

Prevention of Infection Due to *Pneumocystis* spp. in Human Immunodeficiency Virus-Negative Immunocompromised Patients

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INTRODUCTION

Pneumocystis was initially identified in the lungs of rats as a stage in the life cycle of *Trypanosoma cruzi* (in 1909 by Chagas and in 1910 by Carini). The first case of *Pneumocystis* infection in humans was described by van der Meer and Brug in 1942 (167); Jirovec has been credited with describing epidemic infection in humans in the 1950s (85). *Pneumocystis carinii* was thought to be a protozoan parasite based on morphologic appearance, proposed life cycle, and antimicrobial susceptibilities. Subsequent phylogenetic analyses using rRNA sequences suggested that the organism was more closely related to the fungi despite the absence of ergosterol in the cell wall (34). Animal models of *Pneumocystis* pneumonia have been highly predictive of the clinical experience with human infection and are extensively used in studies of disease pathogenesis and therapy. However, some molecular and immunologic studies suggest that *Pneumocystis* associated with human disease is distinct from the strains found in animal models. This distinction has resulted in a suggested reclassification of organisms isolated from humans as *Pneumocystis jiroveci* while *P. carinii* remains the designation of rodent-derived organisms (161). The use of this name remains controversial (72). Some background information about the biology of infection is useful in considering strategies for the prevention or treatment of *Pneumocystis* pneumonia. This review refers to both *P. carinii* pneumonia and *P. jiroveci* pneumonia as PCP (161).

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EPIDEMIOLOGY

Van der Meer and Brug described three patients with PCP, including a 3-month-old child with congenital heart disease (167). Vanek and Jirovec described *Pneumocystis* as the cause of epidemic plasma cell pneumonitis in malnourished or premature infants in institutions in Europe after World War II (45, 85, 141). Similar cases were reported in the United States in the 1950s. By 1980, 68% of cases of PCP reported worldwide occurred in children with malnutrition or prematurity (153). Hughes et al. described PCP in 17 children with malignancies from the St. Jude Children's Research Hospital; acute lymphoblastic leukemia (ALL) was the most common predisposing condition (78). Since then, while most patients with PCP have had some identifiable defect in T-cell immunity, PCP has been associated with a broad array of immune deficits, in particular in association with corticosteroid use and hematologic malignancies. These deficits include those due to organ transplantation, use of corticosteroids, radiation therapy, neutropenia, CD4⁺ lymphopenia, premature birth, malnutrition (protein and calorie), malignancies (especially hematologic), congenital immunodeficiency states, collagen vascular diseases (corticosteroids, tumor necrosis factor alpha (TNF- α blockers), hematologic disorders, Cushing's syndrome, and nephrotic syndrome. In the 1980s, PCP became the first opportunistic infection associated with AIDS. Pioneering studies by Walter Hughes demonstrated the efficacy of prophylaxis for PCP with trimethoprim-sulfamethoxazole (TMP-SMX) in non-AIDS patients; these studies were subsequently replicated with AIDS patients. In the current era, with broader application of hematopoietic and solid-organ transplantation, prolonged survival

of immunocompromised patients, and intensification of immunosuppressive and chemotherapeutic regimens, PCP remains an important infection. Uncommonly, patients without a recognized immune deficiency have developed PCP (152).

Serologic data suggest that most individuals are infected by 4 years of age (133). The rate of identification of organisms in autopsy studies is 0 to 8%. The frequency of infection varies both by institution and by geography. Given the absence of a recognized environmental reservoir, it was generally assumed that reactivation of latent infection was involved in the pathogenesis of PCP in most individuals. However, following treatment of active infection, immunosuppression in animal models does not result in the reemergence of infection in animals maintained in respiratory isolation; reinfection of those animals with airborne organisms is possible (8). Such aerosol transmission of infection has been demonstrated in animals and in clusters of infection described in immunocompromised patients after exposure to patients with PCP (21, 42, 70, 152, 171). Molecular studies of animals and humans have demonstrated that both reinfection and reactivation of latent infection are significant factors in the incidence of disease (64, 97, 103).

DIAGNOSIS

As with any immunocompromised host with infection, early diagnosis and therapy are essential for a good clinical response to therapy in PCP. Hence, it is important to recognize that the clinical presentation of patients with PCP in HIV-negative individuals may differ from that in patients with AIDS (102, 121). The progression of PCP in patients with AIDS tends to be subacute, often evolving over 1 to 2 weeks. In HIV-negative patients, presenting symptoms are more variable but may evolve over a few days with a clinical course that is more severe, often with marked hypoxemia. It is unclear whether the rapid onset of symptoms reflects the relatively more intact pulmonary immune and inflammatory responses in the non-AIDS patients or other factors. Perhaps as a reflection of the rapidity of progression of symptoms and earlier presentation for medical care, the organism burden tends to be lower in PCP in non-AIDS patients, with noninvasive diagnosis being more difficult (92). The chest radiograph may be entirely normal despite significant hypoxemia and diffuse parenchymal involvement (157). Diffuse, fine, ground-glass interstitial infiltrates are common. Other atypical features are also seen: small effusions, asymmetry or focal consolidation, small nodules or cavities, linear opacities, pneumothoraces, and lymphadenopathy (29, 31, 55). A computed tomogram scan often reveals diffuse interstitial and nodular parenchymal involvement even if plain radiographs are normal (40). Nuclear medicine imaging may detect inflammation earlier than other techniques in patients with PCP; however, the tests lack specificity (40). The level of serum lactic dehydrogenase is elevated (>300 IU) in most patients with PCP. However, other pulmonary processes, including pulmonary embolism, lymphoma, other pneumonias, and lymphocytic interstitial pneumonitis, also raise serum lactic dehydrogenase levels (40). The characteristic hypoxemia of PCP produces a broad alveolar-arterial oxygen gradient.

Due to the lack of specificity of clinical and radiological findings, the frequent coexistence of multiple processes or infections in immunocompromised patients, and the potential

TABLE 1. Diagnostic techniques for PCP

Technique (reference)	Yield (%)
Routine sputum (98, 173).....	Poor
Induced sputum (40, 93).....	30-55
Induced sputum with immunofluorescent-antibody staining (93, 96).....	60-97
Bronchoalveolar lavage (40, 160).....	80-95
Bronchoalveolar lavage and transbronchial biopsy (13, 40).....	>95
Open-lung biopsy (139).....	>95

toxicities of the agents used for the treatment of PCP, it is advantageous to have histopathologic confirmation of the diagnosis. In general, noninvasive testing should be attempted in order to make the initial diagnosis, but invasive techniques should be used when necessary and clinically feasible. Suspicion of PCP should lead to early consideration of an invasive diagnosis in the HIV-negative, immunocompromised host. The most commonly used diagnostic techniques and their respective yields are shown in Table 1. Sputum collected for routine bacterial and fungal cultures is rarely useful for the diagnosis of PCP (98). The technique of sputum induction with hypertonic saline has been very useful for all immunocompromised patients (93). Sputum smears can be stained with Giemsa or silver stains. Silver stains do not detect sporozoites and trophozoites; stained cysts represent only 5 to 10% of the total organisms. The Giemsa stain stains sporozoites and trophozoites but is often difficult to interpret. (40). This problem has been overcome by the use of immunofluorescent monoclonal antibodies directed against surface epitopes from *Pneumocystis* cysts and trophozoites (93, 96). This technique has become the diagnostic technique of choice for PCP. Recent PCR assays are promising but are not generally available. Such PCR assays may have a higher sensitivity than the use of immunofluorescent antibodies in induced sputum for the diagnosis of *Pneumocystis* (16). The same techniques can be used for bronchoalveolar lavage specimens. In experienced hands, pulmonary bronchoscopy with bronchoalveolar lavage provides a diagnosis of PCP in over 80% of all patients and in up to 95% of patients with AIDS. The addition of multiple transbronchial biopsies increases the diagnostic yield to over 90% of all patients and should be considered for use in non-AIDS patient with possible PCP (13, 40, 160). Touch preparations from the cut surface of a biopsy specimen may be used for rapid diagnosis before histopathology results are available. Surgical open biopsy remains the "gold standard" for the evaluation of pulmonary processes in the immunocompromised host; this technique is now often in the form of video-assisted thoracoscopic biopsy (139). The results of each technique depend on the level of local expertise; invasive tests may be preferred if the clinical laboratories lack experience with *Pneumocystis*. In individuals receiving second-line prophylactic agents (i.e., those other than TMP-SMX), the organism burden may be low and/or the pulmonary distribution may be altered, reducing the sensitivity of diagnostic testing and altering the clinical presentation of infection (87).

IMMUNOLOGY

The role of T lymphocytes in protection against *Pneumocystis* infection is best illustrated by studies using cyclosporin A in rats and depletion of T-helper lymphocytes (CD4⁺ cells) in

mice (9, 40, 41, 47). Passive transfer of immune T lymphocytes is protective against PCP in mice, whereas transfer of specific monoclonal antibodies is only partially protective (47). These observations are consistent with the high incidence of pneumocystosis in patients with low CD4⁺ cell counts. Mice with defects in macrophage function are also susceptible to PCP (41). Augmentation of the macrophage response by using gamma interferon appears to improve the clearance of infection (9). The roles of growth factors and cytokines are not yet known; mice deficient in granulocyte-macrophage colony-stimulating factor have enhanced susceptibility to infection which is thought to be due to diminished clearance of organisms and surfactant by macrophages (G. Dranoff and J. A. Fishman, unpublished data). Coinfection with *Pneumocystis* and cytomegalovirus (CMV) is common. CMV is a systemic immunosuppressive agent, but the role of CMV in the pathogenesis of *Pneumocystis* infection remains unclear. In vitro, CMV infection enhances adhesion and replication of organisms on feeder cell monolayers (40).

TARGET POPULATIONS FOR ANTI-PNEUMOCYSTIS PROPHYLAXIS

The spectrum of patients developing PCP has changed with the advent of highly active antiretroviral therapy for HIV infection and the routine use of prophylaxis for most patients with hematological malignancies. In most HIV-negative immunocompromised patients, the risk of disease is on the order of 5 to 15% (42). The main risk factors for PCP are deficiencies in cellular immunity and use of corticosteroids; however, the spectrum of risk factors remains broad, as discussed above. The risk factors are reflected in a retrospective study of 116 HIV-negative patients with PCP from the Mayo Clinic, of whom 30.2% had hematologic malignancies, 25% were organ transplant recipients, 22.4% had inflammatory disorders, 12.9% had solid tumors, and 9.5% had other conditions. Corticosteroids use was reported in 90.5% of these patients. The median daily dose was 30 mg of prednisone; however, 25% of the patients had received as little as 16 mg per day. The median duration of corticosteroid therapy before the diagnosis of PCP was 12 weeks. However, 25% of the patients developed PCP after 8 weeks or less of corticosteroid use (177). Table 2 describes the reported attack rates for PCP without prophylaxis based on the underlying disease.

Hematologic and Nonhematologic Malignancies

Patients with PCP were treated with pentamidine isethionate provided by the Centers for Disease Control between 1967 and 1970 (173). In this classic series, ALL was the most common predisposing condition for PCP (in 47% of the patients), followed by chronic lymphocytic leukemia. Other conditions included Hodgkin's disease, non-Hodgkin's lymphoma, other malignancies, primary immune deficiency states, organ transplantation, collagen vascular disorders, and a variety of other disorders. Hughes et al. observed a similar pattern among 1,251 children with malignancies, with an overall incidence of PCP of 4.1% (78). ALL was the most common underlying malignancy (incidence of PCP, 6.5%), with lower PCP rates associated with Hodgkin's disease (1.3%), neuroblastoma

TABLE 2. Reported attack rates for PCP by underlying condition in patients not receiving prophylaxis

Underlying disorder (reference)	Attack rate (%)
Acute lymphoblastic leukemia (73, 78)	6.5–42.9
Severe combined immunodeficiency syndrome (99).....	27–42
Rhabdomyosarcoma (76, 78)	4–25
Wegener's granulomatosis (3, 46, 52, 67, 122).....	3.5–12
Hodgkin's disease (78).....	1.3
Collagen vascular disease (52).....	<2
Primary or metastatic central nervous system tumor (65, 154).....	1.3–1.7

(3.8%), and rhabdomyosarcoma (4%). Neutropenia and radiotherapy were common cofactors in these patients. Over half of the patients did not receive corticosteroids in the month prior to onset of PCP; 20% did not receive corticosteroids within 3 months before the infection. The risk of developing PCP in children with ALL has also been associated with the duration and intensity of chemotherapy, the presence of mediastinal masses, and irradiation (73).

In a recent retrospective study of 55 patients with hematologic disorders, the incidence of PCP in ALL was only 0.5%; this may reflect differences in chemotherapeutic regimens, geographic variation, or prophylaxis (128). Other than bone marrow transplant recipients (28 patients), affected patients had non-Hodgkin's lymphoma (10 patients), ALL (6 patients), acute myeloid leukemia (4 patients), chronic lymphocytic leukemia (4 patients), multiple myeloma (1 patient), myelodysplastic syndrome (1 patient), or myelofibrosis (1 patient). Similar series from France and the Netherlands noted that corticosteroids and intensive chemotherapy for chronic lymphocytic leukemia and non-Hodgkin's lymphoma were the most common predisposing conditions for the development of PCP (3, 138). Other conditions included organ transplantation, solid tumors, multiple myeloma, Waldenström's macroglobulinemia, and myelodysplasia. corticosteroids was used in 92% of patients cytotoxic agents in 71%, and both in 64% (3). In addition to corticosteroids, many chemotherapeutic agents have been associated with PCP. In one series, 34 (9.7%) of 350 patients received immunosuppressive agents other than corticosteroids (15). PCP has occurred during therapy with a single agent, including methotrexate, fluorouracil, bleomycin, asparaginase, dactinomycin, and deferoxamine (154). The risk of PCP has been associated with the intensity of the chemotherapy and the duration of neutropenia (73, 131, 141). The use of cytarabine has been implicated as a strong risk factor for the development of PCP (14, 73, 152). Fludarabine has also been implicated by some authors but not by others (128, 138).

The incidence of PCP among patients with solid tumors has generally been low but may increase with intensification of chemotherapeutic regimens. In a study from Cornell University, 1.34% of patients with solid tumors developed PCP, representing 31% of the 142 HIV-negative patients with PCP (154). The affected patients received corticosteroids for a median duration of 3 months; seven patients received corticosteroids for only 1 month. Of note, 70% of the cases of PCP were detected as corticosteroids therapy was being tapered, suggesting that subclinical infections were masked by immune suppression. At the same center, 264 cases of PCP were subsequently reported (1963 to 1992), with a persistently high rate of

infection identified in patients with solid tumors (152). Similar series of solid-tumor patients with PCP have been reported from other centers, particularly patients with primary or metastatic brain tumors. In a study of 587 patients with primary brain tumors, 11 patients developed PCP (1.7%), most of whom were receiving corticosteroids and who developed symptoms while the medication was being tapered (65). Other case series have also identified radiotherapy and lymphopenia as risk factors in the solid-tumor group (146, 154, 158). Corticosteroids and lymphopenia have also been identified as major risk factors in the few case reports of PCP in patients with breast cancer and other solid tumors receiving high doses of chemotherapy (95, 154).

Hematopoietic Stem Cell Transplantation

Before the routine use of prophylaxis after allogeneic hematopoietic stem cell transplantation (HSCT), PCP developed in 5 to 16% of patients (113, 153, 168). A study from Seattle in the early 1980s described an experience with 525 allogeneic grafts and 100 syngeneic grafts; 6% of allogeneic transplant recipients and 1% of syngeneic transplant recipients developed PCP (113). In the early years of bone marrow transplantation, the majority of patients with PCP were diagnosed during the initial 6 months after transplantation. In recent series, more PCP has been observed beyond this period. This change is explained by increased short-term survival rates and intensified treatment of graft-versus-host disease (GVHD). A study from Finland reported 16 cases of PCP among 110 transplant recipients; 14 episodes occurred more than 6 months posttransplantation, and 3 occurred after 1 year. With only one exception, all patients were receiving corticosteroids for management of GVHD (105). Similar findings were reported by other centers (138, 168). The risk of PCP in patients with autologous HSCT is unknown, although some cases have been reported (153). In a study from France, the incidence of PCP in patients with autologous HSCT was 0.54%, compared to 1.46% in those with allogeneic HSCT (138).

Recent guidelines for preventing opportunistic infections in HSCT recipients recommended the use of prophylaxis in allogeneic transplant recipients during periods of possible immunocompromise following engraftment (33). Prophylaxis should be given from engraftment until 6 months post-HSCT to all patients and beyond 6 months post-HSCT to those receiving immunosuppressive therapy or those with chronic GVHD. *Pneumocystis* prophylaxis may be initiated before engraftment if engraftment is delayed. Some experts recommend an additional 1- to 2-week course of PCP prophylaxis before transplantation (i.e., day -14 to day -2). *Pneumocystis* prophylaxis should be considered for autologous HSCT patients who have underlying hematologic malignancies such as lymphoma or leukemia, are undergoing intense conditioning regimens or graft manipulation, or have recently received fludarabine or 2-chlorodeoxyadenosine (2-CDA). The administration of PCP prophylaxis to other autologous HSCT patients is controversial (33).

Solid-Organ Transplantation

In solid-organ transplant recipients, the risk of *Pneumocystis* infection is greatest between the second and the sixth months

TABLE 3. Reported attack rates for PCP in transplant recipients not receiving prophylaxis

Organ transplanted (reference)	Attack rate (%)
Heart-lung/lung (32, 57)	6.5-43
Heart (57, 83, 116, 125).....	2-41
Renal (41, 104, 116, 153).....	0.6-14
Liver (27, 61, 130)	3-11
Allogeneic bone marrow (112, 153, 168).....	5-16

posttransplantation, during periods of prolonged neutropenia, and during periods of intensified immunosuppression (e.g., due to high doses of corticosteroids, calcineurin inhibitors, or antilymphocyte antibody or to T-cell-depleting therapies). Patients treated with corticosteroids before transplantation (e.g., those with autoimmune hepatitis) may present with PCP in the first weeks after transplantation. Other predisposing factors include concomitant CMV infection, number of episodes of graft rejection, and low CD4⁺ lymphocyte counts (4, 18, 41, 104, 116). Although mycophenolate mophetil appears to have some intrinsic anti-*Pneumocystis* activity in animal studies (127), protection against *Pneumocystis* infection has not been seen in humans. Routine anti-*Pneumocystis* prophylaxis has been recommended, in general, for patients being treated in centers where the incidence of disease in immunosuppressed patients is 3 to 5% or higher (41). Table 3 describes the rates of PCP without prophylaxis as a function of the organ transplanted. The recent introduction of sirolimus (rapamycin) for immunosuppression has been associated with a syndrome of diffuse pulmonary interstitial infiltrates in some patients. Some of these patients have had documented coinfection with a variety of pathogens including *Pneumocystis*; careful evaluation is necessary (156).

PCP occurs in about 2 to 10% of heart transplant recipients not receiving prophylaxis; however, an attack rate as high as 41% has been reported (57, 83, 116, 125). In patients with combined heart-lung transplants, the incidence of symptomatic disease has been higher, between 6.5 and 43% (32, 57). One study investigating the effect of routine bronchoscopy on individuals after combined heart-lung transplantation identified *Pneumocystis* in 43% of patients, compared with only 5.4% in patients who received a heart transplant alone (32). In a prospective study of patients not receiving prophylaxis, 88% of heart-lung transplant recipients were found to have *Pneumocystis* on routine bronchoalveolar lavage, of whom only 35% were symptomatic; symptomatic infection was observed in only 4% of heart allograft recipients (57). In a retrospective study, 28 cases of PCP were found among lung transplant recipients over a period of 10 years; 36% of them developed PCP more than 1 year after transplantation. These data suggest that lung transplant recipients may benefit from PCP prophylaxis for periods longer than 1 year (56). The use of cyclosporin A, the use of corticosteroids, a history of a previous episode of rejection, and CMV coinfection have been associated with PCP in lung transplant recipients (116). A study of infants reported an incidence of PCP of 7% in patients undergoing heart transplantation, with the majority of episodes occurring in the first 6 months (83). Lifelong prophylaxis should be considered in heart and lung transplant recipients, in particular if the incidence in the institution or region is greater than 5% without

prophylaxis, if the patient has a history of PCP or frequent opportunistic infections, if the patient is being treated for CMV or is considered at high risk for CMV infection, or if the patient is receiving therapy for acute rejection. Transplant patients with prolonged neutropenia may benefit from prophylaxis; bone marrow toxicity is a concern but is rarely limiting (41).

The incidence of PCP in renal transplant recipients not receiving prophylaxis is on the order of 0.6 to 14% (41, 104, 116, 153). A study from the University of Pittsburgh in 1994 found an increase in the incidence of PCP in that institution after the addition of cyclosporin A to immunosuppressive regimens in place of azathioprine (58). A study from Germany reported experience between 1986 and 1994 for 1,192 renal transplant recipients without routine prophylaxis. The incidence of PCP varied from 0.6 to 14%, depending on the immunosuppressive regimen; more PCP was observed with use of tacrolimus, ATG, and corticosteroids than with use of cyclosporin A, reflecting the intensity of immune deficits (104). Longer periods of prophylaxis (e.g., 6 to 12 months) should be considered for renal transplant recipients with similar characteristics to those described for heart-lung transplant recipients: patients with immunosuppressive viral infections (CMV, Epstein-Barr virus, hepatitis C virus) or requiring higher than usual levels of immune suppression.

The incidence of PCP in liver transplant recipients in the absence of prophylaxis similarly has been found to be on the order of 3 to 11% in both adults and children (27, 61, 130). Lifelong prophylaxis should be considered for liver transplant recipients, notably those with persistent viral infections or graft dysfunction.

Other Compromised Hosts: Autoimmunity and Connective Tissue Disorders

PCP is occasionally seen in patients with autoimmune disorders (3, 138, 177). Vasculitis or autoimmune disorders were predisposing conditions in 22% of cases in one series (3). A retrospective case series described 34 patients with PCP in association with connective tissue diseases (52). The estimated incidence of PCP for each autoimmune disorder based on hospital statistics was 0.13% for rheumatoid arthritis, 0.8% for systemic lupus erythematosus, 1.2% for polyarteritis nodosa, 2% for polymyositis/dermatomyositis, and 12% for Wegener's granulomatosis. PCP was diagnosed during the first 8 months of the underlying disease in the majority (74%) of patients. Corticosteroids were being used in 94% of those patients; 71% were also receiving cytotoxic therapy. Two patients with systemic lupus erythematosus were not receiving therapy when they developed PCP. In a study of 223 HIV-negative patients with a connective tissue disease and PCP, the estimated number of cases per 10,000 hospitalizations per year was 89 in patients with Wegener's granulomatosis, 65 in those with polyarteritis nodosa, 27 in those with inflammatory myopathy, 12 in those with systemic lupus erythematosus, 8 in those with scleroderma, and 2 in those with rheumatoid arthritis (174). In a retrospective study of 180 patients with Wegener's granulomatosis treated with immunosuppressive agents who were monitored for 7 years, 11 developed PCP (122). Other studies have found incidences of PCP in patients with Wegener's granulomatosis of 3.5 to 12% (3, 46, 67). This high risk may be

explained by therapies utilizing initial high doses of corticosteroids and long-term cyclophosphamide. Low pretreatment total lymphocyte counts and total lymphocyte counts less than 600/ μ l (after 3 months of cyclophosphamide therapy) have been identified as risk factors for the development of PCP in patients with Wegener's granulomatosis (50). A cost-effectiveness analysis of primary prophylaxis against PCP in patients with Wegener's granulomatosis found the intervention to be cost-effective (23). Prophylaxis for PCP is becoming the standard of care during the initial treatment of patients with Wegener's granulomatosis (155). The presence of lymphopenia and interstitial pulmonary fibrosis has been identified as a possible risk factor for the development of PCP in patients with systemic lupus erythematosus or inflammatory myopathies who are taking corticosteroids (88). There have been several reports of PCP in patients with rheumatoid arthritis who are receiving methotrexate, some early in the course of therapy (124, 140). The methotrexate dosage varied (5 to 30 mg per week), and the duration of therapy at the time of diagnosis varied from 2 to 48 months. One-third of these patients were not receiving corticosteroid therapy; lymphopenia was present in two-thirds of the patients. The introduction of TNF- α neutralizing therapy with either a TNF- α type II receptor-immunoglobulin G1 fusion protein (etanercept) or a monoclonal antibody against TNF- α (infliximab or adalimumab) has been associated with reports of opportunistic infections including PCP (30, 94, 162, 175). It is likely that the increasing use of cytotoxic and TNF- α -neutralizing therapy in patients with rheumatoid arthritis and other inflammatory conditions will result in greater incidences of PCP and other opportunistic infections.

In patients with HIV infection, CD4⁺ T-lymphocyte counts are a predictor for the risk of PCP (110, 132). In immunosuppressed HIV-negative patients, CD4⁺ T-lymphocyte counts are less helpful as a marker of disease risk. Lower CD4⁺ T-lymphocyte counts may be a marker for a higher risk of developing PCP but may also reflect viral coinfection or exogenous immunosuppression (50, 104, 107, 138). A prospective study examined the CD4⁺ T-lymphocyte counts of 22 HIV-negative, nontransplant patients with PCP compared with simultaneous control patients (107). Of these, 91% with PCP had CD4⁺ T-lymphocyte counts of less than 300 cells/ μ l, suggesting that a CD4⁺ T-lymphocyte count may be a marker of an increased risk of PCP. Other studies have not found a relationship between CD4⁺ T-lymphocyte count and the risk of PCP (52). Idiopathic CD4⁺ T-cell lymphopenia has been reported as a risk factor for PCP (121, 138).

As regards non-transplant recipients at risk for PCP, it has been recommended that individuals receiving T-cell-depleting therapies or corticosteroids with over 20 mg of prednisone per day for longer than 2 to 3 weeks should be considered for prophylaxis (41). Primary or secondary prophylaxis against PCP can be discontinued for adult or adolescent HIV-positive patients whose CD4⁺ T-lymphocyte count has increased from <200 to >200 cells/ μ l for at least 3 months due to highly active antiretroviral therapy (109). In HIV-negative immunocompromised patients, the value of prophylaxis persists in relation to the nature, intensity, and duration of immunosuppressive therapy or immune deficits. Table 4 summarizes recommendations

for PCP prophylaxis in HIV-negative immunocompromised patients.

PROPHYLAXIS AGAINST *PNEUMOCYSTIS* INFECTION

The need for prophylaxis against PCP in susceptible patients was recognized over 30 years ago (75, 131). Unfortunately, routine, continuous cultivation of *Pneumocystis* in vitro for testing of susceptibility to antimicrobial agents has not been achieved (42). Immunosuppressed-rodent models of *P. carinii* infection have been highly predictive of the clinical efficacy of new anti-*Pneumocystis* therapies (40). Two factors merit consideration when selecting agents for prevention of disease. First, the replication of *P. carinii* is generally slow (7 to 10 days), allowing the use of intermittent therapy. Second, of the available agents, only TMP-SMX has a broad spectrum of antimicrobial activity (e.g., against *Pneumocystis*, bacteria, and/or parasites) that may be advantageous in some immunocompromised hosts.

Advances in molecular biology have delineated some metabolic targets for anti-*Pneumocystis* therapy. The genes encoding dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR), which are the targets of SMX and TMP, respectively, and the cytochrome *b* locus, the site of action of atovaquone, have been cloned and characterized (30). Molecular techniques have identified mutations in the DHPS, DHFR, and cytochrome *b* genes which would be expected to confer resistance to antimicrobial agents (63, 68, 91, 111, 172). Failure of TMP-SMX prophylaxis in patients infected with isolates with mutations in the DHPS gene has been reported (91, 111, 172). However, other studies found no correlation between the presence of mutations and prophylactic or therapeutic failures (89, 120, 170). Sequences for atovaquone resistance in the cytochrome *b* gene of *Pneumocystis* have been found in isolates from persons who have failed prophylaxis and in patients who have previously taken atovaquone (90). It has not been determined whether these sequences account for the ineffectiveness of atovaquone in some individuals (5). Failure of pyrimethamine-sulfadoxine prophylaxis has been associated with mutations in the DHPS gene (118).

Trimethoprim-Sulfamethoxazole

TMP-SMX is the most effective agent against *Pneumocystis*. TMP inhibits DHFR, and SMX inhibits DHPS. TMP is excreted mostly unchanged in the urine, with approximately 10 to 30% metabolized to an inactive form. SMX is metabolized primarily in the liver, with approximately 30% excreted unchanged in the urine. The approximate half-life of each component is 8 to 14 h. Because most drug excretion occurs via the kidneys, the dosage of TMP-SMX should be adjusted for a creatinine clearance of less than 30 ml/min. TMP decreases the tubular secretion of creatinine, leading to elevations of the serum creatinine level without diminution of the glomerular filtration rate. These increases tend to be mild (approximately 10%), and they are reversed with discontinuation of therapy. Toxicities include fever, rash, headache, nausea, vomiting, neutropenia, pancytopenia, meningitis, nephrotoxicity, anaphylaxis, hepatitis, hyperkalemia, and hypoglycemia. Significant toxicities generally evolve within the first month of therapy

TABLE 4. Possible indications for the use of anti-*Pneumocystis* prophylaxis

Solid-organ transplant recipients and allogeneic HSCT or bone marrow transplant recipients with institutional incidence of $\geq 5\%$ or in high-risk patients:
History of PCP or frequent opportunistic infections
With invasive CMV infection or at high risk for CMV disease
During intensified immune suppression for acute allograft rejection or GVHD
Individuals receiving anti-T-cell therapies
Autologous bone marrow transplant recipients with leukemia or lymphoma, undergoing intensive conditioning or graft manipulation, or after fludarabine or 2-CDA
Individuals with prolonged neutropenia (if marrow suppression is tolerable)
Individuals with corticosteroid doses of ≥ 20 mg of prednisone per day for $\geq 2-3$ wk

unless they are masked by immunosuppression. These reactions occur more commonly in HIV-positive patients. In general, the toxicity of TMP-SMX is overemphasized in comparison with its efficacy. Toxicity or allergy should be documented before alternate therapies are selected. Most of the adverse effects seem to be related to the SMX component (108). The simultaneous administration of leucovorin reduces the incidence of neutropenia; however, it may interfere with the efficacy of TMP-SMX and has minimal effect on other toxicities (108, 136). Similar results have been reported for the simultaneous use of folinic acid (143). Interactions with other medications may occur. Combination with methotrexate, azathioprine, or pyrimethamine can enhance the risk for neutropenia (22). TMP-SMX uncommonly causes hemolytic anemia in patients who have glucose-6-phosphate dehydrogenase deficiency. The use of low drug doses and the absence of activity against anaerobic bacteria tend not to predispose to pseudomembranous colitis.

Because of the advantages of TMP-SMX, desensitization of patients who are intolerant of TMP-SMX has been used for many HIV-positive patients (1, 17, 51, 100). Two randomized controlled trials have shown that gradually increasing in the dose of TMP-SMX improves the tolerability of the drug in HIV-positive patients (129). However, this approach should be used with caution. There have been reports of a severe sepsis-like syndrome on rechallenging HIV-positive patients who had previous adverse reactions to TMP-SMX (30). When significant toxicity develops in transplant recipients, particularly acute interstitial nephritis, it rarely resolves without discontinuation of the therapy (41, 42). Given the severity of some reactions, alternative agents should be used for prophylaxis in HSCT and solid-organ transplant recipients with documented allergy to or intolerance of TMP-SMX. For patients with only mild toxicity (e.g., marrow suppression) it is reasonable and worthwhile to consider reintroduction of TMP-SMX when graft function and immunosuppressive regimens are stable. In general, hematopoietic suppression and renal dysfunction due to low dose TMP-SMX is overemphasized; reduction of the amounts of other marrow-toxic agents will allow the use of TMP-SMX. TMP-SMX is the agent of choice for prophylaxis against PCP unless a clear contraindication is identified.

Breakthrough infection in patients receiving TMP-SMX is unusual. The advantages of TMP-SMX over the other prophylactic regimens include increased efficacy, lower cost, availabil-

ity of multiple oral preparations, and protection against other common opportunistic pathogens. TMP-SMX daily provides excellent protection against *Toxoplasma gondii*, *Isospora belli*, *Cyclospora cayetanensis*, and susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus* spp., *Salmonella* spp., and common gram-negative gastrointestinal and urinary pathogens (41, 66, 76, 169). Some breakthrough infections by resistant strains of *Nocardia* or other bacteria may be observed. Protection against toxoplasmosis and bacterial infections is incomplete without daily dosing of TMP-SMX (30).

Multiple studies of HIV-positive patients have demonstrated the efficacy of TMP-SMX for prophylaxis (11, 59, 135, 142). Either a high-dose, consisting of one double-strength tablet (DS) per day, or a low dose, consisting of one single-strength tablet (SS) per day, is superior to aerosolized pentamidine for primary and secondary prophylaxis (11, 59, 150). There is no evidence that an SS dose is inferior to a DS dose (81). The incidence of PCP was similar in patients receiving DS TMP-SMX daily versus three times a week (35). Toxicities in HIV-positive patients are more common with higher doses of TMP-SMX, but they have not been as well studied in other patient populations (35). In patients receiving DS TMP-SMX twice daily as therapy, intolerance occurs in the range of 17 to 79% (11, 39).

The first randomized controlled trial using TMP-SMX for primary prevention of PCP was done with pediatric oncology patients. The results showed a dramatic decrease in the incidence of PCP with the use of TMP-SMX (69, 76). Tolerance of TMP-SMX was excellent, without an increased risk of renal insufficiency or leukopenia and with few patients requiring drug discontinuation. A prospective randomized controlled study of patients with ALL demonstrated equivalent efficacy (no cases of PCP) between daily regimens and administration on three consecutive days per week with DS TMP-SMX twice daily (79). PCP occurred in up to 37% of bone marrow transplant recipients not receiving prophylaxis, while no cases were found in patients receiving TMP-SMX (176). In bone marrow transplant recipients, the use of TMP-SMX is occasionally associated with bone marrow suppression and delayed marrow engraftment (80, 101). A large retrospective study of bone marrow transplant recipients found TMP-SMX to be more effective than comparators in preventing PCP (168). No cases of PCP occurred in TMP-SMX-treated recipients, while 3% of those receiving dapsone and 9.1% of those receiving aerosolized pentamidine developed infection; however, 35.4% developed toxicity, limiting the administration of TMP-SMX. TMP-SMX also decreased the rates of other nonviral infections. The mortality at 1 year in patients receiving TMP-SMX was similar to that in patients receiving dapsone but lower than that in patients receiving pentamidine (168).

The use of TMP-SMX is effective in decreasing the risk of PCP in renal transplant recipients. Low-dose TMP-SMX prevented PCP in renal transplant patients receiving cyclosporin A, azathioprine, and corticosteroids, while 10% of the patients who did not receive prophylaxis developed pneumonia (66). The rate of leukopenia was higher in patients receiving TMP-SMX. This study also found a decrease in the incidence of urinary tract infections among the patients receiving TMP-SMX. In an uncontrolled study of 140 renal transplant recipients, prophylaxis with TMP-SMX prevented PCP in all patients,

compared with historic rates of infection of 11.5% (12). A prospective, randomized, controlled trial with heart transplant recipients showed that TMP-SMX at a dose of one DS tablet twice a day either every day or 3 days per week was superior to placebo (125). No patients in the prophylaxis group developed PCP compared to 41% of the placebo group. Toxicities, including leukopenia, did not differ between prophylaxis and placebo groups. For 50 heart transplant recipients, a prophylaxis schedule of one DS tablet twice a day on Saturdays and Sundays was also effective, with no cases of PCP by 1 year of follow-up and with excellent tolerability and compliance (116). In an uncontrolled trial with liver transplant recipients, the use of daily SS TMP-SMX prevented PCP and was well tolerated, and the incidence of leukopenia and renal insufficiency did not differ from that in historical controls (164). A study of liver and kidney recipients reported intolerance to TMP-SMX in 9.7% of the patients (145).

TMP-SMX is effective in reducing the incidence of PCP in patients with connective tissue diseases with either lymphopenia or interstitial pulmonary fibrosis (123). Drug interactions with other hematopoietic suppressants, including allopurinol, azathioprine, mycophenolate mofetil, and methotrexate, are common, and patients should be monitored very closely for toxicity if one of these agents is given together with TMP-SMX (22, 155). In a case series from France, the incidence of PCP in patients with Wegener's granulomatosis was dramatically decreased by routine prophylaxis with TMP-SMX for patients with CD4⁺ T-lymphocyte counts less than 300 cells/ μ l (138).

Pentamidine

The mechanism of action of pentamidine is unknown; it may be administered intravenously or by inhalation from a nebulizer. Rodent studies suggest that intravenous drug tends to bind preferentially in the lungs. Aerosolized pentamidine is usually well tolerated. Coughing or wheezing occurs in 30 to 40% of patients but can be prevented or diminished by the use of beta-adrenergic agonists such as albuterol (145). Discontinuation of the medication is required in 2 to 7% of HIV patients (20, 166). The rate of toxicity of aerosolized pentamidine in transplant recipients has been 3 to 7.5% (145, 168). Hypoglycemia or hyperglycemia is uncommon but may merit caution if it occurs in pancreas or pancreatic islet transplant recipients. The use of pentamidine prophylaxis in transplant patients also requires the simultaneous administration of a second antimicrobial agent for antibacterial prophylaxis if needed (42).

There have been reports of outbreaks of *Mycobacterium tuberculosis* among health care workers and HIV-positive patients as a result of the coughing induced by aerosolized pentamidine (10). As a result, patients should be screened for tuberculosis before initiation of aerosolized pentamidine therapy; health care providers should follow guidelines for preventing the transmission of tuberculosis in health care settings (19). Aerosolized pentamidine should be administered in individual rooms with negative-pressure ventilation. After the administration of aerosolized pentamidine, patients should not go to common areas unless coughing has subsided (30). Aerosolized pentamidine decreases the sensitivity of bronchoalveolar lavage for the diagnosis of PCP in HIV-positive patients and is also associated with atypical radiographic manifestations (87).

Pentamidine isethionate for PCP prophylaxis is generally used at a dose of 300 mg (inhaled from an ultrasonic nebulizer or intravenously) once every 3 to 4 weeks. Pentamidine delivered by a hand-held nebulizer (60 mg every 2 weeks after a 300-mg loading dose) has also been used by HIV-positive patients (115). Aerosolized pentamidine monthly is inferior to TMP-SMX in HIV-positive patients (11, 59, 150), and dosing at 300 mg twice monthly for secondary prophylaxis may be more effective (137, 150). Breakthrough infection was seen most often in patients with CD4⁺ T-lymphocyte counts of less than 50 cells/ μ l and occurs in 10 to 23% of patients with AIDS (42). Disseminated *Pneumocystis* infection has been found in AIDS patients receiving aerosolized pentamidine (60).

An uncontrolled study of nine lung transplant recipients reported no cases of PCP in patients who received 300 mg of aerosolized pentamidine once a month. Two of the patients developed bronchospasm in response to therapy (119). A retrospective study of 35 transplant recipients (18 liver recipients and 17 kidney recipients) who received aerosolized pentamidine for prophylaxis because of intolerance to TMP-SMX found no cases of PCP (145). Historically in solid-organ transplant recipients at our institution, breakthrough infection with both aerosolized and intravenous pentamidine exceeds 10% (with a 14% baseline incidence of infection in prospective studies). As noted above, a retrospective study of bone marrow transplant recipients found decreased survival and an increased risk of PCP in patients receiving aerosolized pentamidine compared with TMP-SMX and dapsone (168). Aerosolized pentamidine was effective in children with malignancies who were intolerant of TMP-SMX (117). Breakthrough infections are usually seen within 2 months of the period of increased risk (41, 42). They are observed most often in individuals with other predisposing features including tissue-invasive or ganciclovir-resistant CMV infection, those receiving cancer chemotherapy, and those receiving anti-lymphocyte therapies or high-dose corticosteroids for graft rejection.

Dapsone

Dapsone is an inhibitor of DHPS. It has an oral bioavailability of 70 to 80%, with a half-life in plasma that is generally between 10 and 50 h but is often as long as 84 h. A total of 70 to 85% of the drug is excreted in the urine. Administration of 100 mg of dapsone twice a week provides sustained concentrations in lung tissue. Two major advantages of dapsone are the long half-life, allowing intermittent dosing, and the low cost.

Adverse reactions to dapsone that are unrelated to dosage include agranulocytosis, aplastic anemia, rash, nausea, malaise, and a sulfone syndrome (fever, rash, hepatitis, lymphadenopathy, and methemoglobinemia) (114). Dapsone does not have the common myelosuppressive effect of TMP-SMX. In HIV-infected persons, the rate of adverse effects requiring discontinuation of dapsone therapy is similar to that for TMP-SMX and increases with higher doses, ranging from 75% in HIV-positive patients receiving 50 mg twice a day to 10% in patients receiving 100 mg twice a week (71, 166). Between 50 and 85% of TMP-SMX-intolerant HIV-positive patients tolerate dapsone (71, 86). By contrast, in the transplant population, intolerance of TMP-SMX may predict intolerance of dapsone. The toxicities seen with dapsone are long-lived and may limit the

utility of dapsone in non-HIV-infected patients, especially in liver transplant recipients. Adverse effects requiring discontinuation of dapsone therapy occur in up to 43% of HSCT patients, with the most common toxicities being rash and hemolytic anemia (168). Switching from TMP-SMX to dapsone is not recommended for individuals with severe side effects from either agent, including desquamation, neutropenia, severe nephritis, and hepatitis, or in patients with glucose-6-phosphate dehydrogenase deficiency (42).

Dapsone causes a dose-related hemolytic anemia (doses over 200 mg/day) and methemoglobinemia. Methemoglobinemia has been found in HSCT recipients receiving dapsone (134). Dapsone should not be given to patients who have glucose-6-phosphate dehydrogenase deficiency. It is well tolerated in children, without serious adverse events, although protection against *Toxoplasma gondii* is incomplete (106). Dapsone increases cyclosporin A and tacrolimus levels due to interference at the hepatic cytochrome P-450 system; dapsone levels are increased byazole antifungal agents (42).

Dapsone is often considered the best alternative for prophylaxis after TMP-SMX in HIV-positive patients (11, 59, 150). It has similar efficacy to aerosolized pentamidine when used at a dose of 100 mg daily but lower efficacy when used at a dose of 50 mg daily (144, 166). Dose reduction to improve tolerability (50 instead of 100 mg) is not recommended, given that lower doses are associated with breakthrough infection (11). Dapsone alone has no useful antibacterial activity (except against some mycobacteria). The extent of protection provided by dapsone against *T. gondii* is uncertain when it is used without pyrimethamine: a meta-analysis reported similar efficacy to TMP-SMX in preventing toxoplasmosis in HIV-infected individuals (30, 81).

Despite its widespread use, data on dapsone prophylaxis are limited for HIV-negative patients. In a retrospective series, 33 children intolerant of TMP-SMX after bone marrow transplantation received weekly dapsone (50 mg/m²) without experiencing any cases of PCP (106). Dapsone (50 mg twice a day three times per week, with an incidence of 7.2%) is less effective than TMP-SMX (SS twice a day twice per week, with an incidence of 0.37%) in bone marrow transplant recipients (159). Similar studies suggest a failure rate of at least 3% in bone marrow transplant recipients (168).

Dapsone plus Pyrimethamine

Pyrimethamine inhibits DHFR. The combination of dapsone with pyrimethamine as a prophylactic regimen for PCP has been studied in an attempt to allow the use of lower doses of dapsone. A potential advantage of this regimen is predictable activity against *T. gondii*. Increased serum creatinine levels are commonly seen in patients treated with this combination. This abnormality is explained by the action of pyrimethamine in the renal tubular secretion of creatinine while the glomerular filtration rate remains normal. While the combination of dapsone plus pyrimethamine is well tolerated, there is an increased risk of methemoglobinemia compared with that when dapsone alone is used.

Dapsone plus pyrimethamine is inferior to TMP-SMX in multiple studies of HIV-positive patients (30, 135). In HIV-positive patients, the use of twice weekly dapsone (100 mg)

plus pyrimethamine (50 mg) resulted in an incidence of PCP of 6.3% while DS TMP-SMX twice a day three times per week successfully prevented PCP. The incidence of side effects was similar in both arms of the study (135). In HIV-positive patients, dapsone (100 mg weekly) plus pyrimethamine (25 mg twice a week) was less effective than DS TMP-SMX every other day, and dapsone use was associated with shorter survival (2). In multiple studies using a variety of dosing regimens, dapsone plus pyrimethamine was no more effective than aerosolized pentamidine in HIV-positive patients (2, 48, 126). There are no data for the use of this combination in transplant populations, where it is likely that toxicities and drug interactions will outweigh any potential benefits.

Atovaquone

Atovaquone is a structural analogue of protozoan ubiquinone and has potent activity against *Pneumocystis*, *Plasmodium* spp., *Babesia* spp., and *T. gondii*. In *Plasmodium* spp. atovaquone inhibits the binding of ubiquinone to cytochrome *b*, affecting the electron transport mechanism in mitochondria. Similar mechanisms appear to be active in *Pneumocystis* and *Toxoplasma* spp. The half-life of atovaquone is 51 to 77 h. There is no significant hepatic metabolism or renal elimination. Drug penetration into cerebrospinal fluid is minimal (5). Atovaquone is available as an oral suspension; the initial tablet formulation was discontinued because of poor bioavailability. Atovaquone levels in blood are doubled if the drug is taken with fatty meals. Concomitant administration with rifampin leads to a 40 to 50% reduction in atovaquone levels. The most common side effects are rash, headache, nausea, and diarrhea. Elevations of liver function tests have also been documented (5). Generally, side effects are mild and have not required discontinuation of therapy with this drug (5, 27). Hematological toxicity is uncommon. Some patients complain about the flavor and color of the suspension (which stains clothes yellow) (42).

Oral atovaquone is less effective than TMP-SMX for treatment of mild or moderately severe PCP (77). Low plasma atovaquone levels have been associated with a poor response to therapy. Absorption can be unpredictable, and a steady state may not be reached for several days. For prophylaxis, two studies of HIV-positive individuals demonstrated that a daily dose of 1,500 mg of the liquid suspension has comparable efficacy to aerosolized pentamidine or oral dapsone in patients intolerant of TMP-SMX (20, 37). A daily dose of 750 mg was inferior to 1,500 mg for prophylaxis. Atovaquone has anti-*Toxoplasma* activity, but the relative efficacy of this drug in treating and preventing toxoplasmosis has not been fully studied (5, 30). Atovaquone intolerance results in discontinuation of therapy in about 25% of HIV-positive patients (20, 37).

An uncontrolled study found that atovaquone at a dose of 750 mg four times a day was effective as a prophylactic regimen in liver transplant recipients intolerant of TMP-SMX (112). In a study from Massachusetts General Hospital, 25 renal, 14 hepatic, and 5 cardiac transplant recipients who were intolerant of TMP-SMX received prophylaxis with 1,000 mg of atovaquone per day and 400 mg of ofloxacin per day for 6 months (41). Of these 44 patients, 39 completed 6 months of therapy without complications, 2 discontinued therapy because of gastrointestinal intolerance, and 3 developed PCP. One patient

was receiving corticosteroids prior to transplantation for autoimmune hepatitis and developed symptoms 5 days after transplantation. This suggested that the patient had asymptomatic infection prior to surgery. A second patient developed PCP while receiving chemotherapy for hepatocellular carcinoma, while the third patient developed PCP during therapy with OKT3 antibody for acute rejection. In our prospective randomized controlled trial with autologous HSCT recipients, atovaquone at 1,500 mg four times a day with ofloxacin at 400 mg four times a day was compared to DS TMP-SMX four times a day (26). Ofloxacin was used with atovaquone for antibacterial prophylaxis. No cases of PCP developed, and intolerance to TMP-SMX was common (40%). None of the patients treated with atovaquone experienced treatment-associated adverse effects. In transplant recipients, the levels achieved in the serum after administration of prophylactic dosages of 1,000 to 1,500 mg of atovaquone suspension per day exceeds the MIC of atovaquone for rodent *P. carinii* (42). Breakthrough infections have been observed after treatment with less than 1,500 mg/day. Since atovaquone has no antibacterial activity, transplant recipients receiving atovaquone for prophylaxis will require a second antimicrobial agent if desired for antibacterial prophylaxis.

Other Agents

Other agents or combinations have been used empirically or evaluated in small clinical trials. The success of weekly administration of sulfadoxine-pyrimethamine in HIV-positive patients has been variable (37, 151, 163). Sulfadoxine-pyrimethamine has been effective and well tolerated in liver and cardiac transplant recipients (165). This combination agent has also been studied in bone marrow transplant recipients and has achieved good results (44). TMP-dapsone, clindamycin-primaquine (6), and monthly infusions of intravenous pentamidine (37) have been used in small series, without sufficient data being collected to recommend the use of these agents in practice. Patients receiving suppressive therapy for toxoplasmosis with the combination of pyrimethamine and sulfadiazine appear to be protected against PCP (62, 109); however, patients receiving pyrimethamine and clindamycin may not be protected (49). Other agents with activity against *Pneumocystis* but without good clinical data to support their use include α -difluoromethylomithine, trimetrexate, piritrexim, macrolide-sulfonamide, bilobalide, quinghaosu, proguanil, guanyldrazones, nonquinolone topoisomerase inhibitors, analogs of primaquine, analogs of pentamidine (benzimidazoles), albendazole, echinocandins, pneumocandins, terbinafine, and azasordarins (7, 24, 25, 28, 40, 41, 43, 54, 82, 84, 147, 148, 149).

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