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Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014

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Abstract

Pneumocystis jirovecii infection (PJP) is a common cause of pneumonia in patients with cancer-related immunosuppression. 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. Prophylaxis is highly effective and should be given to all patients at moderate to high risk of PJP. Trimethoprim-sulfamethoxazole is the drug of choice for prophylaxis and treatment, although several alternative agents are available.

Introduction

Pneumocystis jirovecii infection causes pneumonia (PJP; also known as PCP) 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)/acquired immune deficiency syndrome, as there are significant differences in the clinical features of PJP between HIV-infected and non-infected individuals.[1–5]

Infection in immunosuppressed HIV-negative individuals has a shorter duration of onset and fewer systemic symptoms than in HIV-infected individuals.[1] Bronchoalveolar lavage fluid from immunosuppressed non-HIV-infected patients shows lower concentrations of organisms but higher inflammatory scores.[6] Clinical disease is generally more severe in these patients, with increased length of hospital stay and higher rates of intensive care unit (ICU) admission and mechanical ventilation, compared with HIV-infected patients.[1–4] Significantly higher mortality rates are also observed in non-HIV-infected individuals (34–39%) compared to those with HIV (6–7%).[1,5,7]

With a focus on HIV-negative populations, this guideline outlines diagnostic approaches and provides recommendations for prophylaxis and treatment of PJP in adults and children undergoing chemotherapy for haematological and solid-organ tumours. It does not discuss *P. jirovecii* affecting extra-pulmonary sites or infection in the setting of organ transplantation.

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Methodology

Questions asked

In preparing this update, we aimed to address the following questions:

1 What are the current diagnostic strategies for PJP?
2 Which patients with haematological and solid malignancies are at risk for PJP?
3 What is the evidence for prophylaxis? Which agents are most effective?
4 What are the first- and second-line agents for treatment of PJP?
5 Is there any evidence to keep patients with confirmed PJP in clinical isolation?

Search strategy

A literature review was performed using PubMed to identify papers published since 2007 that pertained to PJP in patients with haematological and solid tumours. Search terms included (in combination) '*Pneumocystis carinii*', '*Pneumocystis jirovecii*', 'immunocompromised', 'non-HIV', 'treatment', 'prophylaxis' and 'diagnostics'.

Diagnosis of PJP

Microbiological tests

Due to difficulties with isolating and culturing this pathogen, microscopic examination of respiratory specimens using various staining methods is used to visualise and identify the morphological structures of *P. jirovecii*. Methenamine silver and toluidine blue preparations stain only the cyst wall and do not allow detection of trophozoites. However, Giemsa stains detect all life stages of *P. jirovecii*. Direct and indirect immunofluorescent assays (DFA, IFA) are specific for different life stages, depending on the antibody used. Comparative studies have shown DFA and IFA to be the most sensitive stains for *P. jirovecii* in sputum and bronchoalveolar lavage, with sensitivities of 97% and 90% respectively.[8] These assays are also commercially available.

Overall, the accuracy of staining methods is highly dependent on the quality of respiratory specimen, sample processing, reaction of the specimen to the stain chosen and experience of the laboratory observer. The lower burden of *P. jirovecii* in non-HIV-immunocompromised patients, and the likelihood that they may already be on anti-pneumocystis prophylaxis, remains a challenge for diagnosis.[9]

Staining methods have now largely been supplanted by highly sensitive molecular techniques, using semi- or fully quantitative polymerase chain reaction (PCR) targeting *P. jirovecii*-specific genes.[10] A meta-analysis of PCR studies has shown a pooled sensitivity of 99% and specificity of 92% in the non-HIV patient population.[11] A variety of gene targets can be used for PCR amplification, including: major surface glycoprotein (*MSG*) gene, mitochondrial large subunit (*mtLSU*) rRNA gene, dihydropteroate synthase (*DHPS*) gene, dihydrofolate reductase (*DHFR*) gene, heat shock protein (*HSP*) 70 gene and the beta-tubulin gene. Multicopy genes such as *mtLSU* and *MSG* offer the greatest sensitivity for *P. jirovecii* detection.[10] However, they lack specificity and have a low positive predictive value due to the increased detection of *P. jirovecii* in patients who are colonised but otherwise well. With a high negative predictive value, PCR is best utilised for excluding the diagnosis of PJP.[12]

Quantitative PCR (qPCR), with defined upper- and lower-quantitation thresholds of *P. jirovecii* copy number, can be used to distinguish true infection from colonisation.[13–18] However, there remains an indeterminate zone of unclear clinical significance.[14–17] Further, these quantitation thresholds will vary between different patient populations; clinicians should be cautious of relying on them as a measure to guide diagnosis or therapy. To improve accuracy, combined diagnostic algorithms have been proposed. These use qPCR and β(1,3)-D-glucan on serum testing to classify patients into infection and colonisation categories,[19] but validation is still required in patients with malignancy.

Due to heterogeneity of methods and diversity of chosen qPCR targets in published literature, generalisability of reported cut-off values is limited. Each institution must establish and validate its own qPCR cut-off values appropriate to the preferred molecular method. While molecular tests may aid clinical diagnosis, there is a lack of correlation between qPCR and the clinical features or outcomes of PJP.[20] Therefore, clinicians should take an individual's clinical risk of PJP into consideration when interpreting the cycle thresholds.

Studies on the use of molecular diagnosis have largely been based on bronchoalveolar lavage sampling.[15,16] Although induced sputum samples have also been evaluated, they can be demanding to perform on wards and in children.[17] Others have reported the use of oral washes and expectorated sputum, but the clinical validity of these approaches requires further evaluation.[20,21] These approaches certainly produce a lower yield – that may be useful – but, overall, their value in this particular setting remains unclear.

Radiological findings

Imaging studies are an essential companion to microbiological testing for diagnosing PJP. High-resolution computed tomography (CT) is the most commonly used and reliable radiological modality for detecting pneumonic

changes in immunocompromised patients.[22] The most frequent CT findings are bilateral, ground-glass changes with apical predominance and peripheral sparing.[22] In non-HIV-immunocompromised patients with PJP, signs of consolidation are detected more frequently on CT – and cystic changes *less* frequently – than in HIV-positive patients with PJP.[23,24] The range of other radiological features seen in PJP include a combination of ground glass and consolidative opacities, cystic changes, linear-reticular opacities, solitary or multiple nodules and parenchymal cavities.[25] With treatment, the vast majority of these changes resolve.[22]

Nuclear imaging modalities such as 18F-fludeoxyglucose-positron emission tomography (FDG-PET) have been used as an adjunct to plain X-ray or CT.[26] The FDG-PET findings correlate well with conventional imaging, showing bilateral uptake of FDG in the upper zones of the lungs.[27] Abnormalities on PET scans, leading to PJP diagnosis in the setting of normal chest radiographs, have been reported, which suggests a potential role for PET scans in facilitating early diagnosis. However, limited access to FDG-PET is currently a significant barrier to use.[28]

Determining patient risk and the need for PJP 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. Chemoprophylaxis was first demonstrated to be highly effective in preventing PJP in a randomised controlled study of paediatric oncology patients.[29] Pooled data from 11 clinical trials showed a reduction in the relative risk (RR) of PJP (0.09, 95% confidence interval (CI) 0.02–0.32) in patients receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis compared with patients receiving no intervention, placebo or an antibiotic without PJP activity.[30] TMP-SMX prophylaxis has been shown to have a mortality benefit and its use is recommended in settings where the risk of PJP is estimated to exceed 3.5% (grade A recommendation).[30] Prophylaxis is routinely used in children for a wider range of malignancies, including those with a lower risk of PJP, as TMP-SMX is very well tolerated.

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 1). 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.

Table 1 Patients with malignancy at high risk for *Pneumocystis jirovecii* pneumonia

- Heavily pre-treated patients (e.g. multiple lines of chemotherapy for Hodgkin and non-Hodgkin lymphoma, lymphoproliferative diseases or myeloma).
- Relapsed disease.
- High-dose corticosteroids (often in combination with chemotherapy).
- Chemotherapy, monoclonal antibodies or diseases causing prolonged lymphopenia (e.g. ALL, alemtuzumab, R-CHOP14).

PJP risk in patients with haematological malignancy

Specific patient groups with underlying haematological malignancy have been identified to be at high risk of PJP.[31] These findings have been used to inform guidelines regarding institution of PJP prophylaxis. However, there have been important shifts in the treatment of haematological malignancies[30,32] and diagnostic algorithms since the publication of earlier studies. Furthermore, early evaluation did not encompass emerging subgroups of patients with haematological malignancy. The estimated risk of PJP in these groups, such as acute myeloid leukaemia,[3,33,34] myelodysplasia, myeloma[3,35–37] and lymphoma,[38–46] are based on case reports and are incompletely defined.

The most easily quantifiable risk factors in patients with haematological malignancy are choice, dose and combination of chemotherapy agents. Other factors, such as age, comorbidities, type[47] and stage of malignancy, surgery, radiation and immune parameters,[45] also contribute to risk but are more difficult to quantify.

Patients at highest risk of PJP are those undergoing treatment for acute lymphoblastic leukaemia (ALL) (up to 16%)[48] and for allogeneic haemapoietic stem cell transplant (HSCT) (from 0.3% to 15%).[3,49,50] In these populations, the number needed to treat has been estimated to be 11.[30]

Patients receiving prolonged, high-dose corticosteroid treatment (16–25 mg of prednisolone per day or ≥4 mg dexamethasone daily for ≥4 weeks) are also at high risk of PJP, regardless of underlying type or stage of malignancy, or use of other chemotherapy agents.[51] Certain T-cell-depleting agents (e.g. alemtuzumab) will also place patients at a higher risk of PJP, particularly if salvage treatment is being administered.[52] Further, patients who have had PJP previously remain at high risk of a subsequent episode if their underlying immune deficit persists.

Patients in whom the risk of PJP is not conclusively established, but is likely to be moderate, include those with autologous bone marrow transplant,[3] and patients

with haematological malignancy undergoing certain high-intensity chemotherapy regimens. In the latter case, clinicians should be particularly vigilant of R-CHOP14 (rituximab, cyclophosphamide, adriamycin, vincristine, prednisolone chemotherapy on a 14-day cycle),[38,40,42,43,53] FCR (fludarabine, cyclophosphamide, rituximab),[27] AVBD (adriamycin, vincristine, bleomycin, dexamethasone),[54] gemcitabine[55] and high-dose methotrexate. Patients with prolonged CD4 lymphopenia, before or after initiation of chemotherapy, are also likely to be at moderate risk of PJP. However, with limited evidence to assess PJP risk in this group, debate still surrounds the use of prophylaxis in this population.[56,57]

Patients with haematological malignancy at lower risk of PJP include those receiving low-intensity chemotherapy regimens (such as R-CHOP given on a 21-day cycle), provided they do not have other risk factors.[38,45,46,58]

PJP risk in patients with solid-organ malignancy

PJP has been reported to occur in patients undergoing chemotherapy for a broad range of solid-organ malignancies, including breast, pulmonary, renal, genitourinary and colorectal cancer; central nervous system tumours; rhabdomyosarcoma and melanoma.[4,7,59–61] Despite this, there are no clinical efficacy data supporting the routine use of PJP prophylaxis in these patient groups.

The inclusion of corticosteroid therapy in the chemotherapy regimen has been consistently reported as a risk factor for developing PJP in adult patients with solid-organ tumours.[7,61–63] Adult patients who are receiving high-dose corticosteroid therapy (16–25 mg prednisolone or ≥4 mg dexamethasone daily for ≥4 weeks) appear to be at greatest risk, both during high-dose therapy and the steroid-tapering period.[59] Patients receiving these kinds of doses are typically undergoing dose-intensive chemotherapy for lung, breast or brain cancer. There is a paucity of data in the paediatrics setting, although a dosage equivalent to ≥2 mg/kg per day of prednisone or equivalent to a total of ≥20 mg/day for children who weigh more than 10 kg, particularly when given for more than 14 days, is considered to be T-cell immunosuppressive.[64]

Patients with brain tumours are at particular risk of PJP. While the incidence of PJP is low (1.7%) among patients receiving corticosteroids for brain tumours,[65] 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.[66] Temozolomide, an alkylating agent used for the treatment of glioblastoma multiforme, results in significant lymphopenia (<500 cells/uL) in 24–100% of patients, depending on density of dosing.[67,68] In a phase 2 trial, 79% of patients developed grade 3–4 lymphopenia, with two of the first 15 patients (13%) developing PJP.[69] Subsequent cases have led to a black-box warning recommending that PJP prophylaxis accompany the use of this agent.[7,59,70]

Collectively, these data suggest that PJP prophylaxis should be considered in solid-tumour patients undergoing chemotherapy regimens containing 16–25 mg prednisolone or ≥4 mg dexamethasone daily for ≥4 weeks, as well as patients undergoing intensive treatment for cerebral malignancy (grade C recommendation). Prophylaxis should be continued for 6 weeks after the steroid-tapering period. A summary of agents for PJP prophylaxis and their indications for use are provided in Table 2.

Chemoprophylaxis for PJP

TMP-SMX

TMP-SMX is the first-line prophylactic agent for PJP prevention in adults and children, and the only agent demonstrated to be more effective than placebo in prospective randomised trials (grade A recommendation).[29,30] Further, limited evidence suggests that TMP-SMX is superior to other agents, especially in younger patients (<2 years of age) and in patients undergoing HSCT (grade D recommendation).[71] The use of TMP-SMX may also confer some protection against other infections in the high-risk patient such as toxoplasmosis, nocardia and bacterial sepsis. A systematic review in the HIV population also found that the use of TMP-SMX confers some protection against the development of resistance to other antibiotics.[72]

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.[29,30,73] Once- or twice-weekly prophylaxis or 3 non-consecutive days per week may be of equal efficacy, based on retrospective and observational studies (level III-2 evidence).[74] Hughes *et al*. reported that daily and thrice-weekly dosing in children with ALL was equally efficacious.[75] Studies in HSCT patients have reported PJP rates of <1% using doses as low as two single strength (SS) tablets twice weekly, two double strength (DS) tablets twice weekly and two DS tablets thrice weekly.[76–78] In the absence of clear evidence to support various dosing regimens, these guidelines support the use of once-daily dosing in adults with SS or DS or thrice-weekly dosing with DS (grade B recommendation). In children, various regimens are acceptable, although three days per week is preferred practice.

Limitations in TMP-SMX prophylaxis include documented hypersensitivity, renal impairment, drug

Table 2 Indications for *Pneumocystis jirovecii* chemoprophylaxis in patients (adults and children) with malignancy and recommended agent

Haematological malignancy (grade of recommendation)

Note: Patients may have multiple or cumulative risk factors; consider underlying disease, disease status and treatment-related immunosuppression.

Known indications:

- Allogeneic HSCT (all) (C)
- ALL (all) (A)
- AML or lymphoma regardless of treatment protocol (children only) (C)
- Autologous HSCT (all children and selected high-risk adults) (C)
- Regimens: R-CHOP14, high-dose methotrexate (C)
- Lymphocyte-depleting agents (e.g. alemtuzumab) or patients whose CD4 count <200 cells/uL before commencing chemotherapy (C)
- Corticosteroids: where 16–25 mg prednisolone or ≥4 mg dexamethasone for ≥4 weeks is planned (C)
- Regimens: FCR, ABVD, gemcitabine (single centre reports of higher risk for these regimens; consider prophylaxis) (D)

Solid tumours (grade of recommendation)

Regimens where 16–25 mg prednisolone or ≥4 mg dexamethasone for ≥4 weeks is planned (C)

Brain tumours, particularly if temozolomide or craniospinal irradiation is planned (B)

Other solid tumours undergoing myelosuppressive chemotherapy (children only) (C)

First-line prophylactic agent should be trimethoprim-sulfamethoxazole, unless:

(i)	Previous allergy or hypersensitivity to sulfa-drugs
	Recommend: trimethoprim-sulfamethoxazole desensitisation (unless previous anaphylaxis)
(ii)	Planned methotrexate chemotherapy in adults
	Recommend: second-line prophylactic agent

A second-line prophylactic agent should be used if trimethoprim-sulfamethoxazole is contraindicated:

(i)	Dapsone, OR
(ii)	Pentamidine (nebulised, monthly), OR
(iii)	Atovaquone

Prophylaxis should continue for at least 6 weeks after steroid cessation. A longer period of prophylaxis may be required if ongoing chemotherapy (e.g. cytarabine, cyclophosphamide, fludarabine, fluorouracil, methotrexate) is planned. Life-long prophylaxis should be considered if the patient has had a previous episode of PJP and persisting immunosuppression.

interactions, myelosuppression and gastrointestinal disturbance. The true rate of adverse reactions is unknown, but in the adult HSCT population it is estimated to be in the range of 5–15%, and in children it is much lower.[77]

Although one early study suggested increased duration of neutropenia associated with TMP-SMX,[79] this study pre-dated current chemotherapy regimens (including use of granulocyte colony-stimulating factor). More contemporary studies have not demonstrated an impact upon degree or duration of neutropenia. It is reasonable to administer TMP-SMX prior to engraftment in children receiving HSCT, as there is no evidence of delayed engraftment in this population (level III-2 evidence).[80] Myelosuppression may be exacerbated when TMP-SMX is used in combination with methotrexate, although clinical data in adults are conflicting. Concurrent methotrexate administration is not a contraindication for use of TMP-SMX in children receiving treatment for cancer, as there is no evidence for a common, clinically significant adverse drug interaction in this population (level III-2 evidence).[81]

TMP-SMX should be used with caution in all patients with renal and hepatic impairment, and glucose-6-phosphate dehydrogenase deficiency (G6PD).

Mutations in the *fas* gene of *P. jirovecii*, which encodes the DHPS protein, are associated with prior exposure to sulphonamides.[82,83] When these mutations are present, reduced susceptibility to TMP-SMX should be expected. However, the mutations do not appear to correlate with resistance, as HIV-infected patients with *Pneumocystis* isolates containing these mutations respond to TMP-SMX therapy.[84,85] Helweg-Larsen *et al*.[84] reported an association with increased mortality; however, subsequent studies have failed to detect such an effect.[85,86] At present, no recommendation can be made with respect to clinical indications or interpretation of resistance testing.

Oral desensitisation regimens have been used successfully for HIV-infected patients and others with rash, and similar protocols have been used in HSCT patients with a success rate of approximately 80%.[77] Desensitisation may be attempted whenever feasible (level II evidence, grade C recommendation).[32] Desensitisation may be considered for all patients with TMP-SMX-associated rash but is contraindicated in those with a prior history of associated drug rash with eosinophilia and systemic symptoms ('DRESS'), Stevens-Johnson syndrome, or toxic epidermal necrolysis.

Second-line agents for PJP chemoprophylaxis

There are no sufficiently powered trials on which to base a recommendation for alternative prophylactic regimens in patients with malignancies. Many recommendations have been based on studies involving patients with HIV infection. However, these should be interpreted with caution due to possible differences in efficacy and side-effect profiles in patients with malignancy. An alternative agent should be used if TMP-SMX is withheld for any reason for ≥2 weeks (grade D recommendation).

Dapsone

Dapsone is a synthetic sulfone that acts against *P. jirovecii* by inhibiting the synthesis of dihydrofolic acid through competition with para-amino-benzoate for the active site of dihydropteroate synthetase.[87] It has 70–80% oral bioavailability with oral dosing achieving high levels of concentration in bronchoalveolar lavage fluid.[88] Adverse reactions to dapsone include agranulocytosis, aplastic anaemia, rash, nausea and sulfone syndrome (rash, fever, hepatitis, lymphadenopathy and methemoglobinaemia).[89] Dapsone should not be given to patients with G6PD deficiency or to patients who have experienced severe side-effects with TMP-SMX.

Adverse effects requiring discontinuation of therapy occur in up to 43% of HSCT patients, the most common being rash and haemolytic anaemia. Dapsone is not myelosuppressive.[90] Azole antifungal agents elevate dapsone levels so concomitant use should be avoided or monitored with caution.

Dapsone 50 mg BD three times weekly was compared with TMP-SMX DS BD twice weekly in a study of allogenic HSCT patients intolerant of TMP-SMX.[77] The incidence of PJP was significantly higher in the dapsone group (7.2% vs 0.37%), with a relative risk of 18.8 (95% CI 4.0–88.6) – although it should be noted that the dose of dapsone used in this study is lower than that currently used in clinical practice (100 mg daily). In a retrospective study of HSCT patients, Vasconcelles *et al.* reported a failure rate of 3%.[78]

Pentamidine

Pentamidine isethionate is an aromatic diamidine derivative available for parenteral or inhalation use. 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. 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. It should be avoided in patients less than 5 years of age or if there is a history of asthma. In children, intravenous pentamidine is used during the pre-engraftment period in some centres and may be an alternative if no other options are available. However, paediatric data are limited and it should be used with caution if risk factors for pancreatitis exist.[91,92]

In one study of patients undergoing HSCT, nebulised pentamidine had significantly lower treatment-related toxicity compared with TMP-SMX (RR 0.19, 95% CI 0.04–0.89).[78] Aerosolised pentamidine has the convenience of administration at a dose of 300 mg monthly or 150 mg fortnightly. It must be administered through jet-nebuliser in a single or negative-pressure room (grade C recommendation).

Few clinical trials have been undertaken in patients with malignancy. The largest, a retrospective study conducted in patients undergoing HSCT, compared aerosolised pentamidine with TMP-SMX and dapsone. Pentamidine was the least effective, with a higher incidence of PJP: 9.1% compared with 0% in patients treated with TMP-SMX. Significantly, patients who received pentamidine had increased rates of non-PJP infections and a higher mortality 12 months post-transplant compared with patients receiving TMP-SMX or dapsone.[78]

Atovaquone

Atovaquone is a structural analogue of protozoan ubiquinone. It inhibits the binding of ubiquinone to cytochrome *b*, impairing electron-transport mechanisms in *Pneumocystis* mitochondria. It is available as an oral suspension and requires twice-daily dosing. Bioavailability of the suspension is high and is further augmented by administration with a fatty meal. The most common side-effects include rash, nausea, diarrhoea, elevated transaminases and headache, which are usually mild.

Colby *et al.* conducted a prospective randomised trial following adult autologous SCT comparing atovaquone ($n = 20$) with TMP-SMX ($n = 19$) as PJP prophylaxis. No cases of PJP were reported in either group, although the treatment-associated adverse event rate was significantly higher in patients receiving TMP-SMX (40% vs 0%, $P < 0.003$).[93]

Duration and dosing regimens for PJP chemoprophylaxis

Prophylaxis should continue for a period of time after the immunosuppressive regimen is ceased. In the setting of corticosteroid-containing regimens, prophylaxis should be continued while steroids are being weaned and/or for

Table 3 Dosing schedule for *Pneumocystis jirovecii* chemoprophylaxis in adults and children with malignancy

	Adult	Children
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†	In children >1 month of age: 75 mg/m^2/dose or 2.5 mg/kg/dose (max 160 mg/dose) orally, 12-hourly, 3 times a week†
Dapsone	100 mg orally, daily	In children ≥1 month of age: 2 mg/kg/dose orally, daily OR 4 mg/kg/dose orally, once a week
Pentamidine	300 mg inhaled through nebuliser, every 4 weeks (administered through a jet-nebuliser producing a droplet size of 1–2 microns)	Intravenous (≥2 years): 4 mg/kg/dose (max 300 mg) every 4 weeks Through inhalation (>5 years): 300 mg inhaled through nebuliser, every 4 weeks (administered through a jet-nebuliser producing a droplet size of 1–2 microns)
Atovaquone	1500 mg orally, daily with a high-fat meal	1–3 months: 30 mg/kg/dose orally, daily 4–24 months: 45 mg/kg/dose (max 1500 mg) orally, daily >24 months: 30 mg/kg/dose (max 1500 mg) orally, daily

†Either non-consecutive or consecutive days is acceptable. DS, double strength; SS, single strength.

a period of 6 weeks after cessation. With some chemotherapy regimens (e.g. alemtuzumab[52] and FCR[27]), where there are high rates of late-onset PJP, consideration should be given to extended PJP prophylaxis for up to 12 months, particularly in pre-treated patients. CD4$^+$ monitoring has been advocated as a method to quantify risk of disease development and to guide duration of prophylaxis in temozolomide and alemtuzumab regimens.[52,70] However, further studies are required to establish the utility of CD4$^+$ monitoring in the non-HIV patient setting. In patients with ongoing immunosuppression (e.g. graft-vs-host disease), prophylaxis should continue indefinitely.

Dosing regimens for PJP prophylaxis are provided in Table 3.

Treatment of PJP

The treatment recommendations for PJP are summarised in Table 4.

TMP-SMX for the treatment of PJP

In view of its proven clinical efficacy, and the cost and availability of both the IV and oral formulations, TMP-SMX is the preferred therapy for mild, moderate and severe disease for all patients with PJP (grade B recommendation).[95–97] Initial trials in children using a dose of TMP 20 mg/kg/day and SMX 100 mg/kg/day showed an efficacy of 70%, with mortality due to underlying immunosuppressive disease. To date, no agent has been demonstrated to have outcomes superior to TMP-SMX. Lower doses (i.e. TMP 15 mg/kg/day and SMX 75 mg/kg/day) have been recommended for mild-moderate disease, and as step-down therapy in HIV-infected patients with severe disease following response to high-dose therapy.[97] Intravenous therapy is recommended for severe disease due to concerns regarding drug absorption in critically unwell patients; for mild and moderate disease, oral or IV therapy may be administered. Based on HIV literature, recommended treatment duration is 21 days (grade C recommendation).

Role of corticosteroids in the treatment of PJP

The use of corticosteroids in HIV-associated PJP was established following randomised trials in the late 1980s.[98–101] Arterial oxygenation at diagnosis was recognised as the best prognostic indicator of survival.[102] Adjunctive corticosteroid therapy commenced at the time of PJP therapy prevented the early decline in oxygenation that occurs after initiation of PJP therapy in patients with moderate to severe PJP (arterial-alveolar difference >35 mmHg or an arterial oxygen pressure <70 mmHg). This resulted in a reduction in the likelihood of respiratory failure and death. Patients with milder hypoxaemia (arterial oxygen >70 mmHg) may benefit from corticosteroids, but a difference in respiratory failure and death has not been demonstrated.

Studies in non-HIV-infected patients have produced conflicting results. Retrospective studies[3,103,104] showed no benefit in non-HIV-infected patients with moderate to severe disease. In contrast, Pareja *et al*.[105] found patients who received adjunctive steroids required shorter duration of mechanical ventilation and ICU admission, and

Table 4 Recommended dosing for treatment of *Pneumocystis jirovecii* infection†

	Adult	Child	Comments
TMP-SMX	5 + 25 mg/kg oral or IV, 8-hourly for 21 days In severe disease, increase to 6-hourly initially	>1 month Dose as for adult	*First-line therapy for all levels of severity* Consider desensitisation except with known history of immediate hypersensitivity or TEN/SJS
Clindamycin plus primaquine	450 mg clindamycin orally, 8-hourly PLUS 15 mg primaquine orally, daily for 21 days In severe disease, increase clindamycin to 900mg IV, 8-hourly initially then dose as above. Also, increase primaquine to 30 mg	10 mg/kg (max 450 mg) clindamycin orally 8-hourly PLUS 0.25 mg/kg primaquine (max 15 mg) orally, daily for 21 days	*Second-line therapy for severe disease* Test for G6PD deficiency before treatment with primaquine
Pentamidine	In severe disease where TMP-SMX contraindicated: pentamidine 4 mg/kg (max 300 mg) IV, daily for 21 days	In severe disease where TMP-SMX contraindicated: pentamidine 4 mg/kg (max 300 mg) IV, daily for 21 days	*Equal second-line therapy for severe disease*
Dapsone plus trimethoprim	100 mg dapsone orally, daily PLUS 5 mg/kg trimethoprim orally, 8-hourly for 21 days	2 mg/kg dapsone (max 100 mg) orally, daily PLUS 5 mg/kg trimethoprim orally, 8-hourly for 21 days	*Alternative option as first line therapy for mild-moderate disease* There is 20% cross-reaction with sulfonamides and dapsone; contraindicated with immediate hypersensitivity or severe reactions. Consider testing for G6PD deficiency prior to use.
Atovaquone	For mild-moderate diseases: 750 mg orally, 12-hourly for 21 days	<3 months or >24 months: 15–20 mg/kg orally, daily; 3–24 months: 22.5 mg/kg orally, 12-hourly for 21 days	*Third-line therapy*

†Refer to *Therapeutic Guidelines: antibiotic (version 15)* for further details.[94] SJS, Stevens Johnson Syndrome; TEN, toxic epidermal necrolysis.

reduced supplemental oxygen use. No differences in the rates of intubation or in-hospital mortality were observed.

Although there are insufficient data to make a recommendation regarding the use of adjuvant corticosteroids in patients with PJP and malignancy, it may be appropriate to co-administer corticosteroids, at doses used in HIV-associated PJP, in patients with moderate to severe PCP.

Alternative agents for the treatment of PJP in the setting of TMP-SMX intolerance

Desensitisation should be considered for all patients with TMP-SMX-associated rash but is contraindicated in those with a prior history of associated drug rash with eosinophilia and systemic symptoms ('DRESS'), Stevens-Johnson syndrome or toxic epidermal necrolysis. If TMP-SMX remains contraindicated, alternative agents include atovaquone, clindamycin plus primaquine and dapsone plus trimethoprim, although there is extremely limited evidence for efficacy in children, and limited data for safety in children with cancer (grade D recommendation). Few clinical studies have assessed second-line therapies in patients with malignancy. Therefore, recommendations for second-line therapy are based on data from clinical studies involving HIV-infected individuals and are in concordance with the current version of *Therapeutic Guidelines: antibiotic, version 15*.[94]

Intravenous pentamidine has been shown to have similar efficacy to TMP-SMX in HIV-infected individuals with PJP.[106,107] A retrospective review of first- and second-line therapy for HIV-associated PJP[108] found higher rates of unchanged second-line therapy with pentamidine than with TMP-SMX; however, survival rates were significantly lower when compared with TMP-SMX and clindamycin-primaquine. Pentamidine was associated with a higher risk of death (RR 3.3, 95% CI 2.2–5.0). A comparison of aerosolised and reduced-dose intravenous pentamidine therapy in patients with mild to moderate disease found higher rates of early recrudescence and relapse in the aerosolised group.[109]

Clindamycin-primaquine was compared with TMP-SMX in a randomised study of mild and moderately severe PJP in HIV-infected individuals.[110] In a study limited by sample size, efficacy of clindamycin-primaquine was similar to oral TMP-SMX or dapsone-trimethoprim for treatment of mild-moderate PJP in HIV-infected individuals in terms of dose-limiting toxicity, therapeutic failure or survival.[95] Notably, serious

haematological toxicity (neutropenia, thrombocytopenia and methemoglobinaemia) was more common in the clindamycin-primaquine arm.

While dapsone has been shown to be an ineffective treatment as a single agent, a combination of oral dapsone plus trimethoprim was effective in patients with HIV-associated PJP.[111] Major toxicity was seen in only 13% of patients. Dapsone-trimethoprim has been shown to be equivalent to TMP-SMX and clindamycin-primaquine in mild-moderate disease.[95]

Atovaquone (750 mg TDS) has been compared with TMP-SMX in a randomised trial of HIV-infected individuals with mild-moderate PJP.[96] Non-response rates were significantly higher in the atovaquone arm, although tolerability was greater than with TMP-SMX. Overall successful therapy, defined by clinical response and no adverse events, was equivalent.

Animal studies have demonstrated that echinocandins, which target ß(1,3)-D-glucan, have activity against *P. jirovecii*;[112] however, clinical trials in humans have not been performed. Data regarding efficacy are restricted to case reports, and these have revealed inconsistent responses.[113–116] Echinocandins cannot be recommended at this time due to their high cost, lack of an oral formulation and the absence of compelling evidence demonstrating their efficacy (grade D recommendation).

Managing PJP treatment failure

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by reduced arterial oxygen saturation after at least 4–8 days of *Pneumocystis* treatment. Early and reversible deterioration in the first 3–5 days is typical, and clinicians should wait at least 4–8 days before changing therapy due to lack of improvement. Although evidence is limited, intravenous pentamidine, clindamycin-primaquine or addition of an echinocandin can be considered for salvage therapy in cases of treatment failure.[117]

Treatment failure due to drug intolerance appears less common in malignancy-associated PJP than in HIV infection. Relapse has been reported only rarely in non-HIV associated PJP.

PJP infection-prevention measures

A role for isolation precautions to prevent inter-patient transmission of PJP has not been established for patients with malignancy, although there are data that suggest good infection-control measures prevent transmission in outbreaks of infection among kidney transplant patients.[118–121] The predominant method of spread for *Pneumocystis* is believed to be person-to-person transmission through exhaled air. Airborne transmission has been demonstrated in animal studies, and air samples from the rooms of patients with PJP have shown the presence of like organisms in air as far as 8 metres from the patient, suggesting that this may be a route of transmission.[122–124] It is possible that symptomatic patients might be at higher risk of transmission because of apparent higher density of colonisation.[17,125]

Staff members and other patients may be at risk of becoming colonised from direct or indirect contact with an infected patient.[126] However, colonisation of healthy humans and previously infected patients is frequent, without placing individuals at risk of subsequent infection. Most cases of PJP occur sporadically, without a known infected contact.[127,128]

PJP outbreaks in other patient populations (predominantly renal transplantation) have been reported, suggesting person-to-person transmission on the basis of epidemiology and molecular testing.[119,125,129–131] However, epidemiologically distinct cases with identical molecular types may also occur.[118]

While some clinicians and institutions recommend that at-risk patients should not share a hospital room with a patient with known PJP, the current evidence is insufficient to mandate isolation in haematology and solid-tumour groups. It is important that patients at risk of PJP are identified and receive prophylaxis.

Conclusion

Patients with haematological and solid-organ tumours are highly susceptible to PJP due to disease- and treatment-related immunosuppression. In this patient population, PJP is associated with high morbidity and mortality. Appropriate prophylaxis for all moderate- to high-risk patients is a key strategy for improving outcomes, given the proven efficacy of this approach. TMP-SMX is the drug of choice for both prophylaxis and treatment, although several alternative agents are available, as outlined here.

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