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CENTRE *for* EXCELLENCE
in HIV/AIDS

THERAPEUTIC GUIDELINES FOR OPPORTUNISTIC INFECTIONS PNEUMOCYSTIS PNEUMONIA (PCP)

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Abbreviations: ADR, adverse drug reaction; AP, aerosol pentamidine; ART, antiretroviral therapy; BAL, bronchoalveolar lavage; BC-CfE HIV/AIDS, BC Centre for Excellence in HIV/AIDS; BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; D5W, dextrose 5% in water; G-6-PD, glucose-6-phospate dehydrogenase; ICU, intensive care unit; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PLWH, persons living with HIV; TMP-SMX, trimethoprim-sulfamethoxazole

PNEUMOCYSTIS PNEUMONIA (PCP)

I) PROPHYLAXIS

Recommendations:

a) Indications:

i) **Primary prophylaxis** is recommended for patients with either a CD4 count below 200 cells/μL (AI) or a CD4 fraction below 14% (BII), and considered if the CD4 is 200-250 cells/μL and follow-up is uncertain (BII)

ii) **Secondary prophylaxis** (preventing recurrence) is required for any patient who has just completed a course of treatment for PCP, or has previously had an episode of PCP and has not met the prophylaxis stopping criteria (below)

b) Prophylaxis Options (Primary and Secondary):

i) Trimethoprim-sulfamethoxazole (TMP-SMX) 1 double strength (DS) tablet daily (160 mg trimethoprim – 800 mg sulfamethoxazole) (AI); or

ii) TMP-SMX 1 single strength (SS) tablet daily

iii) **Alternatives**:

- Dapsone 100 mg PO daily (BI), or
- Dapsone 50 mg PO daily plus once weekly [pyrimethamine 50 mg/leucovorin 25 mg] (BI), or
- Atovaquone 1500 mg PO daily with food (BI), or
- TMP-SMX 1 DS tablet three days each week (BI)

c) Discontinuing PCP prophylaxis:

i) Antiretroviral (ART) induced CD4 cell count recovery from <200 to ≥200 cells/μL for at least 3 months for primary (AI) or secondary (BII) PCP prophylaxis

ii) Consider stopping primary or secondary PCP prophylaxis in patients whose CD4 counts remain between 100-200 cells/μL, provided the HIV RNA remains below the limit of detection for 3-6 months on ART (BII)

iii) If PCP develops at a CD4 >200 cells/μL while on ART and HIV RNA is below the limit of detection, then continue PCP prophylaxis lifelong, regardless of subsequent CD4 counts (BIII)

d) Restarting PCP prophylaxis:

Primary or secondary PCP prophylaxis should be restarted if:

- The CD4 count falls to <100 cells/μL (AIII), or
- If the CD4 count is between 100-200 cells/μL and the HIV RNA rises above the limit of detection (with the exception of transient low level “blips”, defined as an HIV RNA of 40-500 copies/mL, which is both preceded and followed by an HIV RNA of <40 copies/mL) (AIII).

Discussion

Prior to starting PCP prophylaxis, patients should be assessed to confirm that they do not have active pulmonary disease requiring specific therapy (e.g. PCP or tuberculosis).

Prophylaxis options: TMP-SMX 1 DS tablet daily is preferred[1]; however the lower dose of 1 SS tablet is better tolerated and has similar efficacy[2]. An alternative lower dose regimen of TMP-SMX is 1 DS tablet 3 days each week which is slightly less effective but associated with less hematologic toxicity[3]. TMP-SMX is the most effective and least expensive of the available regimens. It also protects against *Toxoplasma gondii* (at a dose of 1 DS tablet daily) and some bacterial infections. TMP-SMX adverse reactions include allergic reactions, cytopenias, increases in serum creatinine (usually due to interference in creatinine excretion rather than a reduction in glomerular filtration rate), hyperkalemia, hepatitis and gastrointestinal symptoms. Patients should be warned that allergic reactions are frequent, occurring in at least 30% of persons living with HIV (PLWH), and usually characterized by fever and/or an erythematous, pruritic rash. Those with mild adverse reactions may be successfully re-challenged with TMP-SMX, which may be better tolerated with a gradual dose escalation during the first week[4]. However, occasional life-threatening adverse reactions (e.g. Stevens Johnson syndrome, toxic epidermal necrolysis [TEN], or drug rash with eosinophilia and systemic symptoms [DRESS]) to TMP-SMX are contraindications to re-challenge. Monitoring should include CBC, differential, BUN, creatinine, liver enzymes and electrolytes.

Dapsone. Patients should be screened for glucose-6-phospate dehydrogenase (G-6-PD) deficiency and avoid dapsone if deficient. This regimen is the preferred alternative to TMP-SMX and has similar efficacy[5]. Unlike TMP-SMX, dapsone does not also provide prophylaxis for toxoplasmosis unless combined with once weekly pyrimethamine and leukovorin (see Toxoplasmosis). Adverse reactions include dose dependent hemolytic anemia (associated with an elevation of lactate dehydrogenase [LDH]) in G-6-PD deficiency, methemoglobinemia, neutropenia, liver dysfunction, gastrointestinal intolerance, and allergic reactions including rash.

Atovaquone has similar efficacy for the prevention of PCP compared to dapsone or aerosol pentamidine[6,7] and also provides prophylaxis for toxoplasmosis, but is considerably more expensive. Adverse reactions to atovaquone are generally mild to moderate and include diarrhea, upper gastrointestinal symptoms, transaminase elevation, headache, rash, and fever. Atovaquone must be taken with food to ensure optimal absorption and can be obtained through the BC Centre for Excellence in HIV/AIDS (BC-CfE HIV/AIDS) pharmacist at 1-888-511-6222.

Aerosol pentamidine (AP). The use of AP is discouraged given that it is relatively expensive, inconvenient, and less effective than the oral regimens of TMP-SMX or dapsone, particularly in patients whose CD4 counts are <100 cells/μL[5]. In contrast to TMP-SMX, AP does not provide prophylaxis against toxoplasmosis or bacterial infections. AP is delivered via a Respigard II nebulizer and premedication with a beta-2 agonist (e.g. salbutamol 2 puffs) is generally recommended to reduce the possibility of bronchospasm. In recent years there has been no known use of AP prophylaxis among PLWH in British Columbia according to the BC-CfE HIV/AIDS.

Other PCP prophylaxis alternatives: i) First line treatment (induction or suppression) for toxoplasmosis with pyrimethamine plus sulfadiazine provides adequate PCP prophylaxis[8]; however, alternative toxoplasmosis therapy with pyrimethamine plus clindamycin does not[9]. ii) There is little published experience to support the use of pentamidine 4 mg/kg IV q2-4 weeks for PCP prophylaxis.

Discontinuing PCP prophylaxis has been demonstrated to be safe for those patients with sustained ART induced CD4 increases to >200 cells/μL, regardless of whether the prophylaxis was primary or secondary[10,11,12]. A subsequent large observational European study (COHERE), indicated that it was also safe to stop PCP prophylaxis if the CD4 was between 100-200 cells/μL provided that the HIV RNA remained suppressed on ART for at least 3-6 months[13,14].

II) DIAGNOSIS AND DEFINITIONS OF DISEASE SEVERITY

Diagnosis. The clinical presentation, routine blood tests, and chest radiographs are non-specific in PCP. Typical CT chest findings include patchy or nodular ground glass opacities, which are suggestive but not diagnostic. PCP is quite unlikely in a patient with a negative high-resolution CT chest. A definite diagnosis should be established with specimens such as bronchoscopy with bronchoalveolar lavage (BAL) or induced sputum for cytologic diagnosis using special stains (e.g. toluidine blue, Grocott-Gömöri methenamine silver). Transbronchial biopsy for histologic diagnosis is seldom required given the high sensitivity of BAL, but should be considered when there is high clinical suspicion for PCP and a non-diagnostic BAL specimen. *P. jiroveci* cannot be grown in culture. The use of induced sputum samples for PCP diagnosis has not been widely adopted due to the variable sensitivity obtained in different centres. However, the sensitivity for BAL is >90%[15] and for transbronchial biopsy 95-100%. The use of polymerase chain reaction (PCR) for the diagnosis of PCP in HIV is limited by its inability to differentiate disease from colonization[16]. However, a negative PCR from a BAL specimen has high negative predictive value for PCP[17]. PCR has a greater role to play in the diagnosis of PCP among HIV-negative individuals, where the BAL cytologic diagnosis is less sensitive[16] due to the lower fungal burden compared to PLWH[18]. The practical considerations of convenience and improved tolerability with the use of oral wash samples instead of BAL have made this a promising option for PCR diagnosis of PCP in PLWH[19].

An elevated LDH level, although non-specific, is usually present in >90% of patients with PCP. The degree of elevation of the LDH generally parallels the severity of the disease[20,21]. Changes in the LDH level following initiation of treatment also correlate with the course of the disease (i.e. a positive response to therapy is associated with a decrease in the LDH level). However, this may be confounded by dapsone which can cause hemolysis and increase the LDH level.

Serologic testing for beta-D-glucan (a cell wall component of many fungi, including *P. jiroveci*) has usually been elevated (>80 pg/mL) in PCP[22], but is also non-specific and is not currently available in British Columbia.

Definitions of Disease Severity. PCP severity can be defined as **mild** (alveolar to arterial oxygen [A-a] O2 gradient <35, and partial pressure of arterial oxygen [Pa O2]>70 mmHg), **moderate** (A-a O2 gradient 35-44, or Pa O2 60-69 mmHg), or **severe** (A-a O2 gradient >45, or Pa O2 <60 mmHg, or impending respiratory failure [tachypnea at rest, or pCO2 normal or elevated]).

III) TREATMENT

Treatment recommendations:

a) **Outpatient** treatment may be appropriate for mild to moderate PCP (see *Diagnosis and Definitions of Disease Severity* above). Treatment options in descending order of preference are as follows:

1. **Trimethoprim-sulfamethoxazole** (TMP-SMX) 2 double strength (DS) tablets (TMP 160 mg/SMX 800 mg per DS tablet) every 8 hours for 21 days (AI). Alternatively, weight-based dosing of TMP-SMX (TMP 15-20 mg/kg/day and SMX 75-100 mg/kg/day) can be used in 3 divided doses (AI),

OR

2. **Dapsone** 100 mg PO once daily combined with **trimethoprim** 5 mg/kg three times daily for 21 days (AI). Screen patients for G-6-PD deficiency and avoid dapsone if G-6-PD deficient,

OR

3. **Clindamycin** 450 mg orally q6h (or 600 mg orally q8h) combined with primaquine 30mg (base) orally once daily (BI). Screen patients for G-6-PD deficiency and avoid primaquine if G-6-PD deficient,

OR

4. **Atovaquone suspension**, 750 mg PO twice daily with meals for 21 days (BI). Atovaquone should be taken with meals to ensure optimal absorption.

b) **Intravenous treatment** is indicated for moderate to severe PCP (see *Diagnosis and Definitions of Disease Severity* above) or gastrointestinal intolerance to oral medication. The following treatment options are listed in descending order of preference:

1. **Trimethoprim** (15-20 mg/kg/day)-**sulfamethoxazole** (75-100 mg/kg/day) divided q6-8h (AI),

OR

2. **Clindamycin** 600 mg IV q6h (or 900 mg IV q8h) plus **primaquine** 30 mg (base)PO once daily (AI) . Screen patients for G-6-PD deficiency and avoid primaquine if G-6-PD deficient,

OR

3. **Pentamidine isethionate** 4 mg/kg/day IV infusion over 1-2 hours (AI). Dosage may be reduced to 3 mg/kg/day if toxicity, particularly nephrotoxicity (AI).

Discussion

Diagnosis and management should be done in consultation with an experienced specialist. The decision to hospitalize the patient or initiate empiric treatment in the community is based on the level of certainty regarding the diagnosis, the clinical status of the patient (e.g. degree of dyspnea, oxygen saturation), and the anticipated ability to tolerate and comply with oral therapy[23]. Treatment should not be delayed in suspected cases while awaiting bronchoscopy results which may take several days. In one study, the cysts of *P. jirovecii* were still detectable on serial induced sputum samples in 88% of patients 2 weeks after the diagnosis and initiation of treatment for PCP[24]. The recommended treatment duration is 3 weeks.

Oral treatment options:

TMP-SMX is the preferred choice for both inpatient and outpatient treatment of HIV-related PCP[25,26,27]. Although sulfa drug resistance mutations have been reported in *P. jirovecii*, TMP-SMX is usually effective even in the setting of failed TMP-SMX prophylaxis, and remains the drug of choice[28]. TMP-SMX adverse reactions are discussed above (see *Prophylaxis*). Monitoring should include CBC, differential, liver enzymes, BUN, creatinine, and electrolytes.

Dapsone/trimethoprim. If TMP-SMX is contraindicated or poorly tolerated, then dapsone/trimethoprim is a reasonable alternative[25,27]. Dapsone adverse reactions adverse reactions are discussed above (see *Prophylaxis*).

Clindamycin/primaquine should be reserved for those individuals who cannot tolerate TMP-SMX or dapsone/trimethoprim (BI)[27]. Screen patients for G-6-PD deficiency and avoid primaquine if G-6-PD deficient. Adverse reactions include fever, rash, gastrointestinal intolerance, *C. difficile* colitis, methemoglobinemia, and hemolytic anemia (particularly in patients with G-6-PD deficiency).

Atovaquone suspension should be reserved for those individuals who cannot tolerate the above-mentioned treatment options (BI). Atovaquone treatment is associated with reduced survival compared to TMP-SMX[26], and its use should be restricted to those with mild PCP. Atovaquone should be taken with meals to ensure optimal absorption. Adverse reactions are discussed above (see *Prophylaxis*). Atovaquone is expensive but can be obtained through the BC-CfE HIV/AIDS pharmacist 1-888-511-6222.

Intravenous treatment options:

Intravenous therapy is indicated for moderate to severe PCP (see *Diagnosis and Disease Severity Definitions* above), or in patients with gastrointestinal intolerance (e.g. vomiting, esophagitis) or suspected malabsorption. Treatment should be changed to an oral regimen (to complete 21 days of therapy) as soon as there is clinical improvement and it can be tolerated.

Trimethoprim-sulfamethoxazole is the preferred intravenous treatment [29,30,31]. Adverse reactions are discussed above (see *Prophylaxis*). The results of a recent systematic review and meta-analysis highlight the uncertainty regarding the optimal dose of TMP-SMX, with evidence for satisfactory outcomes but lower frequency of treatment-limiting adverse drug reactions using a lower dose (TMP 10 mg/kg/day-sulfamethoxazole 50 mg/kg/day)[32]. However, the lower dose may not be adequate in patients with severe disease or breakthrough PCP while receiving TMP-SMX prophylaxis[32]. In addition, significant intravenous fluid volume of as much as 2000 ml/day of D5W may be required for the IV administration of TMP-SMX and may contribute to pulmonary fluid accumulation related to PCP-induced increased alveolar capillary permeability. Monitoring should include CBC, differential, liver enzymes, BUN, creatinine, and electrolytes.

Clindamycin plus primaquine is the preferred intravenous alternative to TMP-SMX for sulfa allergic patients[33,34] given its improved tolerance and efficacy compared to IV pentamidime[35]. However, primaquine is only available in an oral formulation. Patients need to be screened for G-6-PD deficiency, and if present then primaquine should be avoided. Adverse reactions are discussed above (see *Treatment Options*).

Pentamidine isethionate. Similar tolerance and efficacy have been reported for both

pentamidine and TMP-SMX in randomized clinical trials of HIV-related PCP[31,32]; however, improved survival with TMP-SMX was observed in one small study[32]. Both drugs may be associated with major adverse drug reactions (ADRs). The ADRs for IV pentamidine include renal and liver dysfunction, neutropenia, thrombocytopenia, hyponatremia, hypocalcemia, hypomagnesemia, rash, fever, hypotension, pancreatitis, hypo and hyperglycemia, and cardiac rhythm disturbances[36].

IV) ADJUNCTIVE PREDNISONE THERAPY

Recommendation:

Prednisone is indicated as adjunctive therapy for the treatment of patients with moderate to severe AIDS-related PCP (see *Diagnosis and Definitions of Disease Severity* above). The dose of prednisone is 40 mg PO BID for 5 days, then 40 mg once daily for 5 days, then 20 mg once daily for 11 days (21 days total) (AI).

Discussion. Prednisone has been shown to reduce mortality and morbidity in acute moderate to severe PCP [36,37,38]. Prednisone should be started 15-30 min before TMP-SMX, but otherwise as early as possible within the first 72 hours of PCP therapy. It should be continued until discontinuation of the antimicrobial therapy. Early discontinuation of prednisone therapy has been associated with rebound of signs and symptoms. The equivalent dose of an injectable corticosteroid can be substituted for those patients who are unable to receive oral prednisone.

V) TREATMENT FAILURE

Recommendation:

Lack of response to first line treatment with TMP-SMX should prompt consideration of salvage therapy with clindamycin 600 mg IV q6h (or 900 mg IV q8h) plus primaquine 30 mg (base) PO once daily (AI). Screen patients for G-6-PD deficiency and avoid primaquine if G-6-PD deficient.

Discussion. Patients may worsen clinically during the first 2-3 days of treatment but usually are improving by about the fifth day. Failed therapy is defined as lack of improvement or worsening lung function (on arterial blood gases) after 4-8 days of therapy. Aside from lack of efficacy of the antipneumocystis regimen, other considerations include: pneumothorax, fluid overload, co-existing respiratory tract infection, pulmonary Kaposi's sarcoma, and adult respiratory distress syndrome (ARDS). In the absence of randomized controlled trials of salvage therapy, a meta-analysis suggested that clindamycin plus primaquine was the most effective alternative to the initially prescribed regimen (BII)[39,40]. An observational study including three European/UK cohorts included 287 episodes where patients failed or did not tolerate first line therapy. Survival rates for these patients were different for the various second line treatment regimens: TMP-SMX (85%), clindamycin/primaquine (87%), and pentamidine (60%; p=0.01). Patients failing or intolerant of first line treatment with TMP-SMX should be treated with clindamycin/primaquine; whereas those failing or intolerant of first line treatment with non-

TMP-SMX regimens should be treated with TMP-SMX (BII)[41], unless contraindicated.

VI) PCP IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) AND TIMING OF ANTIRETROVIRAL THERAPY

Recommendation: Unless already receiving an effective regimen, ART should be started or revised as needed within 2 weeks of the diagnosis of PCP (AI).

Discussion. Initiation of ART during therapy for PCP has been associated with a paradoxical worsening of the pulmonary infiltrates and lung function in up to 5-18% of cases[42]. In most cases of PCP-IRIS the clinical deterioration has been observed during the first month after starting ART. However, the results of a randomized clinical trial (ACTG A5164) of early (within 2 weeks) vs late (between 6 to 12 weeks) initiation of ART in patients with acute AIDS-related opportunistic infections (63% were PCP) suggested that concern regarding PCP-IRIS developing due to early ART initiation has been exaggerated[43]. During 48 weeks of follow up, early ART was associated with less AIDS progression/death, no increase in adverse events, and a similar rate of IRIS (early group 5.7%, deferred group 8.5%, p=0.49).

The diagnosis of PCP-IRIS is supported by bronchoscopy with transbronchial biopsy in order to exclude other possible causes; however, there may be few or no demonstrable PCP organisms[44]. Any diagnosis of IRIS should be supported by evidence of a virologic (HIV RNA reduction of ≥1 log) and/or immunologic (CD4 increase) response to the ART regimen. Patients with PCP-IRIS associated with respiratory failure appear to respond to systemic corticosteroids[45].

Randomized controlled trials of ART initiation in patients with intensive care unit (ICU) admission for AIDS-related illness are not available. However, a recent systematic review and meta-analysis of twelve studies suggested improved survival rates for PLWH who received ART during their ICU admission[46]. In the current era, PLWH are most often admitted to an ICU for management of bacterial sepsis or an exacerbation of a chronic comorbidity rather than an opportunistic disease[47]. ART should be initiated early (within 2 weeks) for critically ill PLWH with various opportunistic diseases, except central nervous system infection with either *Cryptococcus or M. tuberculosis* where it should be delayed after starting the respective antimicrobial therapy (4-5 weeks for *Cryptococcus*; 2-8 weeks for *M. tuberculosis*)[47,48].

VII) PREGNANCY

TMP-SMX, dapsone, atovaquone, and pentamidine are all FDA pregnancy category C drugs (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks); and primaquine has also been considered to be a C category drug, despite not having an official FDA designation. Clindamycin is FDA category B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women).

PCP prophylaxis. TMP-SMX is the drug of choice. However, given the small increased risk

of birth defects related to first trimester exposure to trimethoprim, alternative prophylaxis may be considered (e.g. atovaquone) for the first trimester[48]. Folic acid supplementation (6 mg/day) has been associated with a reduction in congenital anomalies where mothers were taking TMP-SMX. However, there have been reports of increased failure of both prophylaxis and treatment when folinic acid was added to TMP-SMX[49,50]. Consequently, folic acid supplementation with TMP-SMX is not recommended past the first trimester[48].

PCP treatment. TMP-SMX is the drug of choice. Dapsone/trimethoprim, atovaquone, clindamycin/ primaquine, and intravenous pentamidine are the alternatives. Adjunctive prednisone is recommended as for non-pregnant patients, although mothers should be monitored for hypertension and glucose intolerance.

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RATING SYSTEM FOR RECOMMENDATIONS (https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/guidelines-adult-adolescent-oi.pdf)

Strength of Recommendation	Quality of Evidence for the Recommendation
A. Strong recommendation for the statement B. Moderate recommendation for the statement C. Optional recommendation for the statement	I. One or more randomized trials with clinical outcomes and/or validated endpoints II. One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes III. Expert opinion