Prophylaxis - Pneumocystis jiroveci (carinii) in cancer patients

ID: 220 v.5 **Endorsed**

Background

Pneumocystis jiroveci infection (PJP, also known as PCP) causes pneumonia in patients with immunosuppression due to underlying malignancy, organ transplantation or other conditions. The infection is best studied in those with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). However, there are significant differences in the clinical features of PJP between HIV infected and non-infected individuals, and mortality rates are generally higher in non-HIV infected individuals (34-39% vs 6-7%).[1]

Risk factors

There are well-defined patients who are at risk of PJP due to the status of their underlying malignancy, treatment-related immunosuppression and/or concomitant use of corticosteroids.[1]

In patients with haematological malignancy, both host and disease factors, as well as chemotherapy regimens need to be considered when determining an individual's risk of PJP (see table below). A patient's risk of PJP is influenced by multiple factors at any given point in time and risk should be continually assessed throughout the treatment period.

The following table is intended as a **guide only**. The decision as to when and which prophylaxis will be used should be based upon local clinical risk factors, individual patient risk factors and local institutional policies.

Note: This table includes commonly used immunosuppressive drugs; prophylaxis may also be necessary for treatment with less commonly used immunosuppressive drugs, and newer monoclonal antibodies and other biological agents.

Cause of immunosuppression	Recommendation*	Comments	Duration of prophylaxis
Blood and marrow transplant (BMT)			
Allogeneic BMT	Recommended	Incidence reported from 0.3% to 15%[2, 3, 4]	Give prophylaxis for 12 months after transplantation or after stopping immunosuppressive therapy, whichever is later.[5] *Note that the pre-emptive dose during conditioning therapy differs from standard prophylaxis dosing*
Autologous BMT	Sometimes indicated	Give PJP prophylaxis if underlying haematological malignancy.	Give prophylaxis for 3 to 6 months after transplantation or after stopping immunosuppressive therapy, whichever is later.[5, 6]
Acute leukaemia			
Acute lymphocytic leukaemia (ALL)	Recommended	Reported as up to 16%[7]	Give prophylaxis for 2 months after stopping chemotherapy (including corticosteroids).[5]
Acute myeloid leukaemia	Sometimes indicated	Factors that increase risk of PJP are:	Give prophylaxis for 2

Cause of immunosuppression	Recommendation*	Comments	Duration of prophylaxis
(AML)		higher glucocorticoid dose, co-administration of steroid-sparing or other immunosuppressive therapy, presence of T-cell defects, low lymphocyte count.	months after stopping chemotherapy (including corticosteroids).[5]
Lymphoma			
Non-Hodgkin lymphoma - standard intensity regimens, e.g. RCHOP21	Sometimes indicated	Factors that increase risk of PJP are: higher glucocorticoid dose, co-administration of steroid-sparing or other immunosuppressive therapy, presence of T-cell defects, low lymphocyte count.	Give prophylaxis for 2 months after stopping chemotherapy (including corticosteroids).[5]
Non-Hodgkin lymphoma - high intensity regimens, e.g. RCHOP14	Recommended	High-intensity chemotherapy regimens (e.g. for Burkitt, central nervous system or relapsed lymphoma), or CD4 count less than 200 cells/microlitre before chemotherapy.[5]	Give prophylaxis for 2 months after stopping chemotherapy (including corticosteroids).[5]
Hodgkin lymphoma	Recommended for ABVD[8] (doxorubicin, bleomycin, vinblastine and dacarbazine)		Give prophylaxis for 2 months after stopping chemotherapy (including corticosteroids).[5]
Multiple myeloma	Risk of infection is dependent on chemotherapy regimen and number of courses of chemotherapy		
Myelodysplastic syndrome	Risk of infection is dependent on chemotherapy regimen: if high-intensity chemotherapy, see acute myeloid leukaemia		
Immunosuppressive drugs used in the treatment of haematological and other malignancies			
Alemtuzumab	Recommended		Give prophylaxis for 12 months or until CD4 count greater than 200 cells/microlitre, whichever is later.[5]
Bortezomib	Sometimes indicated	Factors that increase risk of PJP are: higher glucocorticoid dose, co-administration of steroid-sparing or other immunosuppressive therapy, presence of T-cell defects, low lymphocyte count.[5]	
Corticosteroids Patients receiving prolonged, high-dose corticosteroid treatment (e.g. ≥20 mg of prednisolone daily or ≥4 mg dexamethasone daily for ≥4 weeks)#	Recommended	Factors that increase risk of PJP are: higher glucocorticoid dose, co-administration of steroid-sparing or other immunosuppressive therapy, presence of T-cell defects, low lymphocyte count.[5]	Prophylaxis should be continued while steroids are being weaned and/or for a period of 6 weeks after cessation.[1]
Fludarabine or other T-cell	Recommended		Give prophylaxis for 12

Cause of immunosuppression	Recommendation*	Comments	Duration of prophylaxis
depleting purine analogues, e.g. FCR chemotherapy regimen			months or until CD4 count greater than 200 cells/microlitre, whichever is later.[5]
Gemcitabine	Recommended	**High risk:** Lymphoma during treatment with gemcitabine.[9] **Low risk:** Solid tumours.[9]	**High risk:** Give prophylaxis during gemcitabine cycles and minimise concomitant use of steroids including emesis prophylaxis.[9] **Low risk:** Empiric treatment for PJP if significant respiratory compromise and awaiting diagnostic work up.[9]
Idelalisib +/- rituximab	Recommended		Give prophylaxis for at least the duration of treatment.[10]
Methotrexate (>1 g/m^2)	Recommended	Avoid TMP-SMX in patients taking high-dose methotrexate because there is an increased risk of methotrexate toxicity-dapsone is preferred for PJP prophylaxis in these patients.[5] Alternatively, cease TMP-SMX prophylaxis 48 hours prior to MTX infusion and recommence upon neutrophil recovery.	
Temozolomide PLUS radiation	Recommended	Cranial irradiation increases the risk of PJP. Over a 12 month period, PJP has a reported incidence of 6.2% in this population, with a median time to onset of 10 weeks.[11] For the treatment of glioblastoma, results in significant lymphopenia in 24-100% of patients, depending on density of dosing.[12, 13] In a phase 2 trial, 79% of patients developed grade 3-4 lymphopenia, with two of the first 15 patients (13%) developing PJP.[14]	Give prophylaxis for 2 months after stopping chemotherapy (including corticosteroids).[5]
Other drugs for consideration (e.g. ibrutinib and bendamustine)	Sometimes indicated	Increased susceptibility to PJP has been reported.[10]	

Table adapted from Cooley et al[1] and eTG Therapeutic Guidelines© v.43 October 2014.[5]

[#] The majority of this data comes from continuous corticosteroid use, and the risk associated with repeated exposure from short term high dose steroids is difficult to quantify. The exact glucocorticoid dose and duration associated with increased risk of infection is uncertain; prednisolone 20 mg daily (or equivalent) for 4 weeks is the consensus view of the Antibiotic Expert Groups.

**** Key:***

Recommended: Prophylaxis indicated for all at-risk patients

Cause of immunosuppression	Recommendation*	Comments	Duration of prophylaxis
***Sometimes indicated**:* Prophylaxis may be considered in specific situations (e.g. higher glucocorticoid dose, co-administration of steroid-sparing or other immunosuppressive therapy, presence of T-cell defects, low lymphocyte count), or for selected patients based on patient- and/or therapy-specific risk factors for the infection in question—seek expert advice			

Management

Prophylaxis

Antimicrobial prophylaxis is highly successful in preventing PJP in patients with immunosuppression from a diverse range of causes, including solid-organ transplantation and malignancy.[1] Guidelines have been published for the use of PJP prophylaxis in patients with cancer, including blood and marrow transplant (BMT) recipients.[6, 15] In a meta-analysis of randomized trials of PJP prophylaxis in immunocompromised patients without HIV infection, it was concluded that, in adults, prophylaxis is warranted when the risk of PJP is higher than 3.5%.[16]

First-line agent

Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole (TMP-SMX) is the first-line prophylactic agent for PJP prevention in adults and children. The effectiveness of TMP-SMX prophylaxis was illustrated in a Cochrane review of 13 randomised controlled trials that included 1412 immunocompromised patients without HIV infection who had undergone autologous hematopoietic cell or solid organ transplantation or had a haematologic malignancy.[17] TMP-SMX prophylaxis was associated with an 85 % reduction in the occurrence of PJP compared with no prophylaxis or fluoroquinolone prophylaxis, which is inactive against Pneumocystis (relative risk [RR] 0.15, 95% CI 0.04-0.62). The number needed to treat to prevent one infection was 19. Mortality due to PJP was also significantly reduced (RR 0.17, 95% CI 0.03-0.94), although all-cause mortality was not. Using data from two trials included in the review, no differences in efficacy were found between once-daily and thrice-weekly administration schedules for TMP-SMX.

In addition TMP-SMX has superior efficacy and activity against pathogens other than Pneumocystis jiroveci (e.g. common bacterial infections, listeriosis, nocardiosis and toxoplasmosis), low cost and ease of access.

The optimal dose schedule for TMP-SMX is not clear due to the limited number of studies comparing regimens in patients with malignancy or undergoing stem cell transplantation.[1] In the absence of clear evidence to support various dosing regimens, Cooley et al support the use of once-daily dosing in adults with SS (single strength) or DS (double strength) or thrice-weekly dosing with DS.

For those who are intolerant of TMP-SMX, desensitisation should be attempted when possible. Desensitisation should be considered for all patients with TMP-SMX-associated rash however it is contraindicated in patients with a history of drug rash with eosinophilia and systemic symptoms (DRESS) or Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Desensitisation is only effective if the therapy is uninterrupted; if strict adherence is unlikely, consider an alternative to TMP-SMX.[5] Read more about the sulfonamide desensitisation protocol.

Second-line agents

There are no sufficiently powered trials on which to base a recommendation for alternative prophylactic regimens in patients with malignancies.[1]

1. Dapsone

Dapsone is effective, but inferior to TMP/SMX, and therefore, it is only to be used as an alternative agent in patients whom TMP-SMX is contraindicated or not tolerated.

Dapsone should not be given to patients with G6PD deficiency or to patients who have experienced severe side-effects with TMP-SMX, as cross reactions can occur.

- test for glucose-6-phosphate dehydrogenase (G6PD) deficiency before starting treatment with dapsone—seek expert advice if the patient is G6PD deficient
- the cross-reactivity rate between dapsone and sulfamethoxazole is approximately 20%; do not use dapsone in patients with immediate hypersensitivity or another severe reaction (e.g. drug rash with eosinophilia and systemic symptoms [DRESS] or Stevens–Johnson syndrome / toxic epidermal necrolysis [SJS/TEN]) to sulfonamides

2. Pentamidine

Given the high rates of adverse effects associated with parenteral therapy in adults, including pancreatitis, hypoglycaemia (27%) and nephrotoxicity (25%), aerosolisation is the preferred mode of delivery for prophylaxis.[1]

Unequal distribution in the lungs can lead to breakthrough PJP in the upper lobes. Nursing staff must wear full PPE during preparation including the wearing of a P2 or N95 respirator mask. Administration must occur in an isolated and well ventilated (ideally negative-pressure) room and health care workers should not stay in the room for the whole treatment.

Nebulised pentamidine is usually well tolerated, with the major side-effects being coughing and wheezing, which can be prevented by the use of inhaled beta-agonists.[1] It should be avoided in patients with a smoking or asthma history.

Few clinical trials have been undertaken in patients with malignancy. There is data to suggest that aerosolised pentamidine may be inferior when used prophylactically in allogeneic transplant recipients.[18]

3. Atovaquone

Atovaquone is also proven but less efficacious than TMP/SMX. One such trial that compared atovaquone to TMP-SMX for PJP prophylaxis in 39 patients following autologous SCT showed that atovaquone is well tolerated in this patient population.[17] No firm conclusions can be reached about the relative efficacy of atovaquone since the number of patients studied was small and no patient in either arm developed PJP, although the treatment-associated adverse event rate was significantly higher in patients receiving TMP-SMX (40% vs 0%, P<0.003).

Summary of dosing schedules for PJP chemoprophylaxis

Drug	Dose	Adverse reaction	Additional information
TMP-SMX	160 + 800 mg (one DS tablet) orally, daily OR 80 + 400 mg (one SS tablet) orally, daily OR 160 + 800 mg (one DS tablet) orally, three times a week*	Fever, rash, neutropenia, gastrointestinal upset, transaminase elevation	Note: • in clinical practice many institutions administer one DS tablet TWICE daily TWICE weekly (e.g. Monday and Thursday) • the pre-emptive dose during conditioning therapy differs from standard prophylaxis dosing
Dapsone	100 mg orally, daily	Fever, rash, gastrointestinal upset, methemoglobinemia, haemolytic anaemia (check for G6PD deficiency)	• addition of trimethoprim to dapsone does not appear to add to efficacy in prophylaxis and so is not recommended • dapsone is not myelosuppressive • reduce dapsone dose to 50 mg daily in patients who develop toxicity (methaemoglobinaemia, chemical haemolysis) • azole antifungal agents elevate dapsone levels so concomitant use should be avoided or monitored with caution.
Pentamidine	300 mg inhaled through nebuliser, every 4 weeks (administered through a jet-nebuliser producing a droplet size of 1-2 microns)	Cough, wheezing, extrapulmonary pneumocystosis	
Atovaquone	1500 mg orally, daily with a high-fat meal	Gastrointestinal distress, rash	

**Either non-consecutive or consecutive days is acceptable. DS=double strength; SS= single strength.*
Adapted from Cooley et al. Internal Medicine Journal © 2014[1]

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History

Version 5

Date	Summary of changes
15/09/2009	All approved PCP documents on CI-SCaT reviewed, collated and transferred to eviQ
19/08/2011	Reviewed and presented to haematology reference committee
02/02/2015	Converted to new format
11/09/2015	Reviewed and updated as per "Consensus guidelines for diagnosis, prophylaxis and management of Pneumocystis jirovecii pneumonia in patients with haematological and solid malignancies, 2014" and updated Therapeutic Guidelines Nov. 2014
01/07/2016	Minor changes to wording made. ie. HPCT changed to BMT
31/05/2017	Transferred to new eviQ website. Version number changed to V.4.
22/09/2017	Updated as per current literature and reviewed at eviQ BMT meeting with the following changes: • Idelalisib +/- rituximab and other drugs for consideration (e.g. ibrutinib and bendamustine) added to 'Immunosuppressive drugs used in the treatment of haematological and other malignancies' section of the table under 'Risk factors'. • Aligned the duration of prophylaxis for lymphoma with the eTG recommendations. • Version number changed to v.5.

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