

***Pneumocystis jirovecii* Pneumonia** (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

Prevention of Primary Exposure

- Some experts recommend that consideration be given to not placing a patient with *Pneumocystis jirovecii* pneumonia (PCP) in a hospital room with another patient and not placing an at-risk immunocompromised patient in a room with a patient who has a respiratory tract infection (**BIII**).

Chemoprophylaxis

- Chemoprophylaxis is highly effective in preventing PCP. Prophylaxis is recommended for all HIV-infected children aged ≥ 6 years who have CD4 T lymphocyte (CD4) cell counts < 200 cells/mm³ or CD4 percentage $< 15\%$, for children aged 1 to < 6 years with CD4 counts < 500 cells/mm³ or CD4 percentage $< 15\%$, and for all HIV-infected infants aged < 12 months regardless of CD4 count or percentage (**AII**).
- Infants with indeterminate HIV infection status should receive prophylaxis until they are determined to be HIV-uninfected or presumptively HIV-uninfected (**AIII**). HIV-infected infants should be administered prophylaxis until age 1 year, at which time they should be reassessed on the basis of the age-specific CD4 count or percentage thresholds mentioned above (**AII**).
- Trimethoprim-sulfamethoxazole (TMP-SMX; cotrimoxazole), administered either on 3 consecutive days/week or daily, is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum (**AI**).
- Other effective and safe prophylaxis regimens are available for patients unable to take TMP-SMX. A second choice would be either atovaquone (**AI**) or dapsone (**BI***).
- Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and who are old enough to use nebulization with a Respigard II[®] nebulizer (Marquest; Englewood, CO) (**BI***).
- Intravenous (IV) pentamidine is not recommended for prophylaxis unless no other options are available (**BII**).
- Discontinuation of PCP prophylaxis should be considered for HIV-infected children when, after receiving combination antiretroviral therapy for ≥ 6 months, CD4 percentage is $\geq 15\%$ or CD4 count is ≥ 200 cells/mm³ for patients aged ≥ 6 years (**BII**) and CD4 percentage is $\geq 15\%$ or CD4 count is ≥ 500 cells/mm³ for patients aged 1 to < 6 years (**BII**) for > 3 consecutive months. Thereafter, CD4 percentage and CD4 count should be reevaluated at least every 3 months and prophylaxis reinstated if the age-specific criteria for prophylaxis are reached (**BIII**).

Treatment

- TMP-SMX, administered IV, is the recommended treatment for PCP (**AI**). As the acute pneumonitis subsides, children with mild-to-moderate disease who do not have malabsorption or diarrhea can be transitioned to oral treatment with the same total daily dose of TMP-SMX administered in 3 or 4 divided doses to complete a 21-day course (**AII**).
- IV pentamidine isethionate once daily is recommended for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy (**AI***).
- Atovaquone is an alternative for treatment of mild-to-moderately severe PCP (**BI***).
- Dapsone/TMP is effective in treating mild-to-moderate PCP (**BI***).
- Clindamycin/primaquine has been used to treat mild-to-moderate PCP; data in children are unavailable (**BIII**).
- A short course of corticosteroids is recommended in cases of moderate or severe PCP, starting within 72 hours of diagnosis (**AI***).
- Patients who have experienced an episode of PCP should continue on PCP prophylaxis after completion of treatment until CD4 counts exceed the threshold for initiating prophylaxis (**AI**).
- Children who present with clinical signs and symptoms compatible with PCP after discontinuation of prophylaxis should be evaluated thoroughly despite normal or high CD4 counts or percentages (**BI***).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials *in children*[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Pneumocystis spp. are found worldwide in the lungs of humans and lower animals. The organisms are host specific, and cross-infection between humans and other species does not occur. *Pneumocystis* spp. from all sources are morphologically, tinctorially, and biologically similar, but surface antigens and gene sequencing have demonstrated host-specific differences. Since the original designation of *Pneumocystis carinii* a century ago, several changes in terminology have been suggested. The most recent proposal was to change *P. carinii* to *Pneumocystis jirovecii* for isolates from human lungs. *Pneumocystis* has been designated a fungus on the basis of DNA analysis, but it has several biologic features of protozoa. Most humans are infected with *Pneumocystis* early in life. By ages 2 to 4 years, more than 80% of children in most countries have acquired antibodies to *Pneumocystis*.¹⁻³ Immunocompetent infants with the infection are either asymptomatic or have mild respiratory symptoms. *Pneumocystis jirovecii* pneumonia (PCP) occurs almost exclusively in the immunocompromised host.

PCP remains an important AIDS-indicator disease among HIV-infected children. The highest incidence of PCP in HIV-infected children is in the first year of life, with cases peaking at ages 3 to 6 months.⁴⁻⁶ Data from the Centers for Disease Control and Prevention Pediatric Spectrum of Disease Project (1994–2001) indicate a decline in PCP infection rates (cases per 1000 HIV-infected children) from 25 in 1994 to 18 in 1996 to 6 in 2001.⁷ Similarly, analyses of data from the Perinatal AIDS Collaborative Transmission Study revealed a 95% decline in PCP (cases per 100 child-years) from 5.8 (pre-combination antiretroviral therapy [cART] era) to 0.3 (cART era).⁸ Finally, the incidence rate for PCP (cases per 100 child-years) was 1.3 during the pre-cART era (1981–1988) and <0.5 during the cART era (2001–2004).⁹ This decline probably resulted from implementation of interventions to prevent mother-to-child transmission of HIV, introduction of cART in HIV-infected children in 1995, and chemoprophylaxis for PCP.

PCP continues to be a major cause of death among HIV-infected infants and children in the developing world. Autopsies done in Africa revealed PCP in 16% of children who died with HIV/AIDS during 1992 and 1993,¹⁰ in 29% of those who died during 1997 and 2000,¹¹ and in 44% of those who died during 2000 and 2001.¹²

The mode of transmission of *Pneumocystis* among HIV-infected infants, children, and adults is not firmly established, but airborne human-to-human transmission is likely. Animal studies show *Pneumocystis* is transmitted by air from infected to susceptible rats.^{13,14} Furthermore, *Pneumocystis* can infect normal mice, produce subclinical disease and be transmitted to normal or immunocompromised mice.¹⁵ Human-to-human transmission has been suggested by molecular epidemiology and global clustering of PCP cases in recent studies.¹⁶⁻¹⁸ Intrauterine transmission is considered rare. However, in one report, 1 of 8 infants born to women who had AIDS and PCP during pregnancy had evidence of *Pneumocystis* infection.¹⁹

The single most important factor in susceptibility of HIV-infected patients of all ages to PCP is the status of cell-mediated immunity of the host. Severe compromise, reflected by a marked decrease in CD4 T lymphocyte (CD4) cell count and percentage, is the hallmark of high risk for PCP and is discussed further in the prevention section.

Clinical Manifestations

Prominent clinical features of PCP among HIV-infected children are fever, tachypnea, dyspnea, and cough. The severity of these signs and symptoms varies from child to child. Onset can be abrupt or insidious with nonspecific symptoms such as mild cough, dyspnea, poor feeding, diarrhea, and weight loss. Some patients may not be febrile, but almost all will have tachypnea by the time pneumonitis is evident on chest radiograph. Physical examination sometimes shows bilateral basilar rales with evidence of respiratory distress and hypoxia.

In HIV-infected children with pneumonia, four clinical variables are independently associated with PCP: aged <6 months, respiratory rate >59 breaths per minute, arterial percentage hemoglobin saturation $\leq 92\%$, and absence of vomiting.²⁰ A high plasma HIV RNA concentration strongly predicts PCP and other opportunistic infections (OIs).²¹

Extrapulmonary *Pneumocystis* organisms, often associated with a localized inflammatory reaction, are found in <2.5% of HIV-infected adults and children.^{22,23} This can occur without concurrent PCP and can be located at multiple noncontiguous sites. Involved sites have included ear, eye, thyroid, spleen, gastrointestinal (GI) tract, peritoneum, stomach, duodenum, small intestine, transverse colon, liver, and pancreas. Less frequently involved sites include adrenal glands, muscle, bone marrow, heart, kidney, ureter, lymph nodes, meninges, and cerebral cortex.

Diagnosis

Most children with PCP have substantial hypoxia with low arterial oxygen pressure (PaO₂ typically <70 mm Hg) and an A-a gradient >30 mmHg. CD4 percentage is often <15% and CD4 counts are usually <200 cells/mm³ in children aged 6 years and older. Lactic dehydrogenase is often increased, but this is not specific for PCP. Serum albumin may be depressed. Chest radiographs most commonly reveal bilateral diffuse parenchymal infiltrates with “ground-glass” or reticulogranular appearance, but they also can be normal or have only mild parenchymal infiltrates. The earliest infiltrates are perihilar, progressing peripherally before reaching the apical portions of the lung. Rarely, lobar, cavitary, nodular, or miliary lesions; pneumothorax; or pneumomediastinum are observed.

A definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids in the presence of pneumonitis. Diagnostic procedures are the same as for adults suspected of having PCP (see [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults](#)),²⁴ but some procedures may be more difficult to perform in children.

Induced sputum analysis, during which the patient produces sputum after inhalation of nebulized 3% hypertonic saline, may be difficult in children aged <2 years because of small airways and poor ability to produce sputum. Complications from the procedure include nausea, vomiting, and bronchospasm. Sensitivity of sputum analysis in adults ranges from 25% to 90%. After a negative induced sputum sample, a bronchoalveolar lavage may be necessary for definitive diagnosis.

Nasogastric aspirates, if positive, are of diagnostic value. *Pneumocystis* organisms were found in 48.6% of HIV-infected children with respiratory illnesses in whom gastric aspirates were obtained on three consecutive mornings.²⁵ Other studies have shown the organism only found in gastric contents of patients with PCP.²⁶

Bronchoscopy with bronchoalveolar lavage is the diagnostic procedure of choice for most infants and children. Sensitivity ranges from 55% to 97% and results may be positive for ≥72 hours after initiation of PCP treatment; treatment should not be delayed while awaiting results. Complications include hemoptysis, pneumothorax, transient increase in hypoxemia, a transient increase in pulmonary infiltrates at the lavage site, and post-bronchoscopy fever.

Fiberoptic bronchoscopy with trans-bronchial biopsy is recommended only when bronchoalveolar lavage is negative or non-diagnostic despite a clinical picture consistent with PCP. Sensitivity is 87% to 95%, and cysts can typically be identified up to 10 days after initiation of treatment. Complications include pneumothorax and hemorrhage; this procedure is contraindicated in children with thrombocytopenia.

Open-lung biopsy is the most sensitive and specific diagnostic technique, but not recommended routinely because it requires thoracotomy and often chest tube drainage. It has the advantage of revealing the type and extent of disease as well as the organism. Histopathology shows alveoli filled with eosinophilic, acellular, proteinaceous material that contains cysts and trophozoites but few inflammatory cells. Complications include pneumothorax, pneumomediastinum, and hemorrhage.

Three types of stains can be used to identify *Pneumocystis* organisms in specimens. Gomori methenamine-silver method stains the cyst wall brown or black. Toluidine blue stains the cyst wall blue or lavender. Both methods stain fungal elements. Giemsa, Diff-Quick[®], and Wright stains depict the trophozoites and intracystic sporozoites pale blue with a punctate red nucleus, but unlike other stains, these do not stain the

cyst wall. Monoclonal immunofluorescent antibodies (MERIFLUOR[®], Meridian Bioscience, Inc.; Cincinnati, OH) that identify the cyst wall also can be used for diagnosis and have enhanced specificity and sensitivity compared with the other staining methods. A cyst wall, trophozoite, and immunofluorescent antibody stain is recommended for each specimen studied.

Polymerase chain reaction assays to amplify the human *Pneumocystis* MSG/gpA gene, mitochondrial large subunit (mtLSU) RNA, the dihydropteroate synthase gene, and the internal transcribed spacer region genes have been developed for diagnostic evaluation. These tests are usually more sensitive but less specific than microscopic methods and are not standardized or available in most centers.^{27,28} *Pneumocystis*-specific DNA is found in 18% of bronchoalveolar lavage samples from patients without clinical PCP, HIV, or other infections.²⁹

Coinfection with other organisms such as cytomegalovirus (CMV) or pneumococcus has been reported in HIV-infected children.^{6,30,31} Children with dual infections may have more severe disease. Although CMV in lung secretions of children with PCP indicates colonization, it usually does not require therapy in the absence of histopathologic evidence of invasive CMV disease.

Prevention Recommendations

Preventing Exposure

Clinical data are unavailable upon which to make a decision regarding isolation of patients with PCP. However, animal model experiments, which generally provide an accurate demonstration of the pathophysiology seen in humans, suggest that transmission occurs easily; therefore, isolation should be strongly considered (AIII).³² Immunocompromised patients who are compliant with PCP prophylaxis, especially with trimethoprim-sulfamethoxazole (TMP-SMX), are unlikely to acquire PCP. However, some experts still suggest that such at-risk patients not be placed in a room with another patient with PCP. Caution is also advised in having an at-risk patient share a room with another patient with an undiagnosed respiratory illness that could be PCP (AIII). This is especially true of respiratory illnesses occurring during the first 2 years of life when 85% of children undergo a primary infection with *Pneumocystis*.¹

Preventing First Episode of Disease

Chemoprophylaxis is highly effective in preventing PCP. Criteria for its use are based on a patient's age and CD4 count or percentage.³³ Prophylaxis is recommended for all HIV-infected children aged ≥ 6 years who have CD4 counts < 200 cells/mm³ or CD4 percentage $< 15\%$, for children aged 1 to < 6 years with CD4 counts < 500 cells/mm³ or CD4 percentage $< 15\%$, and for all HIV-infected infants aged < 12 months regardless of CD4 count or percentage (AII).³³

Infants born to HIV-infected mothers should be considered for prophylaxis beginning at 4 to 6 weeks of age. HIV-infected infants should be administered prophylaxis until age 1 year, at which time they should be reassessed on the basis of the age-specific CD4 count or percentage thresholds mentioned previously (AII).³⁴ Infants with indeterminate HIV infection status should receive prophylaxis until they are determined to be definitively HIV-uninfected³⁴ or presumptively HIV-uninfected (AIII).³⁵⁻³⁷ Prophylaxis is not recommended for infants who meet criteria for being definitively or presumptively HIV-uninfected. In non-breastfeeding infants with no positive HIV virologic test results, presumptive exclusion of HIV infection can be based on two negative virologic test results, one obtained at ≥ 2 weeks and one obtained at ≥ 4 weeks of age; one negative virologic test result obtained at ≥ 8 weeks of age; or one negative HIV-antibody test result obtained at ≥ 6 months of age. Definitive exclusion of HIV infection is based on two negative virologic test results: 1 obtained at ≥ 1 month of age and one obtained at ≥ 4 months of age, or on 2 negative HIV-antibody test results from separate specimens obtained at ≥ 6 months of age. For both presumptive and definitive exclusion of infection, a child should have no other laboratory (e.g., no positive virologic test results) or clinical conditions (e.g., no AIDS-defining conditions that cannot be explained on the basis of other causes of immunosuppression) or evidence of HIV infection.³⁵⁻³⁷

Four drug regimens have been found effective and relatively safe for preventing PCP in high-risk HIV-infected children and adults.

TMP-SMX (cotrimoxazole) is the drug of choice for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum (**AI**).³⁸⁻⁴⁰ TMP alone has little, if any, anti-*Pneumocystis* activity, but it enhances the activity of the sulfonamide. The prophylactic dosage is 150 mg/m² body surface area per day TMP and 750 mg/m² body surface area per day SMX (approximately 5.0–10 mg/kg body weight per day TMP and 25–50 mg/kg body weight per day SMX; dosing based on TMP component) administered orally either every day (**AI**)⁴¹ (5.0–10 mg/kg body weight/dose once daily TMP and 25–50 mg/kg body weight/dose once daily SMX) or on 3 consecutive days per week (2.5–5.0 mg/kg body weight/dose TMP and 12.5–25 mg/kg body weight/dose SMX twice per day)⁴² or every other day (e.g., Monday, Wednesday, Friday). The total daily dose should not exceed 320 mg TMP and 1600 mg SMX. In patients with impaired renal function, a reduced dose may be necessary.

TMP-SMX, preferably given daily, also is effective in preventing toxoplasmosis⁴³ and some bacterial infections (e.g., *Salmonella*, *Haemophilus*, *Staphylococcus*).^{41,44-46}

Dihydropteroate synthase gene mutations in *Pneumocystis* from humans have been observed with TMP-SMX and dapsone prophylaxis, suggestive of possible drug resistance, but studies for clinical correlates have not provided conclusive results.²⁷ More apparent is the association of prolonged TMP-SMX prophylaxis for PCP with the emergence of TMP-SMX resistant bacterial species due to selective pressure, a point to be considered in managing bacterial infections in patients receiving prophylaxis.^{47,48}

Other effective and safe prophylaxis regimens are available for patients unable to take TMP-SMX. A second choice would be either atovaquone (**AI**)⁴⁹ or dapsone (**BI***).³⁹ Atovaquone is effective and safe but expensive. Dapsone is effective and inexpensive but associated with more serious adverse effects than atovaquone.

Atovaquone is administered with a meal as an oral yellow suspension as a single daily dose of 30 mg/kg body weight/day for patients aged 1 to 3 months and >24 months to 12 years, as 45 mg/kg body weight/day for infants aged >3 months to 24 months,⁵⁰ and as 1500 mg (10 cc) for adolescents and adults aged ≥13 years (**BI***).^{39,40} Outcomes with atovaquone equaled those of dapsone for the prevention of PCP in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both.³⁹ Unlike TMP-SMX, atovaquone has no antibacterial activity but is effective against *Toxoplasma gondii*. Azithromycin, in a single dosage of 5.0 mg/kg body weight/day, has been used to supplement atovaquone for greater broad-spectrum prophylaxis. The randomized, double-blind, placebo-controlled study the Pediatric AIDS Clinical Trial Group (PACTG) 254 compared TMP-SMX and atovaquone plus azithromycin for 3 years (median) in 366 HIV-infected children qualifying for PCP prophylaxis.⁴⁹ Results showed atovaquone-azithromycin to be as effective as TMP-SMX for preventing serious bacterial infections, as well as PCP.

Dapsone can be administered on a daily or weekly schedule as 2.0 mg/kg body weight/day (maximum total dosage 100 mg/day) or 4.0 mg/kg body weight/week (maximum total dosage 200 mg/week) orally (**AI**).⁵¹ Approximately two-thirds of patients intolerant to TMP-SMX can take dapsone successfully. Studies in adults show dapsone is as effective as atovaquone or aerosolized pentamidine but slightly less effective than TMP-SMX.^{39,50}

Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and are old enough to use nebulization with a Respirgard II[®] nebulizer (Marquest; Englewood, CO) (**BI***).³³ The dosage for all ages is 300 mg once a month.⁴⁵ Adverse reactions in HIV-infected children include cough, sneezing, and bronchospasm.⁵² Atypical systemic presentations of PCP can occur in children on aerosolized pentamidine.

Pyrimethamine-sulfadoxine (Fansidar[®]) also is recognized as an effective prophylactic regimen in adults (**CIH**).⁵³ Although this drug was effective in preventing PCP in Iranian orphanages in the 1960s, it has not been evaluated adequately in HIV-infected children.

Intravenous (IV) pentamidine can be considered in children older than age 2 years when other options are unavailable (**BII***).⁵⁴

Discontinuing Primary Prophylaxis

Studies of HIV-infected adults and children following immune reconstitution after receipt of cART demonstrate acceptably low risks for PCP after discontinuation of prophylaxis.⁵⁵⁻⁶⁰ Data from the PACTG 1008 study evaluated 235 HIV-infected children and adolescents on antiretroviral therapy who received PCP prophylaxis for ≥ 6 months and achieved CD4 percentages $\geq 20\%$ for patients aged >6 years and $\geq 25\%$ for patients aged 2 to 6 years, after which the prophylaxis was stopped.⁵⁵ At median follow-up of 2.5 years (547 person-years), no cases of PCP occurred in children not receiving prophylaxis; 9.4% of patients enrolled required reinstitution of PCP prophylaxis because of low CD4 counts during the observation period. These data, along with data from studies in adults, support the expectation for very low risk for PCP after prophylaxis is discontinued in children who have achieved immune reconstitution.

Discontinuation of PCP prophylaxis should be considered for HIV-infected children when, after receiving cART for ≥ 6 months, CD4 percentage is $\geq 15\%$ or CD4 count is ≥ 200 cells/mm³ for patients aged ≥ 6 years (**BII**) and CD4 percentage is $\geq 15\%$ or CD4 count is ≥ 500 cells/mm³ for patients aged 1 to <6 years (**BII**) for >3 consecutive months.^{55,61}

Subsequently, the CD4 percentage and CD4 count should be reevaluated at least every 3 months and prophylaxis reinstated if the original criteria for prophylaxis are reached (**BIII**). PCP prophylaxis should not be discontinued in HIV-infected infants aged <1 year.⁶²

Treatment Recommendations

Treating Disease

TMP-SMX is the recommended treatment for PCP (**AI**).^{38,63,64} The dose for HIV-infected children aged >2 months is 3.75 to 5 mg/kg body weight/dose of the TMP component and 19 to 25 mg/kg body weight/dose of the SMX component administered IV every 6 hours, with each IV dose infused over 1 hour for 21 days (**AI**).⁶² As the acute pneumonitis subsides, children with mild to moderate disease who do not have malabsorption or diarrhea can be transitioned to oral treatment with the same total daily dose of TMP-SMX administered in 3 or 4 divided doses to complete a 21-day course (**AII**).⁶² Effective therapeutic serum concentrations of 5 to 10 $\mu\text{g/mL}$ TMP can be reached with the recommended dose administered orally in HIV-infected children.⁶⁵

IV pentamidine isethionate (4 mg/kg body weight) once daily is recommended for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy (**AI***).^{62,66,67} No evidence exists for synergistic or additive effects on efficacy of these agents;⁶⁸ therefore, because of potential increased toxicity, their combined use is not recommended (**BIII**).⁶² In patients with clinical improvement after 7 to 10 days of IV therapy with pentamidine, an oral regimen (i.e., atovaquone [**BI**] or TMP/dapsone [**CIII**]) can be considered to complete a 21-day course.⁶²

Atovaquone is an alternative for treatment of mild to moderately severe PCP in adults (**BI**).^{39,63,69} The dosage for adolescents aged ≥ 13 years is 750 mg/dose (5 mL) administered orally twice daily with food.^{39,63,69-71} Therapeutic data are limited for children, but based on studies of prophylaxis, the primary dosage for children <3 months and >24 months to 12 years of age is 30 to 40 mg/kg body weight/dose administered orally once a day with food, and for children aged 2 to 24 months of age is a higher dose of 45 mg/kg body weight/dose once daily (**BI***).^{49,50} Based on adult studies that use twice-daily dosing, some experts also use an alternate dosing regimen for children <3 months and >24 months to age 12 years of 15 to 20 mg/kg body weight/dose administered orally twice daily with food, and for children aged 2 to 24 months, a dose of 22.5 mg/kg body weight/dose twice daily with food (**CIII**). Food increases the bioavailability of atovaquone approximately threefold compared with that achieved with the fasting state. Atovaquone concentration increases with co-

administration of fluconazole and prednisone and decreases with co-administration of acyclovir, opiates, cephalosporins, rifampin, and benzodiazepines. Some experts suggest desensitizing the patient to allow for use of TMP-SMX.

Dapsone/TMP is effective in treating mild-to-moderate PCP in adults (**BI**);⁷² data on toxicity and efficacy among children are limited. The dosage of dapsone for adolescents and adults is 100 mg (total dose)/dose orally once daily and TMP 5 mg/kg body weight/dose three times per day administered for 21 days. In children aged <13 years, a dapsone dosage of 2 mg/kg body weight/dose once daily is required to achieve therapeutic levels (**AI**).⁷³ The pediatric dose of TMP is 5 mg/kg body weight/day/dose three times per day. Dapsone is less effective than the combination.⁷⁴ Clindamycin/primaquine has been found to be effective in treating mild to moderate PCP in adults but can be considered as an alternative therapy for PCP in children despite lack of pediatric data. (**CIII**). Primaquine is contraindicated in patients with glucose-6-dehydrogenase deficiency because of the possibility of inducing hemolytic anemia. Dosing information for treating PCP is available only for adults. For patients who weigh >60 kg, clindamycin 600 mg IV every 6 hours for 10 days, then 300 to 450 mg orally every 6 hours to complete 21 days of treatment, is recommended. Primaquine is administered as 30 mg of base orally for 21 days. Dosing for children is based on use of these drugs for treating other infections; the usual pediatric dose of clindamycin for treating bacterial infection is 10 mg/kg body weight/dose every 6 hours, and the pediatric dose of primaquine equivalent to an adult dose of 20 mg base (when used for malaria) is 0.3 mg/kg body weight/day of the base.

On the basis of studies in both adults⁷⁵⁻⁷⁹ and children,⁸⁰ a short course of corticosteroids is recommended in cases of moderate or severe PCP, starting within 72 hours of diagnosis (**AI***). Pediatric studies have indicated reduced acute respiratory failure, decreased need for ventilation, and decreased mortality with early use of corticosteroids in HIV-infected children who have PCP.⁸⁰⁻⁸² Indications for corticosteroid treatment include a PaO₂ value of <70 mm Hg or an alveolar-arterial gradient of >35 mm Hg. Doses for children vary between studies. A commonly used scheme is prednisone 1 mg/kg of body weight/dose twice daily on days 1 through 5; 0.5 mg/kg/dose twice daily on days 6 through 10; and 0.5 mg/kg of body weight/dose once daily on days 11 through 21. Alternative regimens include:

1. Adult dosage of prednisone: 40 mg/dose twice daily on days 1 through 5; 40 mg/dose once daily on days 6 through 10; 20 mg/dose once daily on days 11 through 21, and
2. Methylprednisolone IV 1 mg/kg/dose every 6 hours on days 1 through 7; 1 mg/kg/dose twice daily on days 8 through 9; 0.5 mg/kg/dose twice daily on days 10 and 11; and 1 mg/kg/dose once daily on days 12–16.

Some case reports have documented improved pulmonary function with use of surfactant in cases of severe disease such as respiratory distress syndrome with established respiratory failure requiring ventilation.⁸³⁻⁸⁵ Alterations in surfactant function and composition have been demonstrated in HIV-infected adults with PCP.⁸⁶ Data are insufficient to recommend surfactant administration for PCP in children.

Monitoring and Adverse Events (Including IRIS)

Clinical parameters for monitoring disease status include temperature, respiratory rate, arterial oxygen saturation, and chest radiograph.⁸⁷ Clinical improvement can be expected at a mean of approximately 4.5 ± 2.5 days and radiographic improvement at approximately 7.7 ± 4.5 days.⁸⁷

Immune reconstitution inflammatory syndrome (IRIS) has been less frequently associated with *Pneumocystis* infection (2% of 44 adults with IRIS) than with several other OIs in HIV-infected adults and children.⁸⁸ Whether this low rate is related to PCP prophylaxis is unknown.

In children, adverse reactions to TMP-SMX include rash (mild maculopapular in most cases but rarely erythema multiforme and Stevens-Johnson syndrome [SJS]), hematologic abnormalities (e.g., neutropenia, thrombocytopenia, megaloblastic or aplastic anemia), GI complaints (usually mild), hepatitis, and renal disorders (e.g., interstitial nephritis).^{89,90} Data from a PACTG study of HIV-infected children at high risk of

PCP receiving TMP-SMX for a median of 3 years showed 28% had a rash, 9.3% had neutropenia, 8.8% had thrombocytopenia, and 2.2% had anemia.⁴⁹ None were fatal or irreversible reactions. Some very mild reactions will resolve while the drug is continued. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided. Based on adult randomized clinical trials, unless the reaction has been life-threatening, TMP-SMX prophylaxis can be resumed in children, preferably by beginning with low desensitizing daily doses and gradually increasing to therapeutic dosing (**CIII**).^{91,92} In adults, 75% of patients affected tolerated re-challenge with TMP-SMX.⁹² The overall frequency of adverse reactions appears to be lower in HIV-infected children than in adults; approximately 15% of children have substantial adverse reactions to TMP-SMX.⁵⁷ If an urticarial rash or SJS occurs, TMP-SMX should be discontinued and not re-administered (**AIII**).^{89,90,92}

The most common adverse drug reaction to pentamidine isethionate is renal toxicity, which usually occurs after 2 weeks of therapy and can be averted by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if infused rapidly), prolonged QT interval (torsades de pointes), and cardiac arrhythmias can occur. Hypoglycemia (usually after 5–7 days of therapy) or hyperglycemia, hypercalcemia, hyperkalemia, pancreatitis, and insulin-dependent diabetes mellitus also have been reported. Patients may report a metallic or bitter taste. Serious adverse reactions to pentamidine have been reported in approximately 17% of children receiving the drug.⁹³ This drug should not be administered with other nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, cisplatin, or vancomycin) or with agents associated with pancreatitis (e.g., didanosine).

With dapsone and TMP, the primary adverse reaction is reversible neutropenia; other reactions include skin rashes, elevated serum transaminases, methemoglobinemia, anemia, and thrombocytopenia.^{72,74} Dapsone is the problematic component of the combination and accounts for most of the adverse reactions.⁵⁰

Skin rashes (10%–15%), nausea, and diarrhea can occur with atovaquone administration. Liver enzymes may increase briefly. No serious toxicity or fatality has been demonstrated from use of atovaquone in adults or children.

Adverse reactions to clindamycin/primaquine include skin rash, nausea, and diarrhea.

Managing Treatment Failure

Occasionally an inflammatory reaction, thought to be due to antibiotic-induced killing of the organism in the lungs, can result in an initial early and reversible deterioration during the first 3 to 5 days of therapy, so an adequate trial of therapy is needed before switching drugs because of lack of clinical improvement. Clinical failure is defined by lack of improvement or worsening of respiratory function documented by arterial blood gases after at least 4 to 8 days of anti-PCP treatment. Other concomitant infections need to be excluded as causes of clinical failure. With evidence of treatment failure after the use of TMP-SMX, therapy can be changed. If tolerated, pentamidine isethionate is the drug of next choice (**AI***).^{94,95} No evidence exists for synergistic or additive therapeutic effects; therefore, because of potential increased toxicity, their combination is not recommended.

Preventing Recurrence

None of the drugs administered to treat and prevent PCP completely eliminates *Pneumocystis*, and prophylaxis is effective only while the selected drug is administered. Patients who have experienced an episode of PCP should remain on a prophylactic regimen after completion of treatment unless they meet criteria for discontinuing secondary prophylaxis (**AIII**).⁹⁵

Discontinuing Secondary Prophylaxis

In most patients, secondary prophylaxis can be discontinued using the same criteria as for discontinuing primary prophylaxis. PCP prophylaxis is not to be discontinued in HIV-infected infants aged <1 year. Children who present with clinical signs and symptoms compatible with PCP after discontinuation of

prophylaxis should be evaluated thoroughly despite normal or high CD4 counts or percentages (AIII).⁹⁶ If PCP recurs at a CD4 count ≥ 200 cells/mm³, lifelong prophylaxis should be administered (CIII).

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Dosing Recommendations for Prevention and Treatment of Pneumocystis Pneumonia (page 1 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
<p>Primary Prophylaxis</p>	<ul style="list-style-type: none"> • TMP-SMX (Cotrimoxazole): TMP 2.5–5 mg/kg body weight/dose with SMX 12.5–25 mg/kg body weight/dose twice per day. Dosing based on TMP component. • The total daily dose should not exceed 320 mg TMP and 1600 mg SMX. Several dosing schemes have been used successfully— <ul style="list-style-type: none"> • Given 3 days per week on consecutive days or on alternate days • Given 2 days per week on consecutive days or on alternate days • Given every day (total daily dose of TMP 5–10 mg/kg body weight given as a single dose each day) 	<p><u>Dapsone</u> <i>Children aged ≥1 months:</i></p> <ul style="list-style-type: none"> • 2 mg/kg body weight (maximum 100 mg) by mouth once daily or 4 mg/kg body weight (maximum 200 mg) by mouth once weekly <p><u>Atovaquone</u> <i>Children Aged 1–3 Months and >24 Months–12 Years:</i></p> <ul style="list-style-type: none"> • 30-40 mg/kg body weight/dose by mouth once daily with food <p><i>Children Aged 4–24 Months:</i></p> <ul style="list-style-type: none"> • 45 mg/kg body weight/dose by mouth once daily with food <p><i>Children Aged ≥13 Years:</i></p> <ul style="list-style-type: none"> • 1500 mg (10 cc oral yellow suspension) per dose by mouth once daily <p><u>Aerosolized Pentamidine</u> <i>Children Aged ≥5 Years:</i></p> <ul style="list-style-type: none"> • 300 mg every month via Respigard II™ nebulizer (manufactured by Marquest; Englewood, Colorado) 	<p><u>Primary Prophylaxis Indicated For:</u></p> <ul style="list-style-type: none"> • All HIV-infected or HIV-indeterminate infants from aged 4–6 weeks to 12 months regardless of CD4 cell count/percentage • HIV-infected children aged 1 to <6 years with CD4 count <500 cells/mm³ or CD4 percentage <15%; HIV-infected children aged 6–12 years with CD4 count <200 cells/mm³ or CD4 percentage <15% <p><u>Criteria for Discontinuing Primary Prophylaxis:</u></p> <p>Note: Do not discontinue in HIV-infected children aged <1 year</p> <p><i>After ≥6 Months of cART:</i></p> <ul style="list-style-type: none"> • Aged 1 to <6 years; CD4 percentage ≥15% or CD4 count is ≥500 cells/mm³ for >3 consecutive months, or • Aged ≥6 years, CD4 percentage ≥15% or CD4 count is ≥200 cells/mm³ for >3 consecutive months <p><u>Criteria for Restarting Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> • Aged 1 to < 6 years with CD4 percentage <15 or CD4 count <500 cells/mm³ • Aged ≥6 years with CD4 percentage <15% or CD4 count <200 cells/mm³
<p>Secondary Prophylaxis Prior PCP</p>	<p>Same as for primary prophylaxis.</p>	<p>Same as for primary prophylaxis.</p>	<p><u>Secondary Prophylaxis Indicated For:</u></p> <ul style="list-style-type: none"> • Children with prior episode of PCP <p><u>Criteria for Discontinuing Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> • Same as for primary prophylaxis <p><u>Criteria for Restarting Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> • Same as for primary prophylaxis

Dosing Recommendations for Prevention and Treatment of Pneumocystis Pneumonia (page 2 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	TMP-SMX 3.75–5 mg/kg body weight/dose TMP (based on TMP component) every 6 hours IV or orally given for 21 days (followed by secondary prophylaxis dosing)	<p><u>If TMP-SMX-Intolerant or Clinical Treatment Failure After 5–7 Days of TMP-SMX Therapy</u></p> <p><i>Pentamidine:</i></p> <ul style="list-style-type: none"> • 4 mg/kg body weight/dose IV/IM once daily is the first choice alternative regimen. <p>Note: Pentamidine can be changed to atovaquone after 7–10 days IV therapy.</p> <p><i>Atovaquone</i></p> <p><u>Daily Dosing:</u></p> <ul style="list-style-type: none"> • Children aged 1–3 months and >24 months–12 years: 30–40 mg/kg body weight/dose by mouth once daily with food • Children aged 4–24 months: 45 mg/kg body weight/dose by mouth once daily with food <p><u>Twice-Daily Dosing*:</u></p> <ul style="list-style-type: none"> • Children aged ≥13 years: 750 mg/dose by mouth twice daily 	<p>After acute pneumonitis resolved in mild-moderate disease, IV TMP-SMX can be changed to oral. For oral administration, total daily dose of TMP-SMX can also be administered in 3 divided doses (every 8 hours).</p> <p>Dapsone 2 mg/kg body weight by mouth once daily (maximum 100 mg/day) plus trimethoprim 5 mg/kg body weight by mouth every 8 hours has been used in adults but data in children are limited.</p> <p>Primaquine base 0.3 mg/kg body weight by mouth once daily (maximum 30 mg/day) plus clindamycin 10 mg/kg body weight/dose IV or by mouth (maximum 600 mg given IV and 300–450 mg given orally) every 6 hours has been used in adults, but data in children are not available.</p> <p><u>Indications for Corticosteroids:</u></p> <ul style="list-style-type: none"> • PaO₂ <70 mm Hg at room air or alveolar-arterial oxygen gradient >35 mm Hg <p><u>Prednisone Dose:</u></p> <ul style="list-style-type: none"> • 1 mg/kg body weight/dose by mouth twice daily for 5 days, then • 0.5–1 mg/kg body weight/dose by mouth twice daily for 5 days, then • 0.5 mg/kg body weight by mouth once daily for days 11 to 21. <p><u>Alternative Corticosteroid Regimens Include:</u></p> <ul style="list-style-type: none"> • Adult dosage of prednisone: 40 mg/dose twice daily on days 1–5, 40 mg/dose once daily on days 6–10, 20 mg/dose once daily on days 11–21, and • Methylprednisolone IV 1 mg/kg/dose every 6 hours on days 1–7, 1 mg/kg/dose twice daily on days 8–9, 0.5 mg/kg/dose twice daily on days 10 and 11, and 1 mg/kg/dose once daily on days 12–16. <p>Chronic suppressive therapy (secondary prophylaxis) with TMP/SMX is recommended in children and adults following initial therapy (see Secondary Prophylaxis).</p>

*Some experts use twice-daily dosing of atovaquone as alternative treatment for PCP in children aged <12 years:

- Children aged 1–3 months and >24 months to 12 years: 15–20 mg/kg body weight/dose by mouth twice daily with food
- Children aged 4–24 months: 22.5 mg/kg body weight/dose by mouth twice daily with food.

Key to Acronyms: cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte cell; IM = intramuscular; IV = intravenous; PCP = *Pneumocystis jirovecii* pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole

Note: Information included in these guidelines might not represent Food and Drug Administration (FDA) approval or approved labeling for products or indications. Specifically, the terms safe and effective might not be synonymous with the FDA-defined legal standards for product approval.