Pneumocystis Pneumonia

Updated: December 22, 2025
Reviewed: December 22, 2025

Panel's Recommendations

Prevention of Primary Exposure

- At-risk immunocompromised patients should not share a room with a patient who has known *Pneumocystis* pneumonia (PCP) or an undiagnosed respiratory tract infection (**strong**, **low**).

Primary Prophylaxis

- PCP prophylaxis is recommended for all children with HIV with stage 3 CD4 T lymphocyte (CD4) cell count (**strong**, **moderate**):
  - Aged ≥6 years: CD4 count <200 cells/mm^3 or CD4 percentage <14% if CD4 count is unavailable
  - Aged 1 year to <6 years: CD4 counts <500 cells/mm^3 or CD4 percentages <22% if CD4 count is unavailable
- For infants, PCP prophylaxis is recommended beginning at age 4–6 weeks and continuing until age 12 months, regardless of CD4 count or percentage (**moderate**, **low**). At age 12 months, infants should be reassessed based on the CD4 count or percentage thresholds above (**moderate**, **low**).
- PCP prophylaxis should also be considered in infants with perinatal HIV exposure if HIV infection cannot be presumptively excluded by 4–6 weeks of age (**strong**, **low**). Prophylaxis should be continued until HIV infection can be presumptively excluded.
- HIV infection may be presumptively excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥2 weeks and one at age ≥4 weeks) or one negative virologic test at age ≥8 weeks at least 2 weeks after discontinuing multidrug antiretroviral (ARV) prophylaxis/presumptive therapy. In breastfed infants of individuals on antiretroviral therapy (ART) with sustained viral suppression and ongoing close monitoring, the risk of postnatal HIV transmission is extremely low (<1%). In this context, the benefits of trimethoprim-sulfamethoxazole (TMP-SMX; cotrimoxazole) are unlikely to outweigh its risks, and most experts would not administer PCP prophylaxis for breastfed infants otherwise meeting the above criteria for negative virologic testing.
- TMP-SMX administered daily or 3 days/week (either consecutively or on alternating days [e.g., Monday, Wednesday, Friday]), is the drug of choice for PCP prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum (**strong**, **high**).
- For children with HIV who are unable to take TMP-SMX, atovaquone (**strong**, **high**) or dapsone (**strong**, **moderate**) is recommended.
- Intravenous (IV) or aerosolized (for children old enough to use Respirgard II nebulizer) pentamidine administered monthly can be used for children unable to take TMP-SMX, atovaquone, or dapsone (**strong**, **moderate**). Of note, atypical systemic presentations of PCP can occur in children on aerosolized pentamidine.

Discontinuing Primary Prophylaxis

- Discontinuation of PCP prophylaxis is recommended for children with HIV who have received stable ART for ≥6 months and meet the following age-specific criteria for >3 consecutive months (**strong**, **moderate**):
  - Aged ≥6 years: CD4 count ≥200 cells/mm^3, or CD4 percentage ≥14% if CD4 count unavailable
  - Aged 1 to <6 years: CD4 count ≥500 cells/mm^3, or CD4 percentage ≥22% if CD4 count unavailable
- Discontinuation of PCP prophylaxis can be considered in patients aged ≥6 years who have had an undetectable viral load for >6 months with a CD4 count 101 to 200 cells/mm^3 and are intolerant of prophylaxis medications (**weak**, **low**).

Panel's Recommendations
• CD4 count and CD4 percentage should be reevaluated every 3–4 months until stabilized, and according to HIV treatment guidelines thereafter. Prophylaxis should be reinstituted if the age-specific criteria for prophylaxis are reached (strong, low). Treatment • IV TMP-SMX is the recommended initial treatment for PCP (strong, high). o As the acute pneumonitis subsides, children with mild-to-moderate PCP 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 (strong, low). • IV pentamidine isethionate once daily is recommended for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5–7 days of TMP-SMX therapy (strong, moderate). Daily IV pentamidine is associated with significant adverse effects (such as renal dysfunction and electrolyte and glucose abnormalities) and requires close monitoring. Allergy consultation and desensitization to TMP-SMX when appropriate should be attempted prior to initiating IV pentamidine. Atovaquone is a suitable alternative for patients with mild-to-moderate PCP (weak, low). • Ideally starting within 72 hours of diagnosis, a 21-day tapering course of corticosteroids is recommended in cases of moderate-to-severe PCP (defined as PaO_2 <70 or alveolar-arterial gradient ≥35 mmHg) (strong, moderate). Secondary Prophylaxis • Children with HIV who have experienced an episode of PCP should continue PCP prophylaxis after completion of treatment until their CD4 counts exceed the threshold for initiating prophylaxis, using criteria described for discontinuation of primary prophylaxis (strong, high). • Children who present with clinical signs and symptoms compatible with PCP after discontinuation of prophylaxis should be evaluated thoroughly despite having normal or high CD4 counts or percentages (strong, moderate).
Rating System *Strength of Recommendation:* Strong; Weak *Quality of Evidence:* High; Moderate; Low; Very Low

Epidemiology

Pneumocystis spp. are found worldwide in the lungs of humans and other animals. The organisms are host-specific, and cross-infection between humans and other species does not occur. *Pneumocystis* spp. from all sources are 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 taxonomy have occurred, including a designation of *P. carinii* exclusively for rat-specific species and *Pneumocystis jirovecii* for human-specific species. *Pneumocystis* has been designated a fungus based on DNA analysis, but it has several biologic features of protozoa. Most humans are infected with *Pneumocystis* early in life. Most children acquire *Pneumocystis* antibodies by age 13, and in some cases, the rate reaches as high as 85% among children aged ≤2 years.[1-3] Immunocompetent infants with the infection are either asymptomatic or have mild respiratory symptoms. *Pneumocystis* pneumonia (PCP) occurs almost exclusively in the immunocompromised host.

Data from the Centers for Disease Control and Prevention Pediatric Spectrum of Disease Project (1994–2001) indicated a decline in PCP rates (cases per 1,000 children with HIV) from 25 in 1994 to <10 in 2001.[4] This decline probably resulted from the introduction of antiretroviral therapy (ART) in

children with HIV in 1995, as well as chemoprophylaxis for PCP. An analysis of PCP-related diagnostic codes from the Kids' Inpatient Database (abbreviated as KID) similarly showed a 65% decrease in the rate of pediatric PCP from 1997 to 2012, with most of the decline seen in children with HIV and stable rates of PCP among children with other immunocompromising conditions.[5] However, PCP remains an important AIDS-indicator disease among children with HIV. For instance, it was the top AIDS-indicator disease in children with perinatally acquired HIV through 2009 in the Ukraine European Collaborative Study Group, 44% of whom had started ART at a median of age 18 months.[6] The Pneumonia Etiology Research for Child Health (PERCH) study also identified *P. jirovecii* as the most common etiology of pneumonia in South African and Zambian children with HIV younger than 5 years of age from 2011 to 2013.[7,8] The highest incidence of PCP in children is in the first year of life, with the number of cases peaking at ages 3 to 6 months.[9-11] PCP is a major cause of death among infants and children with HIV in low- and middle-income countries. Autopsies done in Africa revealed PCP in 16% of children who died with HIV or AIDS during 1992 and 1993,[12] and in 44% of those who died during 2000 and 2001.[13] A 2024 meta-analysis that included 11 worldwide studies on patients of all ages with HIV found a 52% higher mortality rate among patients with PCP than those without PCP diagnosed (odds ratio 1.522, 95% confidence interval [CI] 0.959–2.416).[14]

The mode of transmission of *Pneumocystis* among infants, children, and adults with HIV is not firmly established, but airborne human-to-human transmission is likely. Animal studies show *Pneumocystis* is transmitted by air from infected rats to susceptible rats[15,16] and from immunocompetent mice with subclinical infection to immunocompromised mice.[17] Human-to-human transmission has been suggested by molecular epidemiology and global clustering of PCP cases.[18-20]

The primary determinant of susceptibility to PCP in patients with HIV, regardless of age, is cell-mediated immunity status. Severe immunocompromise, 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. These guidelines apply only to PCP prevention and treatment in children with HIV. The risk factors for developing PCP are less clear in other states of immunodeficiency, and therefore the criteria for implementing prophylaxis and considering infection do not necessarily apply to other patient groups.

Clinical Manifestations

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

In children with HIV hospitalized with pneumonia, four clinical variables are independently associated with PCP: age <6 months, respiratory rate >59 breaths per minute, hypoxia (arterial percentage hemoglobin saturation ≤92%), and absence of vomiting.[21] A high plasma HIV RNA concentration strongly predicts PCP and other opportunistic infections.[22]

Extrapulmonary *Pneumocystis* organisms, often associated with a localized inflammatory reaction, are found in <2.5% of adults and children with HIV.[23,24] Extrapulmonary pneumocystosis can occur without concurrent PCP and can be located at multiple noncontiguous sites. Involved sites have included the ear, eye, thyroid, spleen, gastrointestinal (GI) tract, peritoneum, liver, and pancreas.

Less frequently involved sites include the 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 (PaO_2 typically <70 mmHg) and an alveolar-arterial gradient >30 mmHg. CD4 percentages are often <14% and CD4 counts are usually <200 cells/mm^3 in children aged 6 years and older. Lactate dehydrogenase is often increased, but this finding is not specific to 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 are observed, as well as occurrences of pneumothorax or pneumomediastinum. Coinfection with other organisms, such as cytomegalovirus or pneumococcus, has been reported in children with HIV.[11,25,26] Children with dual infections may have more severe disease.

A definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids in the presence of pneumonitis. Diagnostic procedures for suspected PCP are the same for children as for adults (see the *Pneumocystis* Pneumonia section of the Adult and Adolescent Opportunistic Infection Guidelines), but some procedures may be more difficult to perform in children. Optimal specimens for diagnosis of PCP should be obtained from the bronchial tree and include bronchoalveolar lavage fluid, tissue from transbronchial or open lung biopsy, or induced sputum. Induced sputum analysis, however, has reduced sensitivity and may be difficult in children aged <2 years because of their small airways and poor ability to produce sputum. Additional specimens, such as non-induced sputum, oral secretions, or nasogastric aspirates, can be helpful if positive but have significantly lower sensitivity and should not be used to exclude the diagnosis.[27]

Various stains can be used to identify *Pneumocystis* organisms in specimens. Gomori methenamine-silver and toluidine blue stain the cyst wall. Giemsa, Diff-Quick, and Wright stains depict the trophozoites and intracystic sporozoites but do not stain the cyst wall. Direct immunofluorescent staining should be used in conjunction with stains to detect cysts and trophozoites.[28,29]

Demonstration of the organism by polymerase chain reaction (PCR) is being used more frequently to diagnosis PCP. It is widely available at many major medical centers, generally considered to be more sensitive than staining methods and requires, less expertise. However, its high sensitivity makes PCR more likely to detect colonization than traditional staining methods. The significance of colonization has yet to be determined. The utility of quantitative PCR in monitoring treatment response has not been established.[28,29]

Several serologic biomarkers have been evaluated as adjunctive non-invasive testing strategies for diagnosing PCP in adults with HIV with pulmonary symptoms, including (1→3)-beta-d-glucan (BG), lactate dehydrogenase, procalcitonin, S-adenosyl methionine, and Krebs von den Lungen-6 antigen (KL-6). BG has a high sensitivity (above 90%) in adults with HIV. However, BG and the other biomarkers listed are nonspecific and are also elevated in the presence of other fungal infections and medications. Combined BG and KL-6 testing had the highest accuracy, with sensitivity and specificity approaching 95% and 90%, respectively, in one European study.[30-32] Mildly elevated serum BG levels have also been detected in a case series of immunocompetent

infants suspected of having primary *Pneumocystis* infection, as well as in several children with PCP and underlying hematologic malignancies.[33,34]

Prevention Recommendations

Preventing Exposure

Clinical data upon which to make a decision regarding isolation of patients with PCP are limited. However, animal model experiments suggest that transmission occurs easily,[35] and the organism has been detected in the air around patients with PCP.[36] Additionally, a study in France and Switzerland identified person-to-person transmission of PCP as the cause for increased rates of trimethoprim-sulfamethoxazole (TMP-SMX) resistant strains.[37] Furthermore, molecular analyses of PCP case clusters in solid organ and hematopoietic stem cell transplant recipients reveal that human-to-human transmission has occurred in nosocomial outbreak settings.[38-43] Immunocompromised patients who are adherent with PCP prophylaxis, especially with TMP-SMX, are unlikely to acquire PCP. However, providers should avoid placing at-risk patients in a room with another patient with PCP or an undiagnosed respiratory tract infection **(strong, low).** 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. This is especially true of respiratory illnesses occurring during the first 2 years of life, in which up to 85% of children acquire 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.[44] Prophylaxis is recommended for all children with HIV meeting stage 3 classification by CD4 counts (or by CD4 percentages, if counts are not available). This includes children aged ≥6 years with CD4 counts <200 cells/mm^3 or CD4 percentage <14%, and children aged 1 years to <6 years with CD4 counts <500 cells/mm^3 or CD4 percentage <22% **(strong, moderate).** PCP chemoprophylaxis is also recommended for all infants with HIV beginning at age 4 to 6 weeks of age and continuing until 12 months of age regardless of CD4 count or percentage **(moderate, low).** CD4 cell counts can decrease rapidly in infants with HIV and may not be a useful marker to determine PCP susceptibility in the first year of life.[45] These data were obtained during a time when perinatal transmission was high and combination ART was not available. A recent observational study (IMPAACT P1115) now indicates that infants started on very early ART can maintain high CD4 counts throughout infancy; however, more studies are needed to validate the low risk of PCP in infants who receive early ART.[46]

PCP remains a top AIDS-defining illness in infants and children with perinatally-acquired HIV worldwide. It has a peak incidence during the first year of life with a marked increase starting around 2 months of age. Initial guidelines recommended initiating PCP prophylaxis in perinatally-exposed infants based on CD4 count threshold. CD4 T lymphocytes, however, can decrease rapidly in infants with HIV, making it impractical to monitor closely enough to start prophylaxis in time.[45] Young infants with poorly controlled HIV can also be at risk for PCP regardless of CD4 count. In a study conducted from 1991 to 1993, 18% of children aged less than 12 months in the United States did not receive diagnostic testing.[45]

PCP prophylaxis should be considered in infants with perinatal HIV exposure regardless of CD4 count or percentage if HIV infection cannot be presumptively excluded by 4 to 6 weeks of age **(strong, low).** Prophylaxis should be continued until HIV infection can be presumptively excluded.

Most infants born in the United States who are exposed to HIV will have HIV infection presumptively excluded by this time if current virologic assay diagnostic testing recommendations are followed. HIV infection may be presumptively excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥2 weeks and one at age ≥4 weeks) or one negative virologic test at age ≥8 weeks at least 2 weeks after discontinuing multidrug ARV prophylaxis/presumptive therapy. In infants breastfed by mothers on ART with sustained viral suppression and ongoing close monitoring, the risk of postnatal HIV transmission is extremely low (<1%). In this context, the benefits of TMP-SMX are unlikely to outweigh its risks, and most experts would not administer PCP prophylaxis for breastfed infants otherwise meeting the above criteria for negative virologic testing. Infants with HIV should be administered prophylaxis until age 1 year, at which time they should be reassessed based on the age-specific CD4 count or percentage thresholds mentioned above **(moderate, low).**

The Preventing HIV Transmission During Infant Feeding section of the Pediatric Antiretroviral Guidelines reviews evidence supporting the low risk of postnatal HIV transmission during breastfeeding with sustained viral suppression and recommendation to discontinue breastfeeding when HIV RNA is ≥200 copies/mL. There is no consensus regarding the management of infants who are breastfed, despite persistent maternal viremia due to lack of strong evidence base. Some experts would initiate presumptive HIV therapy for these infants and consider initiating PCP prophylaxis, particularly in the absence of close monitoring.

TMP-SMX (cotrimoxazole) is the drug of choice for PCP prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum **(strong, high).**[47-49] TMP alone has little, if any, anti-*Pneumocystis* activity, but it enhances the activity of the sulfonamide (SMX). The prophylactic dosage of TMP-SMX is calculated based on the trimethoprim (TMP) component: TMP 5 to 10 mg/kg body weight per day (maximum dose: 320 mg) or TMP 150 mg/m^2 body surface area per day (maximum dose: 1,600 mg). TMP-SMX is administered orally as either (1) a single daily dose[50] or (2) divided every 12 hours on 3 consecutive days per week[51] or on alternate days (e.g., Monday, Wednesday, Friday). Alternative dosing schedules, such as twice weekly[52-54] or once weekly,[55] have been used successfully in pediatric oncology patients at risk for PCP. In patients with impaired renal function, a reduced dose may be necessary. The use of TMP-SMX in infants younger than 2 months and premature infants is limited due to the risk of bilirubin displacement. Although TMP-SMX may be considered for short-duration treatment courses while closely monitoring bilirubin levels, this is impractical for indefinite prophylaxis periods. The potential benefits of use in this patient population must be carefully weighed against the potential risk of kernicterus, as well as the feasibility of close laboratory monitoring. TMP-SMX, preferably given daily, is also effective in preventing toxoplasmosis[56] and some bacterial infections (e.g., *Salmonella*, *Haemophilus*, *Staphylococcus*).[50,57-59]

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.[60] 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.[61,62]

Other effective and safe PCP prophylaxis regimens are available for patients unable to take TMP-SMX. However, many patients can safely resume TMP-SMX after resolution of a mild reaction. See

the Monitoring and Adverse Events section for further details and potential adverse reactions to the alternative agents discussed below.

Recommended alternatives include atovaquone[63] **(strong, high)** or dapsone[48] **(strong, moderate).** Atovaquone, formulated as a yellow oral suspension, is administered with food as a single daily dose.[48,49] Dapsone can be administered orally on a daily or weekly schedule.[64] In patients with HIV who cannot tolerate trimethoprim and/or sulfonamides, atovaquone and dapsone were similarly effective.[48] However, atovaquone is a more expensive alternative; dapsone is inexpensive but associated with more serious adverse effects than atovaquone. Additionally, unlike TMP-SMX and dapsone, atovaquone has no antibacterial activity but is effective against *Toxoplasma gondii*. Approximately two-thirds of patients intolerant to TMP-SMX can take dapsone successfully. Studies in adults show dapsone is as effective as atovaquone or monthly aerosolized pentamidine but slightly less effective than TMP-SMX.[48,65] Children should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency before starting dapsone to avoid a potential hemolytic reaction.

Intravenous (IV) or aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone **(strong, moderate).** It has the benefit of monthly administration but carries logistical consideration. IV pentamidine given monthly has been effective in preventing PCP in four retrospective cohorts of pediatric oncology patients. The initial concern regarding its effectiveness in children ages <2 years has been addressed in three subsequent studies.[66-69] If aerosolized pentamidine is considered, children must be developmentally capable of demonstrating proper inhalation technique and maintaining a tight seal on the mouthpiece to effectively use the Respirgard II nebulizer.[44] Dosing in young children (age up to 5 years) is not well established, and compliance with the nebulizer can be difficult.[70,71] Care should be taken to limit health care personnel exposure to the nebulized medication. Atypical systemic presentations of PCP can occur in children on aerosolized pentamidine.

Discontinuing Primary Prophylaxis

Studies of adults and children with HIV following immune reconstitution after receipt of ART demonstrate acceptably low risks for PCP after discontinuation of prophylaxis.[72-77] The Pediatric AIDS Clinical Trials Group (PACTG) 1008 study enrolled 235 children and adolescents with HIV on antiretroviral therapy who received PCP prophylaxis for ≥6 months. Age-specific CD4 percentage criteria for enrollment were ≥20% for participants over age 6 years and ≥25% for those aged 2 to 6 years. PCP prophylaxis was discontinued at study entry.[72] 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 discontinuing prophylaxis in children who have achieved immune reconstitution. A single randomized controlled trial (RCT) and several prospective cohort studies in adults with HIV receiving ART demonstrated that PCP prophylaxis can be safely discontinued—with a breakthrough infection rate of 1.57 per 1,000 person-years—if plasma HIV RNA remains undetectable for at least 6 months, even in the absence of full immune reconstitution. This approach, however, has not yet been demonstrated in children with HIV.[78-82] Discontinuation of PCP prophylaxis is recommended for children with HIV who have received stable ART for ≥6 months and meet the following age-specific criteria for >3 consecutive months **(strong, moderate)**:

- Aged ≥6 years: CD4 count ≥200 cells/mm^3, or CD4 percentage ≥14% if count unavailable
- Aged 1 to <6 years: CD4 count ≥500 cells/mm^3, or CD4 percentage ≥22% if count unavailable

Discontinuation of PCP prophylaxis can be considered in children aged ≥6 years who have had undetectable viral load for >6 months with CD4 count 101 to 200 cells/mm^3 and are intolerant of prophylaxis medications **(weak, low).** CD4 percentage and CD4 count should be reevaluated every 3 to 4 months until stabilized, and according to HIV treatment guidelines thereafter. Prophylaxis should be reinstituted if the age-specific criteria for prophylaxis are reached **(strong, low).**

PCP prophylaxis should not be discontinued in infants with HIV aged <1 year despite immune reconstitution. Studies conducted prior to the availability of combination ART demonstrated that CD4 cell counts may not be a useful marker of PCP susceptibility in these infants, and more evidence is needed among infants who receive early ART to determine if PCP prophylaxis can be safely discontinued in the first year of life.[45,46]

Treatment Recommendations

Treating Disease

Intravenous TMP-SMX is the recommended treatment for PCP in children with HIV **(strong, high).** Although it has not been studied prospectively in children with HIV, studies from animal models and children with cancer indicate that TMP-SMX and pentamidine have equivalent microbiologic effects. However, the toxicities associated with pentamidine make TMP-SMX the preferred treatment.[47,83,84] Effective therapeutic trimethoprim serum concentrations of 5 to 10 µg/mL can be reached with the recommended dose administered orally in children with HIV.[85] As the acute pneumonitis subsides, children with mild-to-moderate PCP 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 **(strong, low).**

Adverse reactions to TMP-SMX are less frequent in children than in adults, and continuation of TMP-SMX is preferred when possible. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided, and allergy consultation for TMP-SMX desensitization in the case of hypersensitivity reactions is recommended. TMP-SMX should be stopped permanently following a life-threatening reaction and listed as an allergy in the patient electronic medical record. See the Monitoring and Adverse Events section for further details and potential adverse reactions to the alternative agents discussed below.

Intravenous pentamidine isethionate once daily is recommended for patients with severe PCP who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5 to 7 days of TMP-SMX therapy **(strong, moderate).** Atovaquone can be used for treatment of mild-to-moderate PCP in patients unable to take TMP-SMX and for whom IV pentamidine is not tolerated or impractical to administer **(weak, low).**[86-89]

Daily intravenous pentamidine is associated with significant adverse effects, including renal dysfunction and electrolyte and glucose abnormalities, and therefore requires close monitoring of electrolytes and kidney function. Allergy consultation and desensitization to TMP-SMX, when appropriate, should be attempted prior to initiating intravenous pentamidine. Combining TMP-SMX with intravenous pentamidine is not recommended, as there is no evidence of enhanced efficacy from the combination, and it may increase the risk of toxicity.[71,77] In patients with clinical improvement after 7 to 10 days of IV therapy with pentamidine, experts consider it reasonable to transition to an oral regimen (i.e., atovaquone alone) to complete a 21-day course of therapy.

Atovaquone, dapsone in combination with trimethoprim, or clindamycin in combination with primaquine can be considered for treating mild-to-moderate PCP in patients unable to take TMP-SMX or pentamidine, but data on their use in children are lacking **(weak, low).** Atovaquone is an alternative for treatment of mild-to-moderate PCP in adults.[48,83,90] Dosing is age-dependent (see the Dosing Recommendations table). The bioavailability of atovaquone is approximately three times greater when taken with food than without food. Coadministration of atovaquone and rifampin is not recommended; atovaquone may increase the serum concentration of rifampin, and rifampin may decrease atovaquone concentration. Coadministration with rifabutin should also be avoided and both drug concentrations may decrease.

Dapsone in combination with trimethoprim is effective in treating mild-to-moderate PCP in adults.[91] Data on the combination's toxicity and efficacy among children are limited. Dapsone alone is less effective than the combination.[92] Clindamycin combination with primaquine has been found to be effective in treating mild-to-moderate PCP in adults. Both combinations can be considered as an alternative therapy for PCP in children despite lack of pediatric data. Primaquine is contraindicated in patients with G6PD deficiency because of the possibility of inducing hemolytic anemia. Dosing information for treating PCP is available only for adults. Dosing for children is based on use of these drugs for treating other infections.

On the basis of studies in both adults[93-99] and children,[100,101] a 21-day tapering course of corticosteroids is recommended in cases of moderate-to-severe PCP, generally defined as a PaO_2 value of <70 mmHg or an alveolar-arterial gradient of ≥35 mmHg **(strong, moderate).** If used, corticosteroids should be ideally started within 72 hours of diagnosis, as data are limited regarding benefit of steroids beyond this timepoint. A 2015 Cochrane review identified six high-quality RCTs evaluating the use of adjunctive corticosteroid treatment in PCP, including one study conducted in infants. This meta-analysis found that, among adults receiving ART, it would take at least 23 patients receiving adjunctive corticosteroid treatment to prevent one death from PCP. Additionally, patients who received corticosteroids had a relative risk of death of 0.59 (95% CI, 0.41–0.85) at 3 to 4 months after acquiring PCP. The randomized placebo-controlled trial of moderate quality that included 100 infants exposed to HIV in South Africa with clinical suspicion of PCP demonstrated a nonsignificant trend toward improved survival with adjunctive corticosteroid use.[101] Retrospective pediatric reviews and case series have indicated reduced acute respiratory failure, decreased need for ventilation, and decreased mortality with early use of corticosteroids in children with HIV who have PCP.[100,102,103] Corticosteroid doses for children varied between studies.

Some case reports have documented improved pulmonary function following surfactant administration in cases of severe disease such as respiratory distress syndrome with established respiratory failure requiring mechanical ventilation.[104-106] Alterations in surfactant function and composition have been demonstrated in adults with HIV and PCP.[107] 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.[108] Clinical improvement is observed at approximately 4.5 ± 2.5 days after initiation of treatment whereas radiographic improvement is not seen until approximately 7.7 ± 4.5 days.[108] Adverse events during treatment of *Pneumocystis* infection may occur as a result of immune reconstitution inflammatory syndrome (IRIS) or as adverse reactions to *Pneumocystis* treatment medications. IRIS is an antigen-driven inflammatory response secondary to

reconstitution of the immune system that can occur in response to ART initiation during an active infection. *Pneumocystis* infection is an infrequent cause of IRIS (1/44 [2.3%] of adults with IRIS) in adults and children with HIV.[109] Symptoms can mimic or worsen that of the initial infection with fever, cough, shortness of breath, and worsening radiographic findings. 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).[110,111] The overall frequency of adverse reactions appears to be lower in children with HIV than in adults; approximately 15% of children have substantial adverse reactions to TMP-SMX.[74] Data from a PACTG study of children with HIV 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.[63] None were fatal or irreversible reactions. Some very mild reactions will resolve without stopping the medication, and continuing treatment is preferred when safe to do so. With any significant adverse effect, TMP-SMX should be withheld until the reaction has subsided. On the basis of adult randomized clinical trials, unless the reaction has been life-threatening (e.g. SJS), TMP-SMX can be resumed in children after the reaction has resolved, preferably by beginning with low desensitizing daily doses and gradually increasing to therapeutic dosing.[112,113] In adults, 75% of patients affected tolerated re-challenge with TMP-SMX.[113] If a life-threatening reaction such as SJS occurs, TMP-SMX should be discontinued and not readministered.[110,111,113] See sections above for alternative prophylaxis and treatment options.

The most common adverse drug reaction to pentamidine isethionate is renal toxicity, which usually occurs after 2 weeks of therapy and can be avoided by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if the drug is 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 for PCP treatment.[114] This medication should not be administered with other nephrotoxic medications (e.g., aminoglycosides, amphotericin B, cisplatin, or vancomycin) or with agents associated with pancreatitis.

With dapsone and TMP, the primary adverse reaction is reversible neutropenia; other reactions include skin rashes, elevated serum transaminases, methemoglobinemia, anemia, and thrombocytopenia.[91,92] Dapsone is the problematic component of the combination and accounts for most of the adverse reactions.[65] Skin rashes (10% to 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, during the first 3 to 5 days of antibiotic therapy, a temporary worsening of symptoms may occur due to an inflammatory reaction caused by the antibiotic-induced killing of bacteria in the lungs. Therefore, an adequate trial of therapy is needed before switching medications due to 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.[115,116] Combining TMP-SMX with intravenous pentamidine is not recommended, as there is no evidence of enhanced efficacy from the combination and it may increase the risk of toxicity.[71,77]

Preventing Recurrence

None of the medications administered to treat and prevent PCP completely eliminate *Pneumocystis*, and prophylaxis is effective only while the selected medication is administered. Children with HIV who have experienced an episode of PCP should continue secondary PCP prophylaxis after completing treatment until CD4 counts exceed the threshold for initiating prophylaxis. The same criteria used for discontinuing primary prophylaxis apply **(strong, high).**[116]

Cases of PCP have been observed after secondary prophylaxis discontinuation in adults with HIV despite evidence of adequate immune reconstitution. Children who present with clinical signs and symptoms compatible with PCP after discontinuing prophylaxis should be evaluated thoroughly despite having normal or high CD4 counts or percentages **(strong, moderate).**[117] If PCP recurs at a CD4 count ≥200 cells/mm^3, lifelong prophylaxis should be considered. PCP prophylaxis is not to be discontinued in infants with HIV aged <1 year **(moderate, low).**

Dosing Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	• TMP-SMX: 5–10 mg/kg/DAY (TMP-component) • Maximum individual dose: 160 mg/DOSE TMP-component. Several dosing regimens have been used successfully: o 3 days per week on consecutive or alternate days in divided doses every 12 hours o Daily as a single dose o Administration 2 days per week on consecutive or alternate days in doses divided every 12 hours has been used successfully in pediatric oncology patients.	Dapsone and atovaquone are both first-line alternatives (see text for relative risks and benefits), followed by aerosolized pentamidine as second line and IV pentamidine as third line. Dapsone • *Children Aged ≥1 Month:* 2 mg/kg/dose (maximum: 100 mg/dose) PO once daily or 4 mg/kg/dose (maximum 200 mg/dose) PO once weekly Atovaquone • *Children Aged 1–3 Months or >24 Months–12 Years:* 30–40 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged 4–24 Months:* 45 mg/kg/dose PO once daily with food (maximum: 1,500 mg/dose) • *Children Aged ≥13 Years:* 1,500 mg PO once daily Aerosolized Pentamidine Via Respirgard II Nebulizer *For Children Able to Comply With Its Use* • *Children Aged <5 Years:* Limited data regarding dosing. 9 mg/kg/dose or 150 mg/dose every month have been suggested. • *Children Aged ≥5 Years:* 300 mg every month IV Pentamidine • 4 mg/kg/dose every 3 to 4 weeks; maximum dose: 300mg/dose • Limited data regarding dosing frequency; based on use in oncology patients	Primary Prophylaxis Indicated for: • All infants with HIV or in whom HIV infection cannot be presumptively excluded beginning from age 4–6 weeks to 12 months, regardless of CD4 count or percentage • Children with stage 3 CD4 count: o *Children Aged 1 Year to <6 Years:* <500 cells/mm^3 or <22% o *Children Aged ≥6 Years:* <200 cells/mm^3 or <14% Criteria for Discontinuing Primary Prophylaxis • *Children Aged <1 Year:* Continue primary prophylaxis in children with HIV throughout the first year of life • Children Aged 1 year and older on ART for ≥6 months with CD4 count above age-specific stage 3 cutoff for >3 consecutive months: o *Children Aged 1 Year to <6 Years:* ≥500 cells/mm^3 *or* ≥22% o *Children Aged ≥6 Years:* ≥200 cells/mm^3 or ≥14% • Discontinuation can be considered in children ≥6 Years if on ART for ≥6 months with undetectable viral load and CD4 count 101–200 cells/mm^3 if intolerant of prophylaxis medications Criteria for Restarting Primary Prophylaxis • CD4 count below age-specific stage 3 cutoff

Dosing Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia

Indication	First Choice	Alternative	Comments/Special Issues
Secondary Prophylaxis Prior PCP	Same as for primary prophylaxis.	Same as for primary prophylaxis.	Secondary Prophylaxis Indicated for: • Children with prior episode of PCP Criteria for Discontinuing Secondary Prophylaxis • Same as for primary prophylaxis Criteria for Restarting Secondary Prophylaxis • Same as for primary prophylaxis
Treatment	TMP-SMX 15–20 mg/kg/day (TMP-component) in divided doses every 6–8 hours IV or PO for 21 days (followed by secondary prophylaxis dosing)	If TMP-SMX-Intolerant or Clinical Treatment Failure After 5–7 Days of TMP-SMX Therapy *Pentamidine* • 4 mg/kg/dose IV/IM once daily is the first-choice alternative regimen for severe disease. • Note: Close electrolyte and glucose monitoring required. Pentamidine can be changed to atovaquone after 7–10 days IV therapy. Atovaquone can be considered for initial therapy in mild-to-moderate disease. *Atovaquone* • Daily Dosing o *Children Aged 1–3 Months and >24 Months to 12 Years:* 30–40 mg/kg/dose PO once daily with food o *Children Aged 4–24 Months:* 45 mg/kg/dose PO once daily with food • Twice-Daily Dosing o *Children Aged ≥13 Years:* 750 mg/dose PO twice daily o Some experts use twice-daily dosing of atovaquone as alternative treatment for PCP in children aged <12 years.	After acute pneumonitis resolved in mild-to-moderate PCP, IV TMP-SMX can be transitioned to oral formulations. For oral administration, total daily dose of TMP-SMX can also be administered in three divided doses (every 8 hours). The following regimens have been used in adults, but data in children are limited: • Dapsone 2 mg/kg/dose PO once daily (maximum 100 mg/day) plus trimethoprim 5 mg/kg/dose PO every 8 hours • Primaquine base 0.3 mg/kg/dose PO once daily (maximum 30 mg/day) plus clindamycin 10mg/kg/dose IV or PO (maximum 600 mg/dose given IV and 300–450 mg/dose given orally) every 6 hours Chronic suppressive therapy (secondary prophylaxis) with TMP-SMX is recommended in children and adults following initial therapy (see Secondary Prophylaxis). Corticosteroids Adjunctive Therapy *Indication* • PaO_2 <70 mmHg at room air or alveolar-arterial oxygen gradient ≥35 mmHg

Dosing Recommendations for Prevention and Treatment of *Pneumocystis* Pneumonia

Indication	First Choice	Alternative	Comments/Special Issues
		▪ *Children Aged 1–3 Months and >24 Months to 12 Years*: 15–20 mg/kg/dose PO twice daily with food ▪ *Children Aged 4–24 Months:* 22.5 mg/kg/dose PO twice daily with food	*Prednisone Dose* • Days 1–5: 1 mg/kg/dose PO twice daily, then • Days 6–10: 0.5–1 mg/kg/dose PO twice daily, then • Days 11–21: 0.5 mg/kg/dose PO once daily. *Alternative Corticosteroid Regimens* • Adult Dosage of Prednisone: o Days 1–5: 40 mg/dose PO twice daily, then o Days 6–10: 40 mg/dose PO once daily, then o Days 11–21: 20 mg/dose PO once daily • Methylprednisolone IV: o Days 1–7: 1 mg/kg/dose every 6 hours, then o Days 8–9: 1 mg/kg/dose twice daily, then o Days 10–11: 0.5 mg/kg/dose twice daily, then o Days 12–16: 1 mg/kg/dose once daily

Note: Information included in these guidelines might not represent U.S. 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.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IM = intramuscular; IV = intravenous; PCP = *Pneumocystis* pneumonia; PO = oral; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

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