Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Epidemiology

Pneumocystis pneumonia (PCP) is caused by Pneumocystis jirovecii, a ubiquitous fungus. The taxonomy of the organism has been changed; Pneumocystis carinii now refers only to the Pneumocystis that infects rats, and P. jirovecii refers to the distinct species that infects humans. The abbreviation PCP is still used to designate Pneumocystis pneumonia. Initial infection with P. jirovecii usually occurs in early childhood; two-thirds of healthy children have antibodies to P. jirovecii by ages 2 to 4 years.1

Rodent studies and case clusters in immunosuppressed patients suggest that Pneumocystis spreads by the airborne route. Disease probably occurs by new acquisition of infection and by reactivation of latent infection.2-11 Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of patients with AIDS;12 the course of treated PCP was associated with a 20% to 40% mortality rate in individuals with profound immunosuppression. Approximately 90% of PCP cases occurred in patients with CD4 T-lymphocyte (CD4 cell) counts <200 cells/mm³. Other factors associated with a higher risk of PCP in the pre-ART era included CD4 cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA levels.13,14

The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; recent incidence among patients with AIDS in Western Europe and the United States is <1 case per 100 person-years.15-17 Most cases now occur in patients who are unaware of their HIV infection or are not receiving ongoing care for HIV,18 and in those with advanced immunosuppression (CD4 counts <100 cells/mm³).19

Clinical Manifestations

In HIV-infected patients, the most common manifestations of PCP are subacute onset of progressive dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks. The fulminant pneumonia observed in patients who are not infected with HIV is less common.20,21

In mild cases, pulmonary examination usually is normal at rest. With exertion, tachypnea, tachycardia, and diffuse dry (cellophane) rales may be observed.21 Oral thrush is a common co-infection. Fever is apparent in most cases and may be the predominant symptom in some patients. Extrapulmonary disease is rare but can occur in any organ and has been associated with use of aerosolized pentamidine prophylaxis.22

Hypoxemia, the most characteristic laboratory abnormality, can range from mild (room air arterial oxygen [pO₂] ≥70 mm Hg or alveolar-arterial O₂ gradient, [A-a] DO₂ <35 mm Hg) to moderate ([A-a] DO₂ ≥35 and <45 mm Hg) to severe ([A-a] DO₂ ≥45 mm Hg). Oxygen desaturation with exercise is often abnormal but is non-specific.23 Elevation of lactate dehydrogenase levels to >500 mg/dL is common but also non-specific.24 The chest radiograph typically demonstrates diffuse, bilateral, symmetrical “ground-glass” interstitial infiltrates emanating from the hila in a butterfly pattern;21 however, a chest radiograph may be normal in patients with early disease.25 Atypical radiographic presentations also occur, such as nodules, blebs and cysts, asymmetric disease, upper lobe localization, intrathoracic adenopathy, and pneumothorax. Spontaneous pneumothorax in a patient with HIV infection should raise the suspicion of PCP.26,27 Cavitation, and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancy, and their presence may indicate an alternative diagnosis or an additional pathology. In fact, approximately 13% to 18% of patients with documented PCP have another concurrent cause of pulmonary dysfunction, such as tuberculosis (TB), Kaposi sarcoma (KS), or bacterial pneumonia.28,29

Thin-section computed tomography (CT) is a useful adjunctive study, since even in patients with mild-to-moderate symptoms and a normal chest radiograph, a CT scan will be abnormal, demonstrating “ground-glass” attenuation that may be patchy, while a normal CT has a high negative predictive value.30,31
Diagnosis
Because clinical presentation, blood tests, and chest radiographs are not pathognomonic for PCP, and because the organism cannot be cultivated routinely, histopathologic or cytopathologic demonstration of organisms in tissue, bronchoalveolar lavage (BAL) fluid, or induced sputum samples is required for a definitive diagnosis. Spontaneously expectorated sputum has low sensitivity and should not be submitted to the laboratory to diagnose PCP. Giemsa, Diff-Quik, and Wright stains detect both the cystic and trophic forms but do not stain the cyst wall; Grocott-Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain the cyst wall. Some laboratories prefer direct immunofluorescent staining. The sensitivity and specificity of respiratory samples for PCP depend on the stain being used, the experience of the microbiologist or pathologist, the pathogen load, and specimen quality. Previous studies of stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: induced sputum <50% to >90%, bronchoscopy with BAL 90% to 99%, transbronchial biopsy 95% to 100%, and open lung biopsy 95% to 100%.

Polymerase chain reaction (PCR) is an alternative method for diagnosing PCP. PCR is highly sensitive and specific for detecting *Pneumocystis*; however, PCR cannot reliably distinguish colonization from disease, although higher organism loads as determined by Q-PCR assays are likely to represent clinically significant disease. 1,3β-D-glucan (a component of the cell wall of *Pneumocystis* cysts) is often elevated in patients with PCP, but while the assay sensitivity appears to be high, and thus a diagnosis of PCP is less likely in patients with a low level (e.g. <80 pg/ml using the Fungitell assay), the specificity for establishing a PCP diagnosis is low, since many other fungal diseases, as well as hemodialysis cellulose membranes and some drugs can produce elevation.

Because several disease processes produce similar clinical manifestations, a specific diagnosis of PCP should be sought rather than relying on a presumptive diagnosis, especially in patients with moderate-to-severe disease. Treatment can be initiated before making a definitive diagnosis because organisms persist in clinical specimens for days or weeks after effective therapy is initiated.

Preventing Exposure
*Pneumocystis* can be quantified in the air near patients with PCP, and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients. Although these strongly suggest that high-risk patients without PCP may benefit from isolation from other patients with known PCP infection, data are insufficient to support isolation as standard practice (CIII).

Preventing Disease
**Indication for Primary Prophylaxis**
HIV-infected adults and adolescents, including pregnant women and those on ART, should receive chemoprophylaxis against PCP if they have CD4 counts <200 cells/mm³ (AI). Persons who have a CD4 cell percentage of <14% should also be considered for prophylaxis (BII). Initiation of chemoprophylaxis at CD4 counts between 200 and 250 cells/mm³ also should be considered when starting ART must be delayed and frequent monitoring of CD4 counts, such as every 3 months, is impossible (BII). Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent (AI). One double-strength tablet daily is the preferred regimen (AI), but one single-strength tablet daily also is effective and may be better tolerated than the double-strength tablet (AI). One double-strength tablet three times weekly also is effective (BI). TMP-SMX at a dose of one double-strength tablet daily confers cross protection against toxoplasmosis and many respiratory bacterial infections. Lower doses of TMP-SMX may also confer such protection, though data addressing this are unavailable. TMP-SMX chemoprophylaxis

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should be continued, if clinically feasible, in patients who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction, re-institution should be considered after the reaction has resolved (AII). Therapy should be permanently discontinued (with no rechallenge) in patients with life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN) (AIII). Patients who have experienced adverse events, including fever and rash, may better tolerate re-introduction of the drug if the dose is gradually increased according to published regimens (BI) or if TMP-SMX is given at a reduced dose or frequency (CIII). As many as 70% of patients can tolerate such re-institution of therapy.48

For patients who cannot tolerate TMP-SMX, alternative prophylactic regimens include dapsone (BI), dapsone plus pyrimethamine plus leucovorin (BI), aerosolized pentamidine administered with the Respirgard II nebulizer (manufactured by Marquest; Englewood, Colorado) (BI), and atovaquone (BI). Atovaquone is as effective as aerosolized pentamidine54 or dapsone55 but substantially more expensive than the other regimens. For patients seropositive for Toxoplasma gondii who cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin (BI), or atovaquone, with or without pyrimethamine, plus leucovorin (CIII).

The following regimens cannot be recommended as alternatives because data regarding their efficacy for PCP prophylaxis are insufficient:
- Aerosolized pentamidine administered by nebulization devices other than the Respirgard II nebulizer
- Intermittently administered parenteral pentamidine
- Oral clindamycin plus primaquine

Clinicians can consider using these agents, however, in situations in which the recommended agents cannot be administered or are not tolerated (CIII).

Discontinuing Primary Prophylaxis

Primary Pneumocystis prophylaxis should be discontinued for adult and adolescent patients who have responded to ART with an increase in CD4 counts from <200 cells/mm³ to >200 cells/mm³ for >3 months (AII). In observational and randomized studies supporting this recommendation, most patients had CD4 counts >200 cells/mm³ for more than 3 months before discontinuing PCP prophylaxis. The median CD4 count at the time prophylaxis was discontinued was >300 cells/mm³, most patients had a CD4 cell percentage ≥14%, and many had sustained suppression of HIV plasma RNA levels below detection limits for the assay employed. Median follow-up was 6 to 19 months.

Discontinuing primary prophylaxis in these patients is recommended because its preventive benefits against PCP, toxoplasmosis, and bacterial infections are limited; stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens. Prophylaxis should be reintroduced if the CD4 count decreases to <200 cells/mm³ (AIII).

A combined analysis of 12 European cohorts and a case series found a low incidence of PCP in patients with CD4 counts between 100 and 200 cells/mm³, who were receiving ART and had HIV plasma viral loads <50 to 400 copies/mL, and who had stopped or never received PCP prophylaxis, suggesting that primary and secondary PCP prophylaxis can be safely discontinued in patients with CD4 counts between 100 to 200 cells/mm³ and HIV plasma RNA levels below limits of detection with commercial assays. Data on which to base specific recommendations are inadequate, but one approach would be to stop primary prophylaxis in patients with CD4 counts of 100 to 200 cells/mm³ if HIV plasma RNA levels remain below limits of detection for at least 3 to 6 months (BII). Similar observations have been made with regard to stopping primary prophylaxis for Toxoplasma encephalitis.67
**Treating Disease**

TMP-SMX is the treatment of choice for PCP (AI).\(^{68,69}\) The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that TMP-SMX is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because efficacy is questionable and some evidence exists for a higher failure rate (AII).\(^{70}\) Oral outpatient therapy with TMP-SMX is highly effective in patients with mild-to-moderate disease (AI).\(^{69}\)

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.\(^{71-74}\) Patients who have PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (BIII).

Patients with documented or suspected PCP and moderate-to-severe disease, defined by room air pO\(_2\) <70 mm Hg or Alveolar-arterial O\(_2\) gradient ≥35 mm Hg, should receive adjunctive corticosteroids as early as possible and certainly within 72 hours after starting specific PCP therapy (AI).\(^{75-80}\) The benefits of starting steroids later are unclear, but most clinicians would use them in such circumstances for patients with moderate-to-severe disease (BIII). Intravenous methylprednisolone at 75% of the respective oral prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone and TMP (BI),\(^{69,81}\) which may have efficacy similar to TMP-SMX and fewer side effects, but is less convenient because of the number of pills; primaquine plus clindamycin (BI)\(^{82-84}\) (the clindamycin component can be administered intravenously [IV] for more severe cases, but primaquine is only available orally); and atovaquone suspension (BI),\(^{55,56,68,85}\) which is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects. Whenever possible, patients should be tested for glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency before primaquine or dapsone is administered.

Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or IV pentamidine (AI).\(^{84,86,87}\) Some clinicians prefer clindamycin-primaquine because of its higher degree of efficacy and lesser toxicity compared with pentamidine.\(^{84,88-90}\)

Aerosolized pentamidine **should not** be used to treat PCP because its efficacy is limited and it is associated with more frequent relapse (AI).\(^{86,91,92}\)

The recommended duration of therapy for PCP (irrespective of regimen) is 21 days (AII).\(^{20}\) The probability and rate of response to therapy depend on the agent used, number of previous PCP episodes, severity of pulmonary illness, degree of immunodeficiency, timing of initiation of therapy and comorbidities.

The overall prognosis remains poor for patients who have such severe hypoxemia that admission to an intensive care unit (ICU) is necessary. However, in recent years, such patients have had much better survival than in the past, perhaps because of better management of comorbidities and better supportive care.\(^{93-96}\) Because long-term survival is possible for patients in whom ART is effective, HIV-infected individuals with severe PCP should be offered ICU admission or mechanical ventilation if needed, just as with HIV-uninfected patients (AII).

**Special Consideration with Regards to Starting ART**

ART should be initiated in patients not already on it, when possible, within 2 weeks of diagnosis of PCP (AI). In a randomized controlled trial of 282 patients with opportunistic infections (OIs) other than TB, 63% of whom had definite or presumptive PCP, a significantly lower incidence of AIDS progression or death (a secondary study endpoint) was seen in subjects randomized to early (median 12 days after initiation of therapy for OI) versus deferred initiation of ART (median 45 days).\(^{97}\) Of note, no patients with PCP and respiratory failure requiring intubation were enrolled in the study,\(^{97}\) and initiating ART in such patients is problematic due to the lack of parenteral preparations and unpredictable absorption of oral medications, as
well as potential drug interactions with agents commonly used in the ICU.98

Paradoxical immune reconstitution inflammatory syndrome (IRIS) is rare but has been reported following PCP.99 Most cases have occurred within weeks of the episode of PCP; symptoms include fever and recurrence or exacerbation of pulmonary symptoms including cough and shortness of breath, as well as worsening of a previously improving chest radiograph. Although IRIS in the setting of PCP has only rarely been life-threatening,100 patients should be closely followed for recurrence of symptoms after initiation of ART. Management of PCP-associated IRIS is not well defined; some experts would consider corticosteroids in patients with respiratory deterioration if other causes are ruled out.

**Monitoring of Response to Therapy and Adverse Events (Including IRIS)**

Careful monitoring during therapy is important to evaluate response to treatment and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially when therapy has been with an agent other than TMP-SMX or was shortened for toxicity.

In HIV-infected patients, rates of adverse reaction to TMP-SMX are high (20%–85%).68,69,81,83,87,101-105 Common adverse effects are rash (30%–55%) (including Stevens-Johnson syndrome), fever (30%–40%), leukopenia (30%–40%), thrombocytopenia (15%), azotemia (1%–5%), hepatitis (20%), and hyperkalemia. Supportive care for common adverse effects should be attempted before TMP-SMX is discontinued (AIII). Rashes often can be “treated through” with antihistamines, nausea can be controlled with antiemetics, and fever can be managed with antipyretics.

The most common adverse effects of alternative therapies include methemoglobinemia and hemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone;69,81 azotemia, pancreatitis, hypo- or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine;85-87,104 anemia, rash, fever, and diarrhea with primaquine and clindamycin;69,82,83 and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.68,103

**Managing Treatment Failure**

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases (ABGs) after at least 4 to 8 days of anti-PCP treatment. Failure attributed to lack of drug efficacy occurs in approximately 10% of those with mild-to-moderate disease. No convincing clinical trials exist on which to base recommendations for the management of treatment failure attributed to lack of drug efficacy. Clinicians should wait at least 4 to 8 days before switching therapy for lack of clinical improvement (BIII). In the absence of corticosteroid therapy, early and reversible deterioration within the first 3 to 5 days of therapy is typical, probably because of the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infections must be excluded as a cause of clinical failure;28,29 bronchoscopy with BAL should be strongly considered to evaluate for this possibility, even if the procedure was conducted before initiating therapy.

Treatment failure attributed to treatment-limiting toxicities occurs in up to one-third of patients.69 Switching to another regimen is the appropriate management for treatment-related toxicity (BII). When TMP-SMX is not effective or cannot be used for moderate-to-severe disease because of toxicity, the common practice is to use parenteral pentamidine or oral primaquine combined with intravenous clindamycin (BII).83,87,105 For mild disease, atovaquone is a reasonable alternative (BII). Although a meta-analysis, systematic review, and cohort study concluded that the combination of clindamycin and primaquine might be the most effective regimen for salvage therapy,84,89,90 no prospective clinical trials have evaluated the optimal approach to patients who experience a therapy failure with TMP-SMX.
Preventing Recurrence

When to Start Secondary Prophylaxis
Secondary PCP prophylaxis with TMP-SMX should be initiated immediately upon successful completion of therapy and maintained until immune reconstitution occurs as a result of ART (see below) (AI). For patients who are intolerant of TMP-SMX, the alternatives are dapsone, dapsone plus pyrimethamine plus leucovorin, atovaquone, and aerosolized pentamidine.

When to Stop Secondary Prophylaxis
Secondary prophylaxis should be discontinued in adult and adolescent patients whose CD4 counts have increased from <200 to >200 cells mm\(^{-3}\) for >3 months as a result of ART (AII). Reports from observational studies\(^{57,63,107,108}\) and from two randomized trials\(^{64,109}\) and a combined analysis of eight European cohorts being followed prospectively\(^{110}\) support this recommendation. In these studies, patients responded to ART with an increase in CD4 counts to ≥200 cells/mm\(^{3}\) for >3 months. At the time prophylaxis was discontinued, the median CD4 count was >300 cells/mm\(^{3}\) and most patients had a CD4 cell percentage >14%. Most patients had sustained suppression of plasma HIV RNA levels below the limits of detection for the assay employed; the longest follow-up was 40 months. Based on results from the COHERE study, secondary prophylaxis in patients with CD4 counts of 100 to 200 cells/mm\(^{3}\) can potentially be discontinued if HIV plasma RNA levels remain below limits of detection for at least 3 to 6 months (BII).\(^{111}\)

When to Restart Primary or Secondary Prophylaxis
Primary or secondary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm\(^{3}\) (AIII) regardless of the HIV plasma viral load. Prophylaxis should also be reintroduced for patients with CD4 counts of 100-200 cells/mm\(^{3}\) with HIV plasma viral load above detection limits of the utilized assay (AIII). Based on results from the COHERE study, primary or secondary prophylaxis may not need to be restarted in patients with CD4 counts of 100 to 200 cells/mm\(^{3}\) who have had HIV plasma RNA levels below limits of detection for at least 3 to 6 months (BII).\(^{16,111}\)

If an episode of PCP occurs at a CD4 count >200 cells/mm\(^{3}\) while on ART, it would be prudent to (then) continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART (BIII). For patients in whom PCP occurs at a CD4 count >200 cells/mm\(^{3}\) while not on ART, discontinuation of prophylaxis can be considered once HIV plasma RNA levels are suppressed to below limits of detection for at least 3 to 6 months, although there are no data to support recommendations in this setting (CIII).

Special Considerations During Pregnancy
PCP diagnostic considerations for pregnant women are the same as for women who are not pregnant.

Indications for therapy are the same as for non-pregnant women. Some data suggest an increased risk of PCP-associated mortality in pregnancy compared with non-pregnant adults, although there are no large, well-controlled studies evaluating the impact of pregnancy on PCP outcomes.\(^{112}\)

The preferred initial therapy during pregnancy is TMP-SMX, although alternate therapies can be used if patients are unable to tolerate or are unresponsive to TMP-SMX (AI).\(^{113}\) In case-control studies, trimethoprim has been associated with an increased risk of neural tube defects and cardiovascular, urinary tract, and multiple anomalies after first-trimester exposure.\(^{114-116}\) One small study reported an increased risk of birth defects in infants born to women receiving antiretrovirals and folate antagonists, primarily trimethoprim, by contrast no increase was observed among those with exposure to either an antiretroviral or a folate antagonist alone.\(^{117}\) Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, women in their first trimester with PCP still should be treated with TMP-SMX because of its considerable benefit (AIII).

Although folic acid supplementation of 0.4 mg/day is routinely recommended for all pregnant women,\(^{118}\)
there are no trials evaluating whether supplementation at higher levels (such as the 4 mg/day recommended for pregnant women with a previous infant with a neural tube defect) would reduce the risk of birth defects associated with first-trimester TMP-SMX use in HIV-infected women. Epidemiologic data suggest that folic acid supplementation may reduce the risk of congenital anomalies.\textsuperscript{115,116} In a large, population-based, case-control study, the increased odds of congenital cardiovascular anomalies associated with TMP-SMX use persisted despite supplemental folic acid, the OR decreased from 6.4 (TMP-SMX, no folic acid) to 1.9 (TMP-SMX plus folic acid). As such, clinicians can consider giving supplemental folic acid (>0.4 mg/day routinely recommended) to women in their first trimester who are on TMP-SMX (BIII). On the other hand, a randomized, controlled trial demonstrated that adding folinic acid to TMP-SMX treatment for PCP was associated with an increased risk of therapeutic failure and death.\textsuperscript{70} In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent folic acid use.\textsuperscript{120} Therefore, if supplemental folic acid (>0.4 mg/day routinely recommended) is to be given, its use should be limited to the first trimester during the teratogenic window (AIII). Whether or not a woman receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 to 20 weeks to assess fetal anatomy (BIII).

A randomized, controlled trial published in 1956 found that premature infants receiving prophylactic penicillin/sulfisoxazole were at significantly higher risk of mortality, specifically kernicterus, compared with infants who received oxytetracycline.\textsuperscript{121} Because of these findings, some clinicians are concerned about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, although no published studies to date link late third-trimester exposure to either drug with neonatal death or kernicterus. Adjunctive corticosteroid therapy should be used to improve the mother’s treatment outcome as indicated in non-pregnant adults (AIII).\textsuperscript{122-125} Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air pO\textsubscript{2} < 70 mm Hg or arterial-alveolar O\textsubscript{2} gradient > 35 mm Hg, should receive adjunctive corticosteroids as early as possible. A systematic review of case-control studies evaluating women with first-trimester exposure to corticosteroids found a 3.4 increase in odds of delivering a baby with a cleft palate.\textsuperscript{126} On the other hand, other large population-based studies have not found an association between maternal use of corticosteroids and congenital anomalies.\textsuperscript{127,128} Corticosteroid use in pregnancy may be associated with an increased risk of maternal hypertension, glucose intolerance/gestational diabetes, and infection.\textsuperscript{129} Maternal glucose levels should be monitored closely when corticosteroids are used in the third trimester because the risk of glucose intolerance is increased (AIII). Moreover, women receiving 20 mg/day of prednisone (or its dosing equivalent for other exogenous corticosteroids) for more than 3 weeks may have a suppressed hypothalamic-pituitary-adrenal (HPA) axis and consideration should be given to use of stress-dose corticosteroids during delivery (BIII). HPA axis suppression is rarely seen among neonates born to women who received chronic corticosteroids during pregnancy.

Alternative therapeutic regimens for mild-to-moderate disease include dapsone and TMP, primaquine plus clindamycin, atovaquone suspension, and IV pentamidine.

Dapsone appears to cross the placenta.\textsuperscript{130,131} Over the past several decades it has been used safely to treat leprosy, malaria, and various dermatologic conditions during pregnancy.\textsuperscript{131,132} Long-term therapy is associated with a risk of mild maternal hemolysis, and exposed fetuses with G6PD deficiency are at potential risk (albeit extremely low) of hemolytic anemia.\textsuperscript{133}

Clindamycin, which appears to cross the placenta, is a Food and Drug Administration (FDA) Pregnancy Category B medication and is considered safe for use throughout pregnancy.

Primaquine generally is not used in pregnancy because of the risk of maternal hemolysis. As with dapsone, there is potential risk of hemolytic anemia in an exposed fetus with G6PD deficiency. The degree of intravascular hemolysis appears to be associated with both dose of primaquine and severity of G6PD deficiency.\textsuperscript{134}
Data on atovaquone in humans are limited but preclinical studies have not demonstrated toxicity.\textsuperscript{134} Pentamidine is embryotoxic but not teratogenic in rats and rabbits.\textsuperscript{135}

All-cause pneumonia during pregnancy increases rates of preterm labor and delivery. Pregnant women with pneumonia after week 20 of gestation should be closely monitored for evidence of contractions (BIIII).

Chemoprophylaxis for PCP should be administered to pregnant women, the same as for other adults and adolescents (AIII). TMP-SMX is the recommended prophylactic agent. Given theoretical concerns about possible teratogenicity associated with first-trimester drug exposures, health care providers may consider using alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone during this period (CIII) rather than withholding chemoprophylaxis.

**Preconception Care**

Clinicians who are providing pre-conception care for HIV-infected women receiving PCP prophylaxis can discuss with their patients the option of deferring pregnancy until PCP prophylaxis can be safely discontinued; that is, until the CD4 cell count is $\geq 200$ cells/mm$^3$ for 3 months (BIIII).

### Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia (PCP)

#### Preventing 1st Episode of PCP (Primary Prophylaxis)

**Indications for Initiating Primary Prophylaxis:**
- CD4 count $<200$ cells/mm$^3$ (AI) or
- CD4% $<14\%$ of total lymphocyte count (BII) or
- CD4 count $>200$ but $<250$ cells/mm$^3$, if ART cannot be initiated, and if CD4 cell count monitoring (e.g., every 3 months) is not possible (BII).

**Note**—Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).

**Preferred Therapy:**
- TMP-SMX, 1 DS PO daily (AI) or
- TMP-SMX, 1 SS PO daily (AI).

**Alternative Therapy:**
- TMP-SMX 1 DS PO three times weekly (BI) or
- Dapsone$^{b,c}$ 100 mg PO daily or 50 mg PO BID (BI) or
- Dapsone$^{b}$ 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI) or
- (Dapsone$^{b}$ 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (BI) or
- Aerosolized pentamidine$^{c}$ 300 mg via Respigard II$^{\text{TM}}$ nebulizer every month (BI) or
- Atovaquone 1500 mg PO daily with food (BI) or
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily with food (CIII).

**Indication for Discontinuing Primary Prophylaxis:**
- CD4 count increased from $<200$ cells/mm$^3$ to $\geq 200$ cells/mm$^3$ for at least 3 months in response to ART (AI)
- Can consider if CD4 count 100-200 cells/mm$^3$ and HIV RNA remain below limit of detection for at least 3-6 months (BII)

**Indication for Restarting Primary Prophylaxis:**
- CD4 count $<100$ cells/mm$^3$ regardless of HIV RNA (AIII)
- CD4 count 100-200 cells/mm$^3$ and with HIV RNA above detection limit of the assay (AIII).
Treating PCP

Note—Patients who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (BIII).

For Moderate to Severe PCP—Total Duration = 21 Days (AII):

Preferred Therapy:
- TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg/kg/day IV given q6h or q8h (AI), may switch to PO after clinical improvement (AI).

Alternative Therapy:
- Pentamidine 4 mg/kg IV once daily infused over at least 60 minutes (AI); may reduce the dose to 3 mg/kg IV once daily because of toxicities (BI) or
- Primaquine\(^b\) 30 mg (base) PO once daily + (Clindamycin [IV 600 q6h or 900 mg q8h] or [PO 450 mg q6h or 600 mg q8h]) (AI).

* Adjunctive corticosteroids are indicated in moderate to severe cases (see indications and dosage recommendations below)

For Mild to Moderate PCP—Total Duration = 21 days (AII):

Preferred Therapy:
- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day), given PO in 3 divided doses (AI) or
- TMP-SMX DS - 2 tablets TID (AI).

Alternative Therapy:
- Dapsone\(^b,c\) 100 mg PO daily + TMP 15 mg/kg/day PO (3 divided doses) (BI) or
- Primaquine\(^b\) 30 mg (base) PO daily + Clindamycin PO (450 mg q6h or 600 mg q8h) (BI) or
- Atovaquone 750 mg PO BID with food (BI)

Adjunctive Corticosteroids:

For Moderate to Severe PCP Based on the Following Criteria (AI):
- \(\text{PaO}_2<70 \text{ mmHg at room air}\) or
- Alveolar-arterial \(\text{O}_2\) gradient \(\geq 35 \text{ mm Hg}\)

Dosing Schedule:
Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy) (AI):

<table>
<thead>
<tr>
<th>Days</th>
<th>Dose</th>
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<tbody>
<tr>
<td>1–5</td>
<td>40 mg PO BID</td>
</tr>
<tr>
<td>6–10</td>
<td>40 mg PO daily</td>
</tr>
<tr>
<td>11–21</td>
<td>20 mg PO daily</td>
</tr>
</tbody>
</table>

IV methylprednisolone can be given as 75% of prednisone dose

Preventing Subsequent Episode of PCP (Secondary Prophylaxis)

Indications for Initiating Secondary Prophylaxis:
- Prior PCP

Preferred Therapy:
- TMP-SMX, 1 DS PO daily\(^e\) (AI) or
- TMP-SMX, 1 SS PO daily\(^e\) (AI).

Alternative Therapy:
- TMP-SMX 1 DS PO three times weekly (BI) or
- Dapsone\(^h\) 100 mg PO daily or 50 mg PO BID (BI) or
- Dapsone\(^h\) 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI) or
- (Dapsone\(^h\) 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (BI) or
- Aerosolized pentamidine\(^i\) 300 mg via Respigard II™ nebulizer every month (BI) or
- Atovaquone 1500 mg PO daily with food (BI) or
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily with food (CIII)
Indications for Discontinuing Secondary Prophylaxis:

- CD4 count increased from <200 cells/mm³ to >200 cells/mm³ for >3 months as a result of ART (BII) or
- Can consider if CD4 count 100-200 cells/µL and HIV RNA remain below limits of detection for at least 3-6 months (BII)
- For patients in whom PCP occurs at a CD4 count >200 cells/mm³ while not on ART, discontinuation of prophylaxis can be considered once HIV plasma RNA levels are suppressed to below limits of detection for at least 3 to 6 months, although there are no data to support recommendations in this setting (CIII).

Note: If an episode of PCP occurs at a CD4 count >200 cells/mm³ while on ART, it would be prudent to then continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART (BII).

Indications for Restarting Secondary Prophylaxis:

- CD4 count falls to <200 cells/mm³ (AII) or

Other Considerations/Comments:

- For patients with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.
- If TMP-SMX is discontinued because of a mild adverse reaction, re-institution should be considered after the reaction has resolved (AII). The dose can be increased gradually (desensitization) (BII) or given at a reduced dose or frequency (CIII).
- Therapy should be permanently discontinued, with no rechallenge, in patients with possible or definite Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII).

a TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; lower dose also likely confers protection.
b Whenever possible, patients should be tested for G6PD deficiency before administration of dapsone or primaquine. Alternative agent should be used if the patient is found to have G6PD deficiency.
c Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for PCP prophylaxis in patients who are seropositive for Toxoplasma gondii.

Acronyms: BID = twice daily; DS = double strength; IV = intravenously; PCP = Pneumocystis pneumonia; PO = orally; q “n” h = every “n” hour; SS = single strength; TID = three times daily; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

References


*Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*  B-13


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