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MINIREVIEW

Prevention of Infection Due to *Pneumocystis carinii*

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Pneumocystis carinii remains an important pathogen for the broad spectrum of immunocompromised individuals, despite significant advances in antimicrobial therapy. The recognition of *P. carinii* pneumonia in oncology patients and malnourished children led to epidemiologic and therapeutic studies of the disease in the 1970s by the Centers for Disease Control and Prevention, which was the source of the only therapeutic agent available at the time, pentamidine methanesulfonate (99, 139). The combination of pyrimethamine and sulfadiazine (105) had some therapeutic efficacy in small groups of patients in the 1960s (142). The combination of trimethoprim (TMP) and sulfamethoxazole (SMZ) (58) (subsequently in fixed combination as TMP-SMX or co-trimoxazole) was subsequently shown to be effective for the prophylaxis and the treatment of mild to moderate infections in animal models and patients and successfully reduced the occurrence of and the morbidity from this infection (56–58, 76). Early clinical trials have been reviewed by Hughes (54). These agents remained the standards for therapy after the recognition of the role of *Pneumocystis* infection in the human immunodeficiency virus (HIV)-infected population. The inability of many patients to tolerate prophylaxis or treatment with either TMP-SMX or pentamidine initiated a search for new agents for the prevention and treatment of *Pneumocystis* infection in immunocompromised hosts. This effort has resulted in the development of a variety of newer therapeutic options. Antimicrobial resistance in *P. carinii* appears to be uncommon clinically; however, standardized techniques for the growth of human-derived organisms in vitro or in animal hosts are not generally available for use for susceptibility testing (discussed below).

The routine use of prophylaxis for *P. carinii* has been successful in improving the survival of persistently immunocompromised individuals, resulting in an increase in the relative frequency in these hosts of other infections including infections caused by mycobacteria, fungi, and viruses (49, 50, 57, 70, 76, 141). Approaches to the prevention and treatment of *Pneumocystis* infection are changing with the increased use of anti-*Pneumocystis* prophylaxis in both AIDS and non-AIDS immunocompromised hosts and by improvements in antiviral therapies for HIV. The long-term impact of the newer antiviral therapies on the incidence of opportunistic infection in AIDS remains to be established. The specific therapy selected for an individual may be adjusted to reflect the nature of the individual's predisposing immune deficit(s), the ability of patients to tolerate specific agents, the geographic location of the patient, and the medical institution (31, 54, 109, 133, 138).

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TARGET POPULATIONS FOR ANTI-*PNEUMOCYSTIS* PROPHYLAXIS

A natural reservoir of *P. carinii* has not been demonstrated. Aerosol transmission of infection has been demonstrated by Hughes (54) and other investigators (20, 111, 135) with animal models, and clusters of infections have developed in clinical settings, including clusters of infections among HIV-infected persons and among renal transplant recipients. *P. carinii* DNA has been detected by PCR in the air of the hospital rooms, bronchoscopy suites, and clinics used by infected individuals. The frequency of infection varies both by institution and by geography.

Serologic testing reinforces the view that subclinical infection is common. Most individuals have serologic evidence of exposure by age 4 (82). As a result, it has been assumed that reactivation of latent infection is involved in the pathogenesis of *P. carinii* pneumonia in most individuals (82). However, the rate of identification of organisms in autopsy studies is only on the order of 0 to 8%. Furthermore, following treatment of active infection with TMP-SMX, immunosuppression in animal models does not result in the reemergence of infection in animals maintained in respiratory isolation; reinfection of these animals with airborne organisms is possible (9). Recent molecular studies in animals and humans with a variety of genetic probes including probes for *P. carinii* ribosomal mRNA internal transcribed spacer regions have suggested that both reinfection and the reactivation of latent infection are significant factors in the incidence of disease (46, 75, 78). As a result, it is reasonable to isolate patients with known *Pneumocystis* pneumonia from other immunocompromised individuals.

P. carinii is an important cause of community-acquired pneumonia in individuals with a wide variety of underlying immune deficits, accounting for 26.7% of community-acquired pneumonias in HIV-infected persons prior to the routine use of protease inhibitors in this population in the United States (17, 89). The incidence of infection relates to the intensity and duration of immune suppression. T-lymphocyte deficiencies are particularly important in predisposing an individual to *P. carinii* infection (11, 37). Passive transfer of immune T lymphocytes is protective against *P. carinii* pneumonia in mice, whereas transfer of immune globulin alone is only partially protective (39). Within susceptible populations, the relative risk of infection with *Pneumocystis* is greatest in the first 6 months after solid-organ transplantation, in patients receiving oral corticosteroid therapy (usually the equivalent of 20 mg or more of prednisone per day) for 3 to 6 months, during periods of prolonged neutropenia, and during periods of acutely increased immune suppression, such as those that occur with high-dose corticosteroid or antilymphocyte antibody therapies during treatment of graft rejection or graft-versus-host disease

TABLE 1. Potential targets in *P. carinii* for antimicrobial agents

Target	Antimicrobial agent(s)
Dihydrofolate reductase	TMP, trimetrexate, piritrexim, diaveridine, pyrimethamine
Thymidyate synthase	Dihydrofolate reductase antagonists
Dihydopteroate synthase	SMX, sulfadiazine, dapsone
6-Hydroxymethyldihydropterin pyrophosphokinase	Sulfonylureas
Glucan synthase	Echinocandins, papulocandins
Chitin synthase	?
Topoisomerase (DNA gyrase)	Etoposide, diamidines (?)
23S ribosomal mRNA	Macrolides
Nucleic acid binding (?)	Pentamidine and diamidine analogs
Dihydroorotate dehydrogenase	Atovaquone, hydroxynaphthoquinones
Ornithine decarboxylase	Difluoromethylornithine
Self-splicing RNA introns	?

or those that occur with flares of autoimmune diseases (31, 42, 44, 47, 53, 64, 72, 79, 92, 112).

Individuals with AIDS have a predisposition to *Pneumocystis* infection on the basis of both the progressive decline in the T-cell population and the macrophage defects which may be present in individuals with HIV infection (27, 33, 67, 90, 93, 121). In patients with AIDS, the risk increases with the progressive fall of the CD4-positive lymphocyte count to below 300/mm^3 and increases further as the CD4 count drops below 200/mm^3 or to less than 20% of the total lymphocyte pool (80). The correlation with T-lymphocyte numbers is such that the rate of infection nearly doubles with a drop in CD4 counts from between 100 and 200/mm^3 to below 100/mm^3. Decay of immune function in patients with AIDS, as may be indicated by the occurrence of new opportunistic infections or by falling CD4-lymphocyte counts, places the AIDS patient at increased risk for *Pneumocystis* infection. A correlation of the risk of *Pneumocystis* infection with the circulating load of HIV type 1 (HIV-1) is suggested by preliminary data for patients in whom antiretroviral therapy has been effective (discussed below).

The rate of *Pneumocystis* infection in homosexual males with AIDS is double that in intravenous drug users with AIDS. Two groups of AIDS patients, those without insurance and intravenous drug abusers, have lower rates of use of prophylaxis and zidovudine and are less likely to receive AIDS diagnoses prior to hospitalization with an initial episode of *Pneumocystis* pneumonia. In the absence of effective prophylaxis, more than 80% of the individuals with AIDS are expected to develop *Pneumocystis* pneumonia.

Corticosteroid use, neutropenia, and immune suppression related to organ transplantation are also major predisposing factors in the development of infection (31, 42, 47, 53, 72, 79). In most non-AIDS, immunocompromised patients, the risk of disease is on the order of 5 to 15% (depending on the nature and duration of the immune suppression). In the solid-organ transplant recipient, chronic immune suppression with regimens which include corticosteroids is most often associated with pneumocystosis. Bolus corticosteroids and cyclosporine may also contribute to the risk for *Pneumocystis* pneumonia (52, 72). Of interest, mycophenylate mofetil, a commonly used immunosuppressive agent used in the care of transplant recipients, may have some intrinsic anti-*Pneumocystis* activity, while tacrolimus (FK506), another such agent, increases *Pneumocystis* growth in vitro (98). Active infection due to cytomegalovirus (CMV) may also enhance the growth of *Pneumocystis* (51). It is unclear whether CMV directly stimulates the proliferation of *Pneumocystis*, acts systemically as an immunosuppressive agent, or is a fellow traveler in the immunocompromised host.

TARGETS FOR ANTIMICROBIAL DEVELOPMENT

Some features of the life cycle of the organism are relevant to a discussion of the antimicrobial agents used for prophylaxis and therapy (Table 1). Three forms of the organism have been identified: the trophozoite, cyst, and sporozoite (or intracystic body) forms. The trophozoite, which is 2 to 5 μm in diameter, is either round or sickle shaped and contains a nucleus, mitochondria, and vacuoles; it also includes pseudopodia and filopodia, which are used for limited motility. The cyst usually measures between 3 and 6 μm in diameter. Its cell wall consists of three layers, with the cytoplasm containing up to eight small, oval, pleomorphic sporozoites. In the alveolus, *Pneumocystis* is covered with a variety of glycoproteins derived from the organism, including specific and nonspecific immunoglobulins, albumin, surfactant proteins, laminin, fibronectin, and other serum and lung proteins. These molecules may diminish susceptibility to opsonization and phagocytosis. The cell wall contains cholesterol but no ergosterol and does not appear to synthesize sterols de novo; this accounts for the lack of susceptibility to many of the antifungal agents (7). The presence of chitin in the cell wall is controversial. The surface of *P. carinii* is carbohydrate-rich with glucose, mannose, and beta-1,3-glucan; the glucan moiety is a target of cell surface receptors involved in phagocytosis of the organism by macrophages and is a target of new antimicrobial agents which inhibit glucan synthesis (3, 27, 88). The surface also contains carbohydrate-binding moieties which may play a role in attachment to epithelial or surfactant layers. The neutral lipid fraction of *P. carinii* includes a variety of phytosterols which are also found in plants and fungi including *Physarum* species (36).

Subspecies of *P. carinii* have been described on the basis of the relative host species specificity of the organism and studies of antigens, enzymes, and genes from organisms derived from various host species. Such strains might differ in their susceptibilities to antimicrobial agents (reviewed by Stringer [128]). Phylogenetic data support the taxonomic assignment of *P. carinii* with the fungi (the *Rhizopoda*, *Myxomycota*, or *Zygomycota* or the *Schizosaccharomyces*, *Neurospora*, *Candida*, and the red yeasts in various studies) on the basis of conserved mRNA sequences including the sequences of a small ribosomal subunit (16S-like rRNA), the TATA-binding protein, an enzyme of aromatic amino acid synthesis (*arom*), and the gene encoding elongation factor 3 (25). The presence of separate genes encoding the thymidylate synthase and dihydrofolate reductase of *P. carinii* (traditional targets of antiprotozoal agents), the presence of a cyst wall which is rich in beta-glucan and which stains with periodic acid-Schiff and silver stains, the poorly

developed mitochondria with lamellar cristae (the proposed target of atovaquone), the absence of typical protozoan intracellular organelles, and the airborne spread of infection all support the taxonomic assignment of *Pneumocystis* with the fungi (26, 140, 141, 143). However, the thick-walled cyst with internal sporozoites and amoeboid trophozoites, the absence of ergosterol, the apparent haploidy of the trophozoites, the low copy number of rRNA genes, the susceptibility to antimicrobial agents used in the treatment of protozoan infections (pentamidine, atovaquone, SMX, primaquine), and the existence in the major surface glycoprotein of the organism (termed gp120, gpA, or MSG) of a form of antigenic variation which has not been described in fungi lend credence to its taxonomic assignment with the protozoa. It is likely that a new category within the *Ascomycota* may be needed for *Pneumocystis*. Unique cell wall components (glucans, phytosterols) and synthetic pathways (e.g., topoisomerases) may participate in the pathogenesis of infection due to *P. carinii* and may provide targets for the development of new antimicrobial agents. Unique self-splicing group I intron RNAs may provide added therapeutic targets in *P. carinii* (81).

ANIMAL MODELS AND IN VITRO CULTIVATION OF *P. CARINII*

Continuous cultivation of *P. carinii* in vitro for purposes of testing of its susceptibility to antimicrobial agents has not been consistently achieved (23, 34, 85, 101). Although data suggestive of the activities of certain agents against *P. carinii* have been obtained in vitro (8, 34, 85), confirmation in rodent models has been used as a basis for clinical trials. In vitro studies have demonstrated a marked difference between the activities of a number of compounds against isolated target enzymes and against intact organisms (e.g., dihydrofolate reductase [8]). Activities in animal models have been highly predictive of the clinical efficacies of anti-*Pneumocystis* agents (see reviews by Hughes [54] and Walzer [138]). The spontaneous development of infection in immunosuppressed animals and infection via direct inoculation of organisms or exposure to infected animals are highly reproducible models of the utility of antimicrobial agents for the prophylaxis and treatment of *Pneumocystis* pneumonia (9, 10, 34, 54). Animal models may also be used to mimic clinically relevant immune deficiencies occurring as a result of corticosteroid or cyclosporine therapy, chemotherapy, humoral and cellular immune depletion and reconstitution, and a variety of other immunodeficiencies (6).

ANTIMICROBIAL SUSCEPTIBILITY

The emergence of resistance of *P. carinii* to the commonly used therapeutic agents has not been demonstrated in vitro for human-derived organisms or in animal models of *Pneumocystis* infection. Techniques that can be used to demonstrate the resistance of *P. carinii* to antimicrobial agents in vitro are not generally available (23). The relatively slow rate of replication of the organism (7 to 10 days) might predict that antimicrobial resistance of *P. carinii* would emerge more slowly than the rate of emergence of resistance in bacterial species. However, improved survival of immunocompromised hosts receiving prolonged periods of low-dose anti-*Pneumocystis* prophylaxis may contribute over time to the development of resistant strains. For example, recent data (74) suggest that polymorphisms in the dihydropteroate synthase genes of *P. carinii* from patients receiving TMP-SMX are consistent with the evolution of dihydropteroate synthase genes under selective pressure from sulfa drugs (74) and may contribute to a diminished susceptibility of the organism to sulfonamide agents in patients with poor clinical responses to therapy. However, the inability to maintain prophylaxis or to complete a course of therapy for *Pneumocystis* infection with specific agents is due more often to drug toxicities than to a lack of a clinical response.

PROPHYLACTIC STRATEGIES FOR PNEUMOCYSTIS

In the pre-AIDS era, the prevention of *P. carinii* pneumonia was associated with time-limited antimicrobial agent use in the setting of prolonged neutropenia or corticosteroid use due to cancer chemotherapy. In non-AIDS, immunocompromised patients, given the potential side effects and costs of therapy, routine anti-*Pneumocystis* prophylaxis has been reserved, in general, for clinical centers or patient groups that are known to have a fixed, high incidence of disease (i.e., on the order of 3 to 5% of susceptible hosts) or for individuals with recurrent *Pneumocystis* disease. Without the use of anti-*Pneumocystis* prophylaxis or antiretroviral therapies, approximately 40,000 cases of *Pneumocystis* pneumonia would be expected in HIV-infected persons each year. Prior to the use of the HIV protease inhibitor antiviral agents, more than 60% of AIDS patients receiving antiviral therapies and who had been cured of *P. carinii* pneumonia would be expected to suffer a recurrence within 1 year without anti-*Pneumocystis* prophylaxis. The benefits of anti-*Pneumocystis* prophylaxis (extension of survival by about 9 to 12 months) are less marked outside North America, where the apparent incidence of infection is lower. Despite these caveats, anti-*Pneumocystis* prophylaxis in AIDS patients has a significant beneficial impact on survival, quality of life, hospitalization frequency, and per patient health care expenditures (38, 62, 69, 137).

Prophylaxis in AIDS patients should be lifelong rather than time limited unless reversal of the predisposing immune deficits can be demonstrated. Antiviral therapies (largely directed against HIV in AIDS patients and CMV in transplant recipients) are central to the prevention and treatment of *Pneumocystis* pneumonia (2, 31, 42, 51, 79). Historically, the rate of *Pneumocystis* pneumonia in AIDS patients was halved by the use of zidovudine for the duration of the effective antiviral effect of this agent. Recent data support a link between the incidence of opportunistic infections and the efficacy of antiviral therapy. Thus, the relative risk of *Pneumocystis* pneumonia increases by up to 2.8-fold for each 1-log increase in viral load (10a); for individuals with CD4 lymphocyte counts of under 50/mm^3, the risk is 3.2-fold higher for a viral load of more than 50,000 copies/ml versus the risk for those with loads under this level. Some individuals are virologically unresponsive to highly active antiretroviral therapy; even in responders with CD4 counts of more than 200/mm^3 and undetectable viral loads, improvements in immune competence (e.g., by delayed-type hypersensitivity testing) may not be detected for more than 12 weeks. Thus, the benefits of antiviral therapies, including the timing of improvements in immune function in relation to decreasing viral loads and increasing CD4 counts, and the duration of these effects must be assessed for each patient. The need for and the duration of prophylaxis in individuals with rising CD4 counts and falling or undetectable HIV loads remains to be established.

The use of appropriate anti-*Pneumocystis* and/or antiviral prophylaxis is complicated by the toxicities associated with the medications, socioeconomic factors, and/or failures in compliance, which may be related to drug side effects and to the large number of medications many patients may be expected to consume. The increased incidence (50 to 60%) of side effects due to TMP-SMX in AIDS patients compared with the inci-

dence in patients without AIDS (approximately 10 to 25%) has led to the development of a variety of alternative regimens for prophylaxis against *P. carinii*. Very few HIV-infected individuals are capable of completing a long-term (36-month) course of any individual agent (14, 119). The median time to the switching of therapies which have begun with either TMP-SMX or dapsone is approximately 2.5 years, with approximately 20% of patients requiring multiple (two or more) changes in their prophylactic regimens (114). Thus, over time, more patients receive less adequate therapies. Approximately 20% of patients with AIDS will develop *Pneumocystis* pneumonia, despite prophylaxis: 16% per person year for primary prophylaxis and 12.1% per person year for secondary prophylaxis (114). The main predictor of failure of prophylaxis is profound CD4 lymphopenia (76% of patients in whom prophylaxis fails have fewer than 50 cells/mm^3).

Adults and adolescents with HIV infection and CD4$^+$ counts of less than 200 cells/mm^3, unexplained fever for longer than 2 weeks, a history of oropharyngeal candidiasis, or rapid progression of disease as measured by rising viral titers or falling CD4 counts should receive prophylaxis for *P. carinii* (19, 69, 100, 122). Prophylaxis is recommended for all HIV-infected children with CD4$^+$ counts of less than 1,500 cells/mm^3 if they are younger than 11 months of age, HIV-infected children with CD4$^+$ counts less than 1,000 cells/mm^3 if they are between 1 and 5 years old, and HIV-infected children with CD4$^+$ counts of less than 500 cells/mm^3 after age 5 and HIV-infected any child in whom the proportion of CD4$^+$ cells falls to less than 24% (123, 130). The greatest risk for children may be at 3 to 6 months of age, making the identification of the HIV-infected infant critical to survival.

The use of appropriate prophylaxis will generally prevent *Pneumocystis* pneumonia in the transplantation recipient (16, 17, 28, 31, 44, 91, 94, 118, 129, 131). Prophylaxis should be maintained in the stable transplant patient for at least 6 months after surgery. It should be noted that in transplant centers without a fixed, high incidence of *Pneumocystis* pneumonia, prophylaxis may be reserved for patients in whom chronic, high-level immune suppression, especially with corticosteroids, is needed to maintain graft function. If immune suppression cannot be reduced after a course of treatment for *Pneumocystis* pneumonia, prophylaxis should be maintained indefinitely. In Europe, where posttransplantation immunosuppressive regimens are often less intensive, such reductions may not be feasible. Prophylaxis should be reinstituted (i) in patients with increases in immune suppression including pulse corticosteroids or antilymphocyte therapies during transplantation; (ii) in patients with persistent or acute CMV infection (in AIDS patients or transplant recipients), (iii) during the treatment of graft-versus-host disease following bone marrow transplantation; and (iv) in patients with neutropenia which is not rapidly reversible (2, 5, 17, 53, 92, 94, 102, 125, 127, 132). Patients who have undergone transplantation during or shortly after a course of corticosteroids (e.g., for pulmonary disease or for autoimmune hepatitis) are at increased risk of early *P. carinii* pneumonia in the first weeks after transplantation. These individuals should receive prophylaxis pretransplantation, if possible, and at the earliest possible time after transplantation.

TMP-SMX. TMP-SMX (co-trimoxazole) is the agent of choice for the prevention of *Pneumocystis* infection in any patient who can tolerate this fixed-combination agent (1, 30, 45, 62, 83, 131). With one single-strength tablet per day (doses of 80 mg of TMP and 160 mg of SMZ) or one double-strength tablet per day, a wide variety of opportunistic infections are generally prevented: those caused by *P. carinii*; *Toxoplasma gondii*; *Listeria monocytogenes*; *Isospora belli*; many community-acquired respiratory, gastrointestinal, and urinary tract pathogens; and *Nocardia asteroides*. However, infections due to *Nocardia* have been described in bone marrow transplant recipients receiving TMP-SMX (120). While the protection against *T. gondii* is incomplete in AIDS patients (80 to 90% effective) receiving this dosage (generally, a double-strength tablet a day might be used for seropositive individuals without a history of *T. gondii* infection), breakthrough *T. gondii* infection has rarely been seen in transplant recipients or cancer patients.

A variety of prophylactic regimens have been studied. Among patients with AIDS, studies of low- and high-dose regimens (single- or double-strength TMP-SMX) for prophylaxis for individuals with CD4$^+$ counts of less than 200/mm^3 suggest no advantage to the prevention of mortality with the higher dose (12% incidence in the high-dose group versus 15% incidence in the lower-dose group) and the earlier occurrence of toxicity in the high-dose group (119). No disease was observed in either group at 1 year when the patients were compliant (43 of 156 patient in this series were noncompliant). Sixty-three of 156 patients dropped out due to toxicity. Drug toxicity is commonly observed even with low-dose regimens, especially in the form of mild bone marrow suppression. Such bone marrow toxicity is most notable when TMP-SMX is used in combination with other agents that suppress hematopoiesis (e.g., azathioprine, ganciclovir, zidovudine, cyclophosphamide [Cytoxan], and allopurinol), with malnutrition, or during infection (infection with HIV, *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, and CMV) (73). For the prevention of *Pneumocystis* infection administration of TMP-SMX (single or double strength) daily or 3 days per week is equally effective (59, 60, 62, 122). In studies with patients receiving either primary or secondary prophylaxis with TMP-SMX (double strength) three times a week, 28% had mild side effects (nausea, rash, pruritis), and 15 of 116 discontinued therapy; 11 of these 116 patients (7%) were considered drug intolerant (113). Toxicity in the form of anemia, neutropenia, and azotemia have been related to TMP levels in patients with AIDS (52). Rash and hepatotoxicity have been related to serum sulfa levels (52). Some patients will not tolerate any dose of sulfa drugs due to significant rash, occasional Stevens-Johnson syndrome, hepatitis (particularly in liver allograft patients), eosinophilic nephritis, or neutropenia.

Significant toxicities generally evolve within the first month of therapy unless they are masked by immune suppression, especially during high-dose corticosteroid use for acute pneumonia or graft rejection. Hyperkalemia may be observed in the setting of normal renal function as a result of the interference of TMP with the secretion of potassium at the renal distal tubule. This is reversible and more common during full-dose therapy than with prophylaxis. Treatment of TMP-SMX-induced neutropenia with folinic acid has been associated with treatment failure in some individuals (115). AIDS patients with mild intolerance of TMP-SMX will often tolerate the reintroduction of the drugs at a lower dose after resolution of acute toxicities (generally rash) (122). Both oral and intravenous desensitization regimens will allow the use of the TMP-SMX in many patients (69%) who are otherwise intolerant of TMP-SMX (18, 110, 122). However, only 37% are able to continue treatment with TMP-SMX; many patients will still manifest the nonallergic side effects of TMP-SMX and are unable to resume prophylaxis with this agent (32%). In patients with AIDS, desensitization, when tolerated, is generally preferable to the use of alternative agents. Rapid oral desensitization is possible and is well tolerated initially in up to 86% of patients tested in

small series. However, intolerance (largely rash) may subsequently emerge, usually within 1 month. Gradual dose escalation is better tolerated, with the proportion of patients ultimately able to use TMP-SMX being related to the total dose administered. By contrast, alternative agents should be used for anti-*Pneumocystis* prophylaxis in bone marrow and organ transplant recipients with similar, mild, drug-related toxicities (bone marrow suppression, nephritis, nausea, hepatitis), at least until graft function and immunosuppressive regimens are stable (31, 73). In organ transplant recipients, toxicity is increased when the concentrations of TMP-SMX in plasma are higher, but toxicity to transplanted organs may occur at any level of drug, and once toxicity is established, it rarely resolves without complete discontinuation of the agent.

Pentamidine. Alternative prophylactic regimens are available for patients intolerant of TMP-SMX. The use of aerosolized pentamidine isethionate (300 mg every 3 to 4 weeks) was pioneered for primary and secondary prophylaxis in AIDS patients and is also well tolerated by organ transplant recipients (106, 117, 118). Pentamidine aerosol prophylaxis is most effective when it is administered by experienced personnel with a nebulizer (e.g., Fisons or Respirgard II) which produces droplets in the 1- to 3-μm range. Dosing at 300 mg twice monthly for secondary prophylaxis may be more effective than monthly administration (21, 62, 108). At 600 mg per month, accumulation of pentamidine in plasma does not occur (21). However, the pentamidine concentration in the lungs continues to rise for the first 6 months of therapy with aerosolized pentamidine. The use of either intravenous or aerosolized pentamidine (300 mg every 3 to 4 weeks) for prophylaxis has been successful in small series of liver transplant patients (91, 118).

Breakthrough infection is seen in a range of from 10 to 23% of patients compliant with aerosolized pentamidine regimens for 1 year, most often in patients with rapidly progressive AIDS and/or CD4 counts of less than 50/mm^3. Either because the distribution of aerosolized drug may not reach the upper lobes or because the growth of *Pneumocystis* may be favored in the upper lobes of the lungs, breakthrough infection of the upper lobes has often been observed (15). The effect of adjusting patient positioning during inhalation is unclear. Breakthroughs are seen in patients receiving primary prophylaxis following transplantation or in AIDS patients who have not yet received two or more doses of antimicrobial agent (i.e., in the first 8 to 10 weeks of primary or secondary prophylaxis) or in patients receiving secondary prophylaxis after the incomplete clearance of infections (31, 102). Breakthrough infection has been seen in transplant patients with tissue-invasive CMV infection, those receiving chemotherapy (for hepatoma or Kaposi's sarcoma), or those receiving antilymphocyte globulins or high-dose steroids for graft rejection (2, 5, 17, 91, 102). In single-lung transplant recipients, prophylactic failures have been observed in the residual (native) lung, despite successful protection of the allograft. When breakthrough infection occurs in patients receiving aerosolized pentamidine by noninvasive means, diagnosis is often complicated by reduced organism numbers and lung biopsy may be required (77).

The side effects of pentamidine therapy are usually minimal (13, 43, 107, 119). Cough and bronchospasm are common and are generally reversible with bronchodilator therapy. Less often, hypoglycemia or hyperglycemia is noted. Transient, mild hypoglycemia or nausea is more common following intravenous administration than following administration of the aerosolized form of the drug. Pneumothorax is a common complication of *Pneumocystis* infection of the upper lobes, but a unique relationship with aerosolized pentamidine therapy has not been demonstrated (15, 43, 87). Toxicity to the alveolar epithelium is suggested by in vitro studies (65). The use of pentamidine prophylaxis requires the simultaneous administration of a second antimicrobial agent (e.g., a quinolone) for antibacterial prophylaxis in transplant recipients, although this is generally not required in patients receiving TMP-SMX.

Dapsone. Alternative prophylactic agents have generally become preferred over pentamidine. In AIDS patients and in transplant recipients, dapsone (diaminodiphenylsulfone), with or without TMP or pyrimethamine, is widely used for prophylaxis in a variety of combinations (12, 41, 62, 95, 104). While low levels of sulfone in serum are attained in vivo, therapeutic levels are maintained in alveolar fluids (21, 22). Dapsone has been shown to have activity equivalent to those of SMX and sulfadiazine in in vitro assays of activity against the enzyme dihydropteroate synthase when the drugs are used at equivalent concentrations (22, 134). Because of a long serum half-life (up to 50 h), dapsone may be administered at dosages of from 50 to 100 mg per day to 100 mg per week. Breakthrough infection has been observed in AIDS patients receiving dosages of up to 50 mg/day; toxicity begins to be limiting at 100 mg/day, limiting the utility of the drug as a single agent for prophylaxis or therapy (61, 84). Therefore, pyrimethamine may be administered weekly (25 or 50 mg) to supplement dapsone (50 to 100 mg/day). Clinical trials with patients with AIDS suggest that daily TMP-SMX is superior to dapsone (at 100 mg/day with pyrimethamine at 25 mg/day) for *Pneumocystis* prophylaxis (at 380 days, 3.7% incidence of *P. carinii* pneumonia with TMP-SMX and 15.2% incidence with dapsone), even though the mortality rate does not differ between the two therapies (66, 103). A meta-analysis of 35 randomized trials of *Pneumocystis* prophylaxis with 6,583 AIDS patients suggested that TMP-SMX is superior to pentamidine and to lower-dose dapsone (the equivalent of 25 mg/day) for prophylaxis but is equivalent to higher-dose dapsone regimens (50 to 100 mg/day) (62). TMP-SMX and dapsone have equal anti-*Toxoplasma* efficacies, and the rates of withdrawal from therapy are equal among patients receiving the two regimens (31/100 person years for TMP-SMX and 28/100 person years for dapsone) (62). Trials of dapsone at dosages of 100 mg two or three times per week show that dapsone therapy is equivalent to pentamidine therapy; therapy with dapsone at dosages of 100 mg per day is equivalent to TMP-SMX therapy. TMP may replace pyrimethamine in combination with dapsone (100 to 200 mg per day) in patients with creatinine clearances of more than 15 ml/min.

The ultimate incidence of intolerance to dapsone (i.e., from mild side effects including anemia and rash to anaphylaxis) is roughly equivalent to that to TMP-SMX (65 to 70%). Up to 40% of the patients who discontinue prophylactic therapy with either of these agents due to toxicity will not be able to tolerate the other drug (66). Switching from TMP-SMX to dapsone cannot be recommended for individuals with severe side effects from either agent including desquamation, neutropenia, severe nephritis, or hepatitis or in patients with documented glucose-6-phosphate dehydrogenase (G6PD) deficiency. The toxicities observed with dapsone are long-lived and may limit the utility of dapsone, especially in liver transplant recipients. Severe methemoglobinemia has been observed in some AIDS patients receiving dapsone and/or primaquine (86, 124). In general, neutropenia (especially in the G6PD-deficient host), hepatitis, and rash are limiting for each of these regimens, and they offer no benefit over low-dose TMP-SMX. In the transplant recipient, intolerance of TMP-SMX generally predicts intolerance of dapsone. Furthermore, dapsone is metabolized via the hepatic P-450 system (CYP3A), which predicts interference with cyclosporine and tacrolimus (FK506) metabolism and increased

serum dapsone levels in the presence of ketoconazole or fluconazole. Dapsone may increase the levels of the HIV retroviral protease inhibitors, with the resultant enhancement of toxicities. In vitro, dapsone may increase the level of replication of HIV-1, an effect that bears further investigation (24). One unblinded clinical trial which is often cited compared dapsone (50 mg/day) with aerosolized pentamidine (300 mg/month) for secondary prophylaxis for *Pneumocystis* pneumonia (116). This trial with 196 AIDS patients was discontinued due to excess mortality in the dapsone group (42%) versus the pentamidine group (21%). While the dapsone group had a lower mean CD4-lymphocyte count at the baseline, the outcome suggested the possibility of interactions between dapsone and zidovudine, an oxidative effect of dapsone, or an adverse effect of the iron protoxalate given with the dapsone (116). Similar mortality data have not been observed in other prophylaxis trials with dapsone alone or in combination with other agents (1, 41, 48, 96, 97, 104, 126).

In a primary prophylaxis trial (AIDS Clinical Trials Group protocol 081) with AIDS patients with CD4 counts of less than 200/mm^3, dapsone (50 mg twice daily), TMP-SMX (one double-strength dose once daily), and pentamidine aerosol (300 mg monthly) were compared (14). *P. carinii* pneumonia occurred at an equal frequency in each group on the basis of an intent-to-treat analysis. In the subgroup of individuals with fewer than 100 CD4$^+$ cells/mm^3, the estimated 36-month risks of *P. carinii* pneumonia was 19% for the TMP-SMX group, 22% for the pentamidine group, and 33% for the dapsone group. The mean time to the discontinuation of therapy was 14.6 months for the TMP-SMX group, 17.1 months for the pentamidine groups, and 13.7 months for the dapsone group, reflecting the incidence of intolerance. The cost-effectiveness of TMP-SMX has been calculated to be significantly better than that of aerosolized pentamidine for secondary prophylaxis in AIDS patients in a retrospective analysis of published clinical trials (35).

Pyrimethamine and atovaquone. Pyrimethamine-sulfadoxine (Fansidar; weekly) has successfully been used to prevent pneumocystosis (29). Atovaquone (formerly BW566c80) has been approved by the U.S. Food and Drug Administration for the treatment of mild to moderate *P. carinii* infections, but it may also be useful for prophylaxis. Atovaquone is well tolerated, undergoes enterohepatic circulation without metabolism, and has a long serum half-life ($\geq$70 h) (55). Atovaquone is a hydroxynaphthoquinone and an inhibitor of mitochondrial electron transport. It is active against a broad range of protozoa and *P. carinii*, but it has no antibacterial activity. In part, this effect may be mediated by inhibition of dihydroorotate dehydrogenase, a pyrimidine biosynthetic enzyme linked to the mitochondrial respiratory chain (63). In AIDS patients receiving 750 mg orally (three 250-mg tablets) three times daily, some breakthrough infections have been observed. The bioavailability of atovaquone tablets (discontinued) in AIDS patients was approximately 26%, which is half to two-thirds of the bioavailability in healthy hosts. Bioavailability has been significantly improved via reformulation of the drug as a suspension. Absorption is enhanced by fatty foods and is decreased by diarrhea. In transplant patients, the levels achieved in the serum after the administration of prophylactic dosages of the reformulated atovaquone suspension in the range of 1,000 to 1,500 mg/day exceeds the MIC of atovaquone for rodent-derived *P. carinii*. However, some breakthrough infections have been seen with this dosage. Thus, higher dosages (1,500 to 2,250 mg/day) may ultimately be needed if the drug is to be developed for this indication. Atovaquone has the potential advantage of having activity against the bradyzoites (intracystic bodies) of *T. gondii*, a major cause of encephalitis (in AIDS patients) and carditis (in cardiac transplant recipients). Transplant or AIDS patients requiring a multiple opportunistic pathogen prophylaxis strategy will require a second antimicrobial agent in addition to atovaquone for this purpose.

The incidence of side effects from atovaquone treatment is low. Rash, nausea, and elevated liver transaminase levels were occasionally documented (53). The incidence of rash correlates with the concentration in serum. Some patients complain about the flavor and color of atovaquone liquid (which stains clothes) but find it preferable to aerosolized pentamidine. Large-scale studies have not been performed with non-HIV-infected hosts. In small numbers of transplantation recipients, interactions of atovaquone with cyclosporine and tacrolimus have not been documented; prospective randomized trials are under way.

Clindamycin-pyrimethamine and other agents. Both treatment and prophylaxis with the combination of clindamycin and pyrimethamine are effective as alternatives to treatment and prophylaxis with TMP-SMX (4, 68). However, while small prospective trials have indicated some efficacy of prophylaxis (68), in one large trial, the rate of *Pneumocystis* pneumonia in clindamycin-pyrimethamine-treated recipients (primary and secondary prophylaxis) was 30.7 per 100 patient years versus 3.4 per 100 patient years for TMP-SMX and 11.0 per 100 patient years for dapsone (4). This difference was maintained for the subgroup receiving primary prophylaxis. While higher doses of these agents would likely prove to be effective for prophylaxis on the basis of data from trials of therapy with these agents, clinical trials of the combination of clindamycin and primaquine for the prevention of pneumocystosis have been complicated by a high incidence of colitis and anemia (especially in glucose-6-phosphate-deficient hosts).

Patients receiving prophylaxis for toxoplasmosis (sulfadiazine, triple sulfa, atovaquone, or clindamycin with pyrimethamine or primaquine) have also been protected against *P. carinii* (104). Patients receiving quinolone antimicrobial agents (e.g., for prophylaxis against urinary tract infection following renal transplantation) will be at the same risk for *Pneumocystis* pneumonia as the general population. Studies of azithromycin and clarithromycin as prophylaxis for *M. avium* complex infection suggest up to a 50% reduction in the incidence of *Pneumocystis* pneumonia with the use of these agents. Trials by Hughes and coworkers (54) suggest that the macrolides may have a place in the prophylaxis of *Pneumocystis* infection but that these agents are unlikely to be effective as single agents for this purpose. The combination of atovaquone and azithromycin for prophylaxis in HIV-infected children is under study (AIDS Clinical Trials Group protocol 254). Tacrolimus (FK506) is a macrolide, and therefore, the metabolism of this agent is altered to a significant degree by both erythomycin and clarithromycin and to a lesser extent by azithromycin.

BREAKTHROUGH INFECTION

Breakthrough infection is uncommon in patients taking TMP-SMX, for which systemic absorption is routinely adequate (114). All other prophylactic agents may be considered second-line agents. The occurrence of infection while receiving prophylaxis reflects (i) inadequate treatment prior to the initiation of secondary prophylaxis or the occurrence of infection before adequate levels in tissue are established (e.g., pneumonia between the times of administration of the first and third doses of aerosolized or intravenous pentamidine for primary prophylaxis); (ii) noncompliance, which is often due to the occurrence of side effects; (iii) inadequate dosing, which is due

to the malabsorption of oral agents or rapid metabolism or clearance of the drug; (iv) progressive immune deficiency with the use of a second-line prophylactic agent (CD4 counts less than 50/mm^3 in patients with AIDS, CMV infection, or acute immunosuppression for allograft rejection); (v) high-level exposure in the community, a theoretical concern suggested by the clustering of cases; and (vi) resistance to the antimicrobial agent, the mechanisms of which are incompletely understood (74). One example of inadequate dosing is the development of either extrapulmonary pneumocystosis or apical pulmonary infection with pneumothorax while receiving aerosolized pentamidine. This may reflect inadequate delivery to the sites of infection rather than drug resistance per se. In the 476 AIDS patients with CD4 counts of less than 200/mm^3 followed for 2 years in the Multicenter AIDS Cohort MAC (*M. avium* complex) Trial, 92 (19%) had breakthrough infection (114). The incidences of breakthrough infection were 9.8% for the TMP-SMX group, 13% for the dapsone group, and 14% for patients on aerosolized pentamidine. The most important risk factor was the CD4 count (76% of the breakthrough infections were in patients with fewer than 50 CD4 cells/mm^3), with fever being the most common sign of infection (114).

VACCINE DEVELOPMENT

The development of vaccines for the prevention of *Pneumocystis* pneumonia has been hindered by the inability to define for the organism invariant antigens which generate protective immunity, especially in immunocompromised individuals. Patients with *P. carinii* pneumonia generally carry both antibodies and T lymphocytes against *Pneumocystis* antigens at the time of presentation. Thus, the assumption has been made either that such immunities are not protective, that the correlates of protection (the target antigens) have not yet been identified, that the antigens expressed on the surface of the organism have changed, or that protection rests primarily with the cellular immune control of alveolar macrophage function. The organism produces a relatively limited array of surface glycoproteins which have been characterized at the glycoprotein and molecular levels. The major surface glycoprotein (MSG) represents the main humoral immunogen in rats, although other antigens (gp45-55) may have importance in human infection (32, 40, 71, 136). MSGs are encoded by a large family of related genes (>30), many of which are located in tandem repeated arrays in the subtelomeric regions and which may contribute to the generation of the variety of antigenic types (136). Data from a number of laboratories, including my own, suggest that each genomic copy of a MSG includes an upstream highly conserved expression site and downstream a unique segment encoding the differing antigenic characteristics of each clone. No evidence of the active switching of genotypes has been developed to date, e.g., under selective immune pressure. Clusters of organisms carrying multiple different MSG types (up to three) have been observed in individual animals and patients with *Pneumocystis* pneumonia. It is unclear whether a single organism can express multiple MSGs or switch MSG expression during the life cycle. The possibility of the exchange of membrane lipids and perhaps glycoproteins between *P. carinii* and host cells may further decrease the effectiveness of the host's immune response to infection.

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