



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 organism that is classified as a fungus but also shares biologic characteristics with protozoa. 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 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 Most cases occur in patients who are unaware of their HIV infection or are not receiving ongoing care for HIV,¹⁶ and in those with advanced immunosuppression (CD4 counts <100 cells/mm³).¹⁷

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.^{18,19}

In mild cases, pulmonary examination usually is normal at rest. With exertion, tachypnea, tachycardia, and diffuse dry (cellophane) rales may be observed.¹⁹ 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.²⁰

Hypoxemia, the most characteristic laboratory abnormality, can range from mild (room air arterial oxygen [pO₂] ≥70 mm Hg or alveolar-arterial O₂ difference, [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.²¹ Elevation of lactate dehydrogenase levels to >500 mg/dL is common but non-specific.²² Chest radiograph typically demonstrates diffuse, bilateral, symmetrical interstitial infiltrates emanating from the hila in a butterfly pattern;¹⁹ however, a chest radiograph may be normal in patients with early disease.²³ Atypical radiographic presentations also occur, such as nodules, blebs and cysts, asymmetric disease, upper lobe localization, and pneumothorax. Spontaneous pneumothorax in a patient with HIV infection should raise the suspicion of PCP.^{24,25} Cavitation, intrathoracic adenopathy, and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancy, and their presence may indicate an alternative diagnosis. 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.^{26,27}

Thin-section computed tomography (CT) demonstrating patchy ground-glass attenuation^{28,29} increases the likelihood that a diagnostic study, such as bronchoscopy, will demonstrate PCP in patients with mild-to-moderate symptoms and normal chest radiograph and, therefore, may be useful as an adjunct.

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^{18,26,27,30} 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; Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain the cyst wall. Some laboratories prefer direct immunofluorescent staining. Previous studies of stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: induced sputum <50% to >90% (the sensitivity depends on the pathogen load and specimen quality, while the specificity depends on the experience of the microbiologist or pathologist), bronchoscopy with BAL 90% to 99%, transbronchial biopsy 95% to 100%, and open lung biopsy 95% to 100%.

Polymerase chain reaction (PCR) is an emerging method for diagnosing PCP.³¹ The sensitivity of PCR for bronchoalveolar lavage appears to be high; the ability of PCR to distinguish colonization from disease is less clear.³¹⁻³⁴ 1,3β-D-glucan (a component of fungal cell walls) may be elevated in patients with PCP, but the assay's sensitivity and specificity for establishing a PCP diagnosis are problematic,^{35,36} and other fungal diseases can produce elevation.

Because certain 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.³⁰

Preventing Exposure

Pneumocystis can be quantified in the air near patients with PCP,³⁷ and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients.^{5-11,38} 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 (**CI**).

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**) or a history of oropharyngeal candidiasis (**AI**).^{12,13,39} Persons who have a CD4 cell percentage of <14% or a history of an AIDS-defining illness, but who do not otherwise qualify, should be considered for prophylaxis (**BI**).^{12,13,39} Initiation of chemoprophylaxis at CD4 counts between 200 and 250 cells/mm³ also should be considered when frequent monitoring of CD4 counts, such as every 3 months, is impossible (**BI**).¹³ Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (**AI**).⁴⁰

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent (**AI**).^{39,41-43} One double-strength tablet daily is the preferred regimen (**AI**), but one single-strength tablet daily⁴³ 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**).⁴⁴ TMP-SMX at a dose of one double-strength tablet daily confers cross protection against toxoplasmosis⁴⁵ and many respiratory bacterial infections.^{41,46} Lower doses of TMP-SMX likely also confer such protection. TMP-SMX chemoprophylaxis 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 (**AI**). 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) (**AI**).

Patients who have experienced adverse events, including fever and rash, may better tolerate re-introduction of the drug if the dose is gradually increased (desensitization) according to published regimens **(BI)**^{47,48} 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.⁴⁶

For patients who cannot tolerate TMP-SMX, alternative prophylactic regimens include dapsone **(BI)**,⁴¹ dapsone plus pyrimethamine plus leucovorin **(BI)**,⁴⁹⁻⁵¹ aerosolized pentamidine administered with the Respirgard II nebulizer (manufactured by Marquest; Englewood, Colorado) **(BI)**,⁴² and atovaquone **(BI)**.^{52,53} Atovaquone is as effective as aerosolized pentamidine⁵² or dapsone⁵³ 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)**,⁴⁹⁻⁵¹ or atovaquone with or without pyrimethamine plus leucovorin **(CIII)**.

The author panel has issued a statement on the availability of pyrimethamine. For more information, please visit <https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine>.

Oral pyrimethamine plus sulfadoxine also has activity against PCP.⁵⁴⁻⁵⁶ However, this combination is associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,⁵⁷ and the long half-life of both pyrimethamine and sulfadoxine results in delayed clearance when the drug is stopped. Because TMP-SMX has superior safety, widespread availability, and is low cost, oral pyrimethamine plus sulfadoxine should **not** be used in the United States **(AIII)**.

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 **(AI)**. 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.⁵⁸⁻⁶⁷ 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 are limited to PCP, toxoplasmosis, and bacterial infections;^{60,66} 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 cohorts⁶⁸ and a case series⁶⁹ 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 PCP prophylaxis can be safely discontinued in selected patients with CD4 counts 100 to 200 cells/mm³ and HIV plasma RNA levels below limits of detection with commercial assays. Data on which to base recommendations for this approach are inadequate, but some experts believe it is reasonable and recommend it for their patients.

Treating Disease

TMP-SMX is the treatment of choice for PCP (**AI**).^{70,71} 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 (**AI**).⁷² Oral outpatient therapy with TMP-SMX is highly effective in patients with mild-to-moderate disease (**AI**).⁷¹

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.⁷³⁻⁷⁶ 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 pO₂ <70 mm Hg or Alveolar-arterial O₂ gradient ≥35 mm Hg, should receive adjunctive corticosteroids as early as possible and certainly within 72 hours after starting specific PCP therapy (**AI**).⁷⁷⁻⁸² 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**). Methylprednisolone at 75% of the respective prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone and TMP (**BI**),^{71,83} 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**)⁸⁴⁻⁸⁶ (the clindamycin component can be administered intravenously [IV] for more severe cases, but primaquine is only available orally); and atovaquone suspension (**BI**),^{53,58,70,87} 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 (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**).^{86,88,89} Some clinicians prefer clindamycin-primaquine because of its higher degree of efficacy and lesser toxicity compared with pentamidine.^{86,90-92}

Aerosolized pentamidine **should not** be used to treat PCP because its efficacy is limited and it is associated with more frequent relapse (**AI**).^{88,93,94} Trimetrexate is no longer commercially available.

The recommended duration of therapy for PCP is 21 days (**AI**).¹⁸ 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.⁹⁵⁻⁹⁸ Because long-term survival is possible for patients in whom ART is effective, individuals with AIDS and severe PCP should be offered ICU admission or mechanical ventilation if their functional status is such that it would be appropriate, just as with HIV-uninfected patients (**AI**).

Special Consideration with Regards to Starting ART

In patients not on ART, ART should be initiated, 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 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).⁹⁹ Of note, no patients with PCP and respiratory failure requiring intubation were enrolled in the study.⁹⁹ Paradoxical immune reconstitution inflammatory syndrome (IRIS) has been reported following PCP.¹⁰⁰ 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. Although IRIS in the setting of PCP has only rarely been life threatening,¹⁰¹ 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 anti-PCP 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. PCP prophylaxis should be initiated immediately upon completion of therapy and maintained until the CD4 count is >200 cells/mm³ for at least 3 months.

In patients with AIDS, rates of adverse reaction to TMP-SMX are high (20%–85%).^{70,71,83,85,89,102-106} 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;^{71,83} azotemia, pancreatitis, hypo- or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine;^{87-89,105} anemia, rash, fever, and diarrhea with primaquine and clindamycin;^{71,84,85} and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.^{70,104}

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;^{26,27} 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.⁷¹ 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**).^{85,89,106} 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,^{86,91,92} 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

Patients who have a history of PCP should be given chemoprophylaxis for life with TMP-SMX (i.e.,

secondary prophylaxis or chronic maintenance therapy) unless immune reconstitution occurs as a result of ART (see below) **(AI)**.¹⁰⁷ For patients who are intolerant of TMP-SMX, the alternatives are dapsone, dapsone combined with pyrimethamine, 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/mm³ for >3 months as a result of ART **(AII)**. Reports from observational studies^{59,65,108,109} and from two randomized trials^{66,110} and a combined analysis of eight European cohorts being followed prospectively¹¹¹ support this recommendation. In these studies, patients responded to ART with an increase in CD4 counts to ≥ 200 cells/mm³ for >3 months. At the time prophylaxis was discontinued, the median CD4 count was >300 cells/mm³ 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. Prophylaxis should be reintroduced if the CD4 count decreases to <200 cells/mm³ **(AIII)**.

If an episode of PCP occurs at a CD4 count ≥ 200 cells/mm³, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART **(BIII)**.

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 ARV drugs and folate antagonists, primarily trimethoprim, whereas no increase was observed among those with exposure to either an ARV drug 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. Epidemiologic data do suggest, however, that folic acid supplementation may reduce the risk of congenital anomalies.^{115,116} In a large, population-based, case-control study, the increased odds of congenital cardiovascular anomalies associated with TMP-SMX use in pregnancy were not seen in women also receiving folic acid supplementation, most of whom received 6 mg/day (odds ratio [OR] 1.24; 95% confidence interval [CI]: 0.94-1.62).¹¹⁹ Although the risk of multiple congenital anomalies associated with TMP-SMX use persisted with 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 folic acid to TMP-SMX treatment for PCP was associated with an increased risk of therapeutic failure and death.⁷² In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent folic acid use.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/sulfoxazole were at significantly higher risk of kernicterus and mortality, specifically kernicterus, compared with infants who received oxytetracycline.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 nonpregnant adults (**AIII**).¹²²⁻¹²⁵ Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air pO₂ <70 mm Hg or arterial-alveolar O₂ 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.¹²⁶ On the other hand, other large population-based studies have not found an association between maternal use of corticosteroids and congenital anomalies.^{127,128} Corticosteroid use in pregnancy may be associated with an increased risk of maternal hypertension, glucose intolerance/gestational diabetes, and infection.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 the use of stress-dose steroids during delivery (**BIII**). HPA axis suppression is rarely seen among neonates born to women on 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.^{130,131} It has been used safely over the past several decades to treat leprosy, malaria, and various dermatologic conditions during pregnancy.^{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.¹³³

Clindamycin, which appears to cross the placenta, is a Food and Drug Administration (FDA) Pregnancy Category B medication and 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 exposed fetuses with G6PD deficiency. The degree of intravascular hemolysis appears to be associated with both dose of primaquine and severity of G6PD deficiency.¹³⁴

Data on atovaquone in humans are limited but preclinical studies have not demonstrated toxicity.¹³⁴

Pentamidine is embryotoxic but not teratogenic in rats and rabbits.¹³⁵

Pneumonia during pregnancy increases rates of preterm labor and delivery. Pregnant women with pneumonia after 20 weeks' gestation should be monitored for evidence of contractions (**BIII**).

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

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/mm³ **(AI)** or
- Oropharyngeal candidiasis **(AII)** or
- CD4% <14% **(BII)** or
- History of AIDS-defining illness **(BII)** or
- CD4 count >200 but <250 cells/mm³ 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^a **(AI)** or
- TMP-SMX, 1 SS PO daily^a **(AI)**.

Alternative Therapy:

- TMP-SMX 1 DS PO three times weekly^a **(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™ 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/mm³ to ≥200 cells/mm³ for at least 3 months in response to ART **(AI)**

Indication for Restarting Primary Prophylaxis:

- CD4 count <200 cells/mm³ **(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 corticosteroid may be indicated in some 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 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):

- PaO₂ <70 mmHg at room air *or*
- Alveolar-arterial O₂ gradient ≥35 mmHg

Dosing Schedule:

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

Days 1–5	40 mg PO BID
Days 6–10	40 mg PO daily
Days 11–21	20 mg PO daily

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^a (AI) *or*
- TMP-SMX, 1 SS PO daily^a (AI).

Alternative Therapy:

- TMP-SMX 1 DS PO three times weekly^a (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™ 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 (AII) *or*
- If PCP diagnosed when CD4 count ≥200 cells/mm³, prophylaxis should be continued for life regardless of CD4 cell count rise as a consequence of ART (BIII).

Indications for Restarting Secondary Prophylaxis:

- CD4 count falls to <200 cells/mm³ (AIII) *or*
- If PCP recurred at a CD4 count ≥200 cells/mm³, lifelong prophylaxis should be administered (BIII).

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) (BI) 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

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