has been reported that, compared to the general population, patients with SLE are at higher risk of developing adverse drug reactions (ADRs) to TMP/SMX. The main ADR of concern is cutaneous rash. In a study by Pope et al., skin rash was reported to occur in 52% of SLE patients exposed to sulfa antibiotics, as compared to 19.4% of age- and sex-matched control patients with other types of inflammatory arthritis.[6] Similarly, in a study by Petri and Allbritton, 31% of SLE patients reported an allergy to sulfonamide antibiotics, and the risk of sulfonamide allergic reaction was estimated to be 2.4 times more likely in SLE patients compared to controls (family and/or best friends).[7] 21% of sulfonamide reactions were lupus exacerbations, but the majority were rash. Both of these studies were surveys, and it is therefore possible that the reported ADR rates were inflated by volunteer bias. Given the high mortality rate of PCP and the possibly superior efficacy of TMP/SMX over alternatives,[8] we do not recommend that TMP/SMX be withheld in SLE patients in an effort to reduce the risk of ADRs, unless contraindications exist. Rather, SLE patients should be counselled and monitored closely for ADRs upon initiation of PCP prophylaxis with TMP/SMX.

Additional risk factors for developing opportunistic infections:

Some patients are considered to be at a higher risk of opportunistic infections, regardless of the

immunosuppressive treatment received. In addition to having decreased resistance to infection, these patients are also at risk of infections developing more extensively.

The European Crohn's and Colitis Organization (ECCO) consensus recommends to consider the additional risk factors of age (> 50 years old), comorbidities (chronic lung disease, alcoholism, organic brain disease, diabetes) and malnutrition (BMI < 20 kg/m^2) when assessing the patient's risk of opportunistic infections.[9] The American Society of Transplantation (AST) guidelines on PCP also acknowledge that the assessment of a patient's PCP risk should not be limited to the immunosuppressive therapy received. Other factors such as cytomegalovirus (CMV) infection, lymphopenia/low CD4 count, and prolonged neutropenia are listed as risk factors in non-HIV patients.[10] These factors are pertinent to the GN population, and we have summarized them in **Table 1** and **Table 2**.

The conditions listed in **Table 1** are known risk factors for PCP that are relevant in GN patients and that we consider to be major risk factors. If a patient develops any of these conditions, modification of the current immunosuppressive regimen may be warranted; however, recommendations for this are outside the scope of this guideline. We recommend that PCP prophylaxis be considered for all GN patients with one or more of these risk factors while they are on immunosuppression, regardless of the regimen they are receiving. Low CD4 count is included as a risk factor in **Table 1**, but we recognize that CD4 counts are typically not monitored in non-HIV GN patients. PCP prophylaxis recommendations in the context of HIV/AIDS are outside the scope of this guideline.

Of note, advanced age and hypogammaglobulinemia are indicated as PCP risk factors in the AST guidelines,[10] but we have excluded these factors from **Table 1**. Advanced age was excluded because we do not believe that it alone is significant enough to warrant PCP prophylaxis at this time. However, it is listed as a risk factor for opportunistic infections in **Table 2** (see paragraph below). Hypogammaglobulinemia was excluded because it occurs in nephrotic syndrome and resolves as the disease responds to treatment; recommending PCP prophylaxis on the basis of hypogammaglobulinemia would likely lead to overprescribing of prophylaxis in GN patients.

Table 2 lists known risk factors for opportunistic infections that are not specific to PCP. The role of initiating PCP prophylaxis on the basis of these risk factors is not well-defined. It is our opinion that PCP prophylaxis should be considered for GN patients with one or more of these risk factors if they are receiving certain immunosuppressive regimens (see **Table 3** for details). These regimens are those that have not been clearly associated with PCP in the available literature but that we believe may pose significant immunosuppressive burdens in vulnerable populations. Certain risk factors for opportunistic infections carry more significance than others (e.g. chronic lung disease is more important than an age of 51 years), and clinical judgement is therefore required when making decisions about prophylaxis initiation.

Table 1. Risk factors for PCP

▶ **BC Renal GN Committee recommends consideration for PCP prophylaxis in patients with one or more of these risk factors, regardless of the immunosuppressive regimen received.**

- CMV infection
- lymphopenia (lymphocyte count < 0.5 x 10^9 cells/L) or low CD4 count (< 200 cells/microL)
- prolonged neutropenia

Table 2. Risk factors for opportunistic infections

▶ **BC Renal GN Committee suggests/recommends consideration for PCP prophylaxis in patients with one or more of these risk factors if they are receiving certain immunosuppressive regimens (see Table 3 for details). Certain risk factors carry more significance than others, and clinical judgment is therefore required when making decisions about prophylaxis initiation.**

- age (> 50 years old)
- chronic lung disease
- alcoholism
- organic brain disease
- diabetes
- malnutrition (BMI < 20 kg/m^2)

3. Methodology

A PICO question was developed for each immunosuppressant regimen used to treat GN. These questions were used in PubMed searches to find articles published between 1946 and the end of November 2019. A total of eight distinct searches were conducted. With the exception of single case reports, all studies (i.e., randomized controlled trials, cohort studies, case-control studies and case series) were included if they were published in English and conducted in humans. The total number of articles identified in PubMed was 413, with 72 full-text papers selected for appraisal and analysis. Two review authors independently assessed trial quality and one reviewer extracted data. Trial data on benefits and harms were collected. A summary of the search strategy is available in **Appendix 1**, with full details available in the **Supplementary Appendices**.

4. Recommendations

PCP incidences associated with each immunosuppressant regimen in patients with GN were not able to be reliably determined due to limitations in the available data; hence, this data could not be compared against the prophylaxis thresholds discussed above. Recommendations are therefore based on risk-benefit assessments and alignment with published guidelines. Recommendations on when to provide prophylaxis, along with the rationale, are provided in **Table 3**. Recommendations on which prophylaxis agents to select, in addition to information on dosing, side-effects, and costs, are provided in **Table 4**.

Table 3. PCP prophylaxis recommendations according to immunosuppressive therapy used to treat patient with GN

- **PCP prophylaxis should be considered for patients on immunosuppression with one or more of the following PCP risk factors, regardless of the immunosuppressive regimen received:**
  - **CMV infection**
  - **lymphopenia (lymphocyte count < 0.5 x 10^9 cells/L) or low CD4 count (< 200 cells/microL)**
  - **prolonged neutropenia**

Immunosuppressive Therapy	Applicable Regimen(s)	PCP Prophylaxis Recommendations	Rationale
Prednisone		Recommend prophylaxis if the planned prednisone regimen is ≥ 20 mg/day for at least 4 weeks. Recommend to consider discontinuing prophylaxis when the prednisone dosage is tapered to < 20 mg/day. Regardless of the prednisone dosage, we recommend that PCP prophylaxis be considered if the patient has one or more risk factors for PCP (see **Table 3** caption).	There is currently no high-quality evidence to guide the specific prednisone dosage and treatment duration at which PCP prophylaxis should be recommended in patients with GN. The authors of two studies conducted by the same investigators suggested that prednisone ≥ 30 mg/day for ≥ 4 weeks is a reasonable threshold at which to initiate PCP prophylaxis. However, these studies were both limited by their retrospective designs.[13,21] Due to the high mortality rate of PCP, it is our opinion that it is prudent to err on the side of caution and use a more conservative evidence-based approach. Our recommendation to initiate prophylaxis in patients receiving prednisone ≥ 20 mg/day for ≥ 4 weeks is derived from the widely-cited American Thoracic Society (ATS) statement on treatment of fungal infections in adult pulmonary and critical care patients.[22] ATS' recommendation was based on one cohort study.[3] No high-quality evidence is available to guide the timing of PCP prophylaxis discontinuation when tapering prednisone. Our recommendation is opinion-based and takes into account the practicality of using the same prednisone dose threshold to initiate and discontinue prophylaxis.

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Immunosuppressive Therapy	Applicable Regimen(s)	PCP Prophylaxis Recommendations	Rationale
Antiproliferative agent monotherapy	AZA or MMF monotherapy	We do not recommend routine prophylaxis. However, we recommend that PCP prophylaxis be considered if the patient has one or more risk factors for PCP (see **Table 3** caption).	There are no reported cases of PCP in patients treated with antiproliferative agent monotherapy.
Antiproliferative agent plus low-dose prednisone	AZA or MMF + Prednisone < 20 mg/day	We do not recommend routine prophylaxis at this time. However, we recommend that PCP prophylaxis be considered if the patient has one or more risk factors for PCP (see **Table 3** caption). We *suggest* that PCP prophylaxis be considered if the patient has one or more risk factors for opportunistic infections (see **Table 2** above), recognizing that certain factors carry more significance than others. Clinical judgement is required.	In one small RCT, no patients developed PCP while on azathioprine plus prednisone ≤ 0.5 mg/kg/day.[23] However, it is difficult to determine the true risk of PCP based on the available data.
Calcineurin inhibitor monotherapy	CsA or TAC monotherapy	We do not recommend routine prophylaxis. However, we recommend that PCP prophylaxis be considered if the patient has one or more risk factors for PCP (see **Table 3** caption).	A retrospective study of 203 liver transplant patients on calcineurin inhibitor monotherapy found no PCP cases in a 5-year period.[26]

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Immunosuppressive Therapy	Applicable Regimen(s)	PCP Prophylaxis Recommendations	Rationale
Calcineurin inhibitor plus low-dose prednisone	CsA or TAC + Prednisone < 20 mg/day	We do not recommend routine prophylaxis at this time. However, we recommend that PCP prophylaxis be considered if the patient has one or more risk factors for PCP (see **Table 3** caption). We *suggest* that PCP prophylaxis be considered if the patient has one or more risk factors for opportunistic infections (see **Table 2**), recognizing that certain factors carry more significance than others. Clinical judgement is required.	It is difficult to determine the true risk of PCP based on the available data. There are two retrospective case series (totaling 19 patients) describing PCP cases in kidney transplant patients taking cyclosporine in combination with prednisone 10 to 20 mg/day.[24,25] In one of these studies, 12 patients with PCP were described. The risk factors of lymphopenia and CMV infection were noted in eight and four patients, respectively. The clinical features of the patients in the second study were not described in detail.
Calcineurin inhibitor, plus antiproliferative agent	CsA or TAC + AZA or MMF	It is our opinion that PCP prophylaxis is not routinely required. However, there is controversy in this regard. We recommend that PCP prophylaxis be considered if the patient has one or more risk factors for PCP (see **Table 3** caption). We also recommend that PCP prophylaxis be considered if the patient has one or more risk factors for opportunistic infections (see **Table 2**), recognizing that certain factors carry more significance than others. Clinical judgement is required.	It is difficult to determine the true risk of PCP based the available data; patients in retrospective studies who developed PCP on this combination were likely also on corticosteroid therapy. BC Transplant recommends lifelong PCP prophylaxis for renal transplant patients, most of whom receive this combination of immunosuppressants; however, we believe that there is currently insufficient evidence to support this approach in patients with GN. Long-term PCP prophylaxis is not the standard of practice for liver and heart transplant patients in BC. In addition, the AST guidelines do not provide any recommendation to give PCP prophylaxis on the basis of this immunosuppressant combination. The AST recommendation is to continue PCP prophylaxis for at least 6 to 12 months post-transplantation.[10]

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Immunosuppressive Therapy	Applicable Regimen(s)	PCP Prophylaxis Recommendations	Rationale
Triple immunosuppression (Calcineurin inhibitor, antiproliferative agent, and prednisone)	AZA or MMF + CsA or TAC + Prednisone (any dose)	Recommend prophylaxis in patients on triple immunosuppressive therapy, irrespective of the prednisone dosage.	These recommendations align with the AST guidelines. The AST recommendation is to continue PCP prophylaxis for at least 6 to 12 months post-transplantation,[10] during which time most transplant patients receive this combination of immunosuppressants. In addition, PCP prophylaxis is routinely recommended for renal, heart, and liver transplant patients receiving this combination in BC.
Cyclophosphamide		Recommend prophylaxis until cyclophosphamide is discontinued and any lymphopenia has resolved. In the absence of contraindications, we do not recommend withholding PCP prophylaxis in any GN patient treated with cyclophosphamide.	Cyclophosphamide has been shown to be associated with the development of PCP in several studies (see Supplementary Appendix). However, it is difficult to determine the true risk of PCP based on the available data. Data from a small case series of three patients suggested that PCP prophylaxis should be continued for months beyond cyclophosphamide discontinuation;[11] however, persistent lymphopenia was a common feature among these patients who developed PCP. Therefore, rather than define a duration for prophylaxis post-discontinuation of cyclophosphamide, we recommend continuing prophylaxis until any lymphopenia has resolved. With regards to whether the type of GN influences the need for PCP prophylaxis, data synthesis from multiple studies[12–15] have suggested that SLE patients treated with cyclophosphamide are at a lower risk of PCP.[14] However, the majority of these studies were retrospective. In addition, most made no mention of PCP, which does not exclude the possibility that PCP occurred. We therefore do not recommend withholding PCP prophylaxis in a patient solely due to their type of GN.

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Immunosuppressive Therapy	Applicable Regimen(s)	PCP Prophylaxis Recommendations	Rationale
Rituximab monotherapy		There is currently insufficient evidence to make firm recommendations for or against routine prophylaxis. We *suggest* discussing the risks and benefits of PCP prophylaxis with the patient as part of the decision-making process. However, we recommend that PCP prophylaxis be considered if the patient has one or more risk factors for PCP (see **Table 3** caption). We also recommend that PCP prophylaxis be considered if the patient has one or more risk factors for opportunistic infections (see **Table 2**), recognizing that certain factors carry more significance than others. Clinical judgement is required. If PCP prophylaxis is initiated, we *suggest* continuing it for at least 6 months after the last rituximab dose or until repletion of B cells.	It is difficult to know whether PCP prophylaxis is warranted in patients receiving rituximab monotherapy. There have been a few cases of PCP documented in the literature; however, limited information was provided on the patients' other risk factors for opportunistic infections. The true risk of PCP during rituximab monotherapy is currently unknown. PCP prophylaxis was recommended for patients in the rituximab arm of the MENTOR trial, but it was not mandated. Neither the use of PCP prophylaxis nor the incidence of PCP was reported. Long-term rituximab monotherapy without routine PCP prophylaxis is frequently used to treat patients with rheumatoid arthritis. Currently, the American College of Rheumatology, British Society of Rheumatology and Canadian Rheumatology Association do not provide any guidelines for PCP prophylaxis in patients receiving rituximab monotherapy.[16–18] Our suggestion for the duration of prophylaxis (if used) is consistent with the RAVE trial protocol, which required PCP prophylaxis to be continued for 6 months after the last rituximab dose.[19] However, the patients in the RAVE trial also received high-dose prednisone, and the incidence of PCP was not reported.

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Immunosuppressive Therapy	Applicable Regimen(s)	PCP Prophylaxis Recommendations	Rationale
Rituximab plus one other immunosuppressant	Rituximab + AZA, MMF, CsA, TAC, or prednisone (any dose)	Recommend prophylaxis that is continued for at least 6 months after the last rituximab dose or at least until repletion of B cells. The total duration of prophylaxis may depend on the other immunosuppressant used (refer to relevant sections of **Table 3**).	There have been several reports of PCP occurring in patients receiving rituximab in combination with corticosteroids (see Supplementary Appendix). One such case occurred in the MAINRISTAN trial, in which all patients randomized to rituximab also received high-dose prednisone that was subsequently tapered.[20] PCP prophylaxis was not required for all patients, but it was mandated for patients with low CD4 counts. It is important to note that one of the patients in the rituximab arm did not receive PCP prophylaxis and developed PCP. No other details were provided, but the authors stated that this underscored the recommendation that PCP prophylaxis be used independently of the CD4 count. Our recommendation for duration of prophylaxis is consistent with the PCP prophylaxis protocol of the RAVE trial.[19] In this trial, all patients randomized to rituximab also received high-dose prednisone that was tapered with an aim to discontinue it by 5 months. PCP prophylaxis was required for 6 months after the last rituximab dose. The incidence of PCP in this trial was not reported. There is limited data available to guide PCP prophylaxis recommendations for patients on combination therapy with rituximab and a non-corticosteroid immunosuppressant. It is our opinion that the resultant immunosuppressive burden would likely be high enough to justify PCP prophylaxis.

AZA = azathioprine; CsA = cyclosporine; MMF = mycophenolate (mycophenolate mofetil or mycophenolate sodium); TAC = tacrolimus

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Table 4. Summary of PCP prophylaxis agents to aid prescribing

Drug and Strength	Dose	Side effects	Precautions	Comments	Cost and Coverage
First-line therapy					
Trimethoprim/ sulfamethoxazole (TMP/SMX) SS tab: 80/400 mg DS tab: 160/800 mg	CrCl > 30 mL/min: 1 SS tab PO daily, OR 1 DS tab PO 3x/week CrCl < 30 mL/min: 1 SS tab PO 3x/week	GI intolerance; hepatoxicity (including hepatitis, cholestasis, hepatic necrosis); hyperkalemia; rash; Stevens-Johnson syndrome (rare); toxic epidermal necrolysis (rare); photosensitivity; bone marrow suppression	Pregnancy: Avoid in 1st trimester (congenital malformations, including neural tube defects and cardiovascular malformations); avoid after 32 weeks gestation (kernicterus)	Nephrotoxicity can occur due to the sulfonamide component (hypersensitivity interstitial nephritis, tubular necrosis, crystalluria); however, trimethoprim also reduces tubular secretion of creatinine, which can cause an increase in serum creatinine without any true reduction in glomerular filtration rate	$0.05/day BC PharmaCare benefit
Second-line therapy					
Dapsone 100 mg tab	100 mg PO daily	Hemolytic anemia [seen in patients with and without glucose-6-phosphate-dehydrogenase (G6PD) deficiency]; methemoglobinemia; leukopenia; rash; cholestatic jaundice; hepatitis; GI intolerance	Screen for G6PD deficiency and avoid if deficient (increased risk of hemolysis and methemoglobinemia) Unclear if there is cross-reactivity between dapsone (a sulfone) and sulfonamide antibiotics; avoid in patients who have had severe reactions to TMP/SMX (e.g., Stevens-Johnson syndrome) Pregnancy: Because of the potential increased risk of hyperbilirubinemia and kernicterus, neonatal care providers should be informed if maternal dapsone is used near term		$0.76/day BC PharmaCare benefit
Third-line therapy					
Aerosolized pentamidine 300 mg/vial	300 mg nebulized once monthly	Dizziness; fatigue; cough; bronchospasm (more common in patients with asthma or a smoking history); metallic taste	Due to the risk of bronchospasm, use caution in patients with asthma or a smoking history; pretreatment with a bronchodilator (e.g., salbutamol) may ameliorate symptoms		$6.23/day ($190/month) Not a BC PharmaCare benefit
Atovaquone 750 mg/5 mL suspension	1500 mg (10 mL) PO daily with food	Headache; insomnia; rash; pruritis; GI adverse effects (diarrhea, nausea, vomiting, abdominal pain)	Must be taken with food (preferably high-fat foods/meals) for optimal absorption; consider an alternative PCP prophylaxis agent for patients who have difficulty taking atovaquone with food	Very expensive; review whether patient has 3rd party insurance coverage prior to prescribing Must be taken with food (preferably high-fat foods/meals such as peanuts or ice cream) for optimal absorption	$31/day Not a BC PharmaCare benefit Difficult to obtain supply [only available through certain wholesaler(s)]

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Appendix 1: Down-selection of Relevant Articles