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MINIREVIEW

Treatment of Infection Due to *Pneumocystis carinii*

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The therapy of infection due to *Pneumocystis carinii* has evolved in two areas over the past 20 years. First, improvements in the diagnosis of *Pneumocystis* infection have facilitated early diagnosis; treatment can often be initiated before marked deterioration in pulmonary function is observed. Second, the prolonged survival of immunocompromised patients has altered the presentation of *Pneumocystis* pneumonia, with there being an increased incidence of patients presenting with, in addition to *P. carinii*, multiple opportunistic infections often with some degree of resistance to common antimicrobial agents; the development of atypical (e.g., extrapulmonary) presentations of disease; and a growing number of patients requiring alternative prophylactic regimens due to drug toxicity (19a). Because *Pneumocystis* infection can be rapidly progressive and the success of therapy is related to the severity of disease at the time of the initiation of therapy, early therapy is essential. The short-term use of treatment (48 h) will not impair the histopathologic diagnosis of infection if, for example, bronchoscopic or laboratory support services are temporarily unavailable. The risk of opportunistic infection may be reduced by decreasing the level of immune suppression in patients receiving exogenous immune suppression for autoimmune diseases or following organ transplantation or by decreasing the viral load in patients infected with human immunodeficiency virus (HIV). Treatment of *Pneumocystis* should be successful if a 14- to 21-day course of therapy is tolerated.

CLINICAL PRESENTATION

A number of atypical clinical features may alter the choice of therapy for *Pneumocystis* infection.

Multiple infections are often present simultaneously with *Pneumocystis* infection. Multiple infections are often present simultaneously with *Pneumocystis* infection. Thus, failure to respond to appropriate anti-*Pneumocystis* therapy may reflect the progression of another process which may require treatment before clinical improvement is observed.

Response to appropriate therapy may be slow. Response to appropriate therapy may be slow, especially in those with severe respiratory compromise or concurrent underlying lung disease.

Radiologic appearance lags behind clinical deterioration or improvement. Radiologic appearance lags behind clinical deterioration or improvement, most commonly in the patient with altered pulmonary parenchyma due to radiation therapy, chemotherapy, or prior surgery; or in the patient receiving corticosteroid therapy; or in the patient with neutropenia.

Empiric therapy is generally avoided in the immunocompromised host without AIDS. Empiric therapy is generally avoided in the immunocompromised host without AIDS due to the urgency for specific antimicrobial therapy and the high frequency of side effects from the commonly used therapies. Given the efficacy of prophylaxis and the potential deleterious impact of such therapies on the yields of diagnostic procedures, empiric therapy in the patient receiving anti-*Pneumocystis* prophylaxis is also not recommended.

Extrapulmonary disease may be present in the absence of significant pulmonary disease. Extrapulmonary disease may be present in the absence of significant pulmonary disease, particularly in AIDS patients receiving aerosolized pentamidine prophylaxis (19, 35, 45).

Solid organ transplant recipients suffer nephrotoxicity with full-dose TMP-SMX treatment. Solid organ transplant recipients, particularly those with renal and hepatic transplants, frequently suffer nephrotoxicity with full-dose trimethoprim (TMP)-sulfamethoxazole (SMX) treatment (and often with pentamidine treatment) and may not recover normal renal function subsequent to drug-induced renal injury. In the HIV-infected, transplant, or chemotherapy patient receiving a variety of hematopoiesis-suppressive therapies, drug-related toxicities are common and may necessitate dose reduction or the switching of antimicrobial agents.

TOXICITIES OF ANTIMICROBIAL AGENTS AND CAUSES OF TREATMENT FAILURE

The incidence of adverse reactions to antimicrobial agents, i.e., those which necessitate a switching of antimicrobial agents, is increased in AIDS patients and in organ and bone marrow transplant recipients. Bone marrow suppression is often observed due to the synergistic effects of infections (HIV, cytomegalovirus [CMV], mycobacteria), drug toxicities, and nutritional deficits. Neutropenia following organ transplantation may be due to azathioprine, infection with CMV, and treatment for CMV infection (e.g., with ganciclovir or foscarnet) and may be further exacerbated by prophylaxis with TMP-SMX. Fever in transplant recipients may reflect TMP-SMX toxicity, occult infection, or graft rejection. In the transplant recipient, the evaluation of the patient with elevated creatinine levels may be complicated by the use of multiple drugs (cyclosporine, tacrolimus, ganciclovir, acyclovir, TMP-SMX, antihypertensive agents), infection (CMV, bacteria), urinary outlet obstruction, vascular blockage, graft rejection, or recurrence of the underlying renal disease. Thus, while the incidence of intolerance by transplant recipients to one or another agent is closer to 25% than the 50% seen in AIDS patients, significant toxicity remains a common feature of therapy in both groups.

Treatment failure with an accepted regimen is uncommon. Thus, changing antimicrobial agents other than for toxicity is not generally indicated. While there are patients who appear to do better on one agent instead of another, it is much more common to recognize a second process (infection, tumor,

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TABLE 1. Treatment of *P. carinii*[a]

Agent(s) (route)[b]	Dose	Options or comments[b]
First line: TMP-SMX (i.v. or p.o.)	15–20 mg of TMP/kg/day and 75–100 mg of SMX/kg/day	Treat through rash with reduced dose; desensitize
Second line		
Dapsone (p.o.) with TMP (p.o. or i.v.)	100 mg of dapsone/day and 15–20 mg of TMP/kg/day	Side effects include methemoglobinemia and glucose-6-phosphate dehydrogenase deficiency; may be tolerated in patients with sulfa drug allergy
Atovaquone (p.o.)	750 mg of liquid p.o. t.i.d.	Variable absorbance; absorbance is improved with fatty food; few side effects
Pentamidine isethionate (i.v.)	4 mg/kg/day; 300 mg/day maximum	Lower dose (2–3 mg/kg may be used); intramuscular administration not advised
Third line		
Trimetrexate (i.v.) with folinic acid	30–45 mg of trimetrexate/m^2/day with 80–100 mg of folinic acid/m^2day	Efficacy equal to that of pentamidine; anemia, marrow toxicity; early relapse
Clindamycin (i.v. or p.o.) and primaquine	450–600 mg of clindamycin every 6 h and 15–30 mg of primaquine base once a day	Side effects include methemoglobinemia and diarrhea (may substitute pyrimethamine for primaquine)
Others		
Pyrimethamine (p.o.) with sulfadiazine (p.o.)	Load of 50 mg of pyrimethamine b.i.d. for 2 days and then 25–50 mg q.d., load of 75 mg/kg of sulfadiazine and then 100 mg/kg/day	Not studied fully; maximum of 4 g of sulfadiazine in two doses (up to 8 g total)
Pyrimethamine-sulfadoxine	Not standardized	Long half-life; should not be used in patients with sulfa drug allergy
Piritrexim-folinic acid	Under study	Like trimetrexate
8-Aminoqunoline	Under study	
Macrolides and sulfonamides	Under study	Synergy; macrolides alone are inactive

[a] Adjunctive therapies (see text) include corticosteroids (high dose with rapid taper), possibly gamma interferon, and GM-CSF. Abbreviations: i.v., intravenous; p.o., oral; t.i.d., three times a day; q.d., once a day; b.i.d., twice a day.

[b] Based on the clinical judgment of the physician; some agents are not approved by the U.S. Food and Drug Administration for this indication (ranking of therapies is based on the author's experience) (see also references 26 and 48).

allergy, adult respiratory distress syndrome) complicating *Pneumocystis* pneumonia than a resistance to antimicrobial therapy. The chest radiograph is less reliable than the level of arterial blood oxygenation as an indicator of treatment failure. The addition of pentamidine to TMP-SMX offers no advantage over the switching of agents. Furthermore, experiments with animals suggest the possibility of antagonism between these agents when used in combination. As a rule, those patients who need to be switched from TMP-SMX to pentamidine or vice versa have worse survival rates than those who can tolerate 14 to 21 days of either agent alone. The success rate for treatment with TMP-SMX or pentamidine is on the order of 60 to 80%. In patients with minor intolerance (minor rash, gastrointestinal intolerance), desensitization to TMP-SMX is preferred to the switching of agents for moderate to severe pneumonia. The addition of adjunctive therapies (e.g., corticosteroids and hematopoietic growth factors) may be more useful than the switching of antimicrobial agent regimens.

The proper duration of therapy has not been studied, but it is generally 14 to 21 days in all patients. Residual viable organisms may persist after treatment for up to a year (57). Many of the morphologically intact organisms isolated after the completion of therapy are nonviable, particularly after therapy with TMP-SMX. New, community-acquired infection is observed in successfully treated patients. Relapse in the immunocompromised patient without AIDS should not be expected after therapy with TMP-SMX, as long as immunosuppression can be reduced (notably, use of corticosteroid therapy) and other immunomodulating viral infection (e.g., CMV) does not occur. The preferred agents for the therapy of *P. carinii* pneumonia are outlined in Table 1.

Extrapulmonary pneumocystosis. Extrapulmonary pneumocystosis is probably more common than is generally appreciated on the basis of the frequent demonstration of organisms or nucleic acids in the peripheral blood or in extrapulmonary sites (for a review, see reference 19). The histologic demonstration of organisms is essential in extrapulmonary disease. Collections of *Pneumocystis* outside the lungs may be coinfected (e.g., with *Mycobacterium avium* complex or *Aspergillus* species), and infarction of tissues has been observed. The success of therapy for extrapulmonary infection can generally be assessed by radiologic regression of masses or abscesses. Intravenous therapy may be preferred initially for this indication. Complete regression occurs over 4 to 12 weeks. Secondary prophylaxis with aerosolized pentamidine may allow the reemergence of extrapulmonary infection and should be avoided in these patients.

SPECIFIC AGENTS

Trimethoprim-sulfamethoxazole. TMP-SMX is the agent of choice for the treatment of *Pneumocystis* pneumonia and extrapulmonary disease in all hosts who tolerate this combination agent (11, 26, 48, 59). TMP-SMX has the advantage of excellent tissue penetration, the most rapid clinical response of the anti-*Pneumocystis* agents (often 3 to 5 days in patients with mild to moderate disease), and bioavailability from oral therapy comparable to that of parenteral administration. Data from studies with animals suggest that the majority of the anti-*Pneumocystis* activity is vested in the SMX and that a variety of sulfa drugs might suffice as monotherapy for *Pneumocystis* pneumonia (25). Survival without intubation and mechanical ventilation appears to be greater with TMP-SMX than with

pentamidine (by up to 20%). Unfortunately, the incidence of side effects from TMP-SMX therapy is also greater than that from therapy with other agents. In part, this may reflect the use of dosage schedules developed for children in adults and the use of TMP-SMX without dosage adjustment in the setting of abnormal or changing renal function. In fact, the proper dosing in adults has not been completely studied. Therapy is initiated with 15 to 20 mg of the TMP component per kg of body weight per day (100 to 150 mg of SMX per kg per day) divided into three or four doses. Therapy should be initiated intravenously if there is uncertainty about gastrointestinal function or marked hypoxemia. Peak levels are obtained about 2 h after oral dosing and should approach the range of 100 to 150 μg of SMX per ml (5 to 15 μg of TMP per ml), although these levels are generally not tolerated by transplant recipients. After a clinical response is observed, the dosing can be reduced to 10 to 15 mg/kg/day in divided doses. Levels of more than 200 μg of SMX per ml are associated with a higher incidence of side effects, especially bone marrow suppression. In studies of AIDS patients receiving TMP-SMX for the treatment of *P. carinii* pneumonia, the incidence of anemia, neutropenia, and azotemia increased with increasing TMP concentration, while other events (rash, gastrointestinal intolerance, fever, and hepatic enzyme abnormalities) were independent of the concentrations of either component in plasma (25, 27, 29). However, levels in serum are highly variable and are difficult to correlate with the incidence of side effects (30).

Therapy can be continued (with adjustments) through mild side effects (rash, transaminase level elevations, neutropenia) which are tolerable to the patient and the physician. Dose reduction will often eliminate toxicity in AIDS patients. Desensitization to TMP-SMX may be used in patients with mild to moderate pneumocystosis. With renal dysfunction, dosing must be reduced; once-daily dosing is sufficient (3 to 5 mg/kg/day) for those with a glomerular filtration rate of 10 to 50 ml/min. The development of renal impairment in patients receiving TMP-SMX should prompt a search for urinary eosinophils and an assessment of the need for further therapy with this agent. Nephrotoxicity occurs frequently in the renal transplantation recipient receiving full-dose therapy; this toxicity is both idiosyncratic and dose related. In these patients, interstitial nephritis may occur without demonstrable urinary eosinophils, perhaps as a reflection of the use of corticosteroids for immune suppression, and eosinophils may be found on renal biopsy. The transplanted liver is particularly susceptible to TMP-SMX toxicity (eosinophilic infiltrates, hepatocyte necrosis, bilirubinemia) and may be confused with or complicate treatment for early rejection or systemic infection.

The side effects of TMP-SMX are generally those of sulfa drug allergy: rash (in 19% of patients; this includes Stevens-Johnson syndrome), fever in 19% of patients, transaminase level elevation, neutropenia, thrombocytopenia, erythema multiforme exudativum, and nephrotoxicity (48). In patients with AIDS, allergy to TMP is also observed, and allergies to the carriers in the various preparations of the drugs (dyes, coatings, filler) have also been reported. Both components of TMP-SMX interfere with folate metabolism. The bone marrow suppression is marked in patients with underlying hematological disorders; folinic acid supplementation is rarely useful and probably should be avoided in patients with acute leukemia (49). Drug rash, fever, azotemia, and increased levels of transaminases in blood will reverse only when therapy is stopped. Manifestations of sulfa drug and TMP toxicity may be masked by corticosteroids. The side effects of azathioprine (hepatitis, macrocytic anemia, neutropenia, hepatic veno-occlusive disease) may be accentuated by TMP-SMX.

Pentamidine isethionate. Pentamidine isethionate has been the main alternative parenteral agent for the treatment of *Pneumocystis* pneumonia. Pentamidine isethionate was first administered intramuscularly during an epidemic of the infantile form of the disease. It decreased the mortality rate from 50 to 3.5% among those affected. Subsequently, less dramatic effects were obtained with this agent in older children and adults: survival rates of 25 to 85% have been reported following its use (28). Pentamidine is now judged to be about 70% effective (28). Pentamidine isethionate may be administered either intravenously or intramuscularly; however, only the intravenous route is recommended. Complications with intramuscular therapy occurred in up to 50% of patients, notably, sterile abscesses at the site of injection. Intravenous pentamidine isethionate is given by slow (1- to 2-h) infusion in 5% glucose solution as a single dosage of 4 mg/kg/day. Evidence exists that lower dosages (3 mg/kg/day) are equally effective (14, 15). Pentamidine achieves therapeutic levels in the lungs slowly (5 to 7 days) due to high levels of extrapulmonary tissue binding. Slow accumulation of pentamidine in pulmonary tissue may account for the delayed onset of activity when compared with that for TMP-SMX. However, increased levels in serum with a long serum half-life and gradual accumulation in the lungs may play a role in the continued therapeutic effect of pentamidine after the cessation of therapy. Because this agent has a long serum half-life (6.4 h) and delayed excretion due to extensive tissue binding (longer than 240 h), pentamidine tends to accumulate during therapy. The reduction of symptoms by pentamidine may be due, in part, to suppression of the secretion of tumor necrosis factor by alveolar macrophages as well as to treatment of infection. Pentamidine has been supplanted by TMP-SMX for initial therapy of *Pneumocystis* infection in most patients (28, 52, 59). Pentamidine continues to be useful for infection in patients with adverse reactions to TMP or to sulfonamides.

Idiosyncratic side effects of pentamidine treatment are seen more often with daily therapy than with prophylactic dosing. These include transient hypoglycemia, pancreatitis, diabetes (after prolonged therapy, with or without prior pancreatitis), pancytopenia, hypotension, and renal dysfunction (42). These side effects are exacerbated by intravenous administration and in the presence of decreased renal function. Pentamidine should be avoided in pancreas transplant recipients due to the potential for islet cell necrosis. Newer pentamidine analogs under development appear to have significantly superior therapeutic and toxicity profiles compared to that of pentamidine (10, 18, 46, 54).

Dapsone. Dapsone (4,4′-diaminodiphenyl sulfone; orally at 100 mg per day) has been used in combination therapy with TMP (orally at 15 mg/kg/day divided into three doses) as an effective alternative oral therapy (34, 48). Many AIDS patients intolerant of SMX will tolerate dapsone, which is metabolized by the liver (half-life, ≥30 h). However, the long half-life and side effect profile (neutropenia in 1 of patients, anemia, fever, hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, rash, hepatitis) may be particularly disadvantageous in the marrow or organ transplant recipient.

Atovaquone. Atovaquone (a 750-mg suspension given orally three times a day) is approved by the U.S. Food and Drug Administration for the treatment of mild to moderately severe *Pneumocystis* pneumonia. The side effects of atovaquone are relatively uncommon and are generally mild. Comparative trials between atovaquone (tablets) and TMP-SMX suggest that TMP-SMX should be preferred in patients who tolerate this therapy (29). The bioavailability of atovaquone has been improved by reformulation as a suspension. Up to 7% of HIV-

infected patients develop limiting toxicity while on atovaquone during therapy (versus 20% for those on TMP-SMX therapy); however, significantly more patients in the atovaquone group than in the TMP-SMX group failed therapy due to a lack of a response. When pentamidine was compared to atovaquone for the treatment of mild to moderate infection, a lack of response was observed in 29% of atovaquone-treated patients and 19% of pentamidine-treated patients. However, atovaquone was better tolerated, with treatment-limiting side effects occurring in 9% of atovaquone-treated patients and 24% of pentamidine-treated patients. The incidence of rash, the most common side effect of atovaquone treatment, correlates with increasing serum drug levels (29). Other toxic effects include diarrhea, nausea, vomiting, fever, and increased enzyme levels in liver function tests (29, 60). Preliminary data for small numbers of stable organ transplantation patients suggests no interaction with cyclosporine or tacrolimus. Data from studies with animals suggest the possible presence of an interaction between atovaquone and erythromycin which merits further study.

Trimetrexate. Trimetrexate (45 mg/m^2/day) with folinic acid (80 mg/m^2/day) has been approved for use in patients with moderately severe pneumonia (1, 33, 51). Trimetrexate is a dihydrofolate reductase inhibitor and is lipid soluble with a serum half-life of up to 34 h. It will produce severe neutropenia in the absence of folinic acid supplementation (which should be continued for 3 to 5 days after the cessation of trimetrexate treatment) in some patients with simultaneous infections due to HIV or CMV, or during therapy with antiviral agents. Side effects include fever, rash, leukopenia, and transaminase level elevation. Relapsed infection in AIDS patients has been somewhat more frequent with trimetrexate therapy than with other therapies. The survival rate following therapy in AIDS patients is higher with TMP-SMX than with trimetrexate for moderately severe *Pneumocystis* pneumonia.

Piritrexim. Piritrexim is pharmacologically similar to trimetrexate but has been most useful in combination with a sulfonamide. A variety of chemical modifications of the methotrexate molecule may lead to more selective activity against *P. carinii* (5).

Clindamycin-primaquine. The combination of clindamycin (600 to 900 mg given intravenously or orally every 6 to 8 h) and primaquine (15 to 30 mg of primaquine base/day given orally) is effective in patients with mild to moderate infection (3, 9, 32, 41, 47, 48, 55, 56). No significant differences were observed among treatment groups consisting of AIDS patients receiving TMP-SMX, dapsone-TMP, or clindamycin-primaquine for mild to moderate *Pneumocystis* pneumonia in terms of survival, dose-limiting toxicity, therapeutic failure, or the ability to complete 21 days of therapy (48). Among the patients receiving all three regimens, dose-limiting toxicity was experienced by 30.9% of patients and 6.1% of the patients were considered to be therapeutic failures by day 7 (48). Thus, for an individual patient, the side effect profile is the main determinant of the choice of therapy. The main toxicities of clindamycin include rash (16% [48]) methemoglobinemia, anemia, neutropenia, and the development of *Clostridium difficile* colitis.

Pyrimethamine with sulfadiazine or trisulfapyrimidines. Pyrimethamine (50 to 100 mg/day orally after receiving a 100- to 200-mg load) with sulfadiazine or trisulfapyrimidines (4 to 8 g/day) is also effective but requires folinic acid (10 mg/day) supplementation. Pyrimethamine will decrease the renal clearance of creatinine without altering the glomerular filtration rate.

Macrolides. The macrolides (azithromycin, clarithromycin) have little efficacy as monotherapy, but appear to enhance the efficacy of SMX. However, this combination provides little benefit over TMP-SMX.

DFMO. The clinical utility of α-difluoromethylornithine (DFMO) has not been well established. The presence of the target enzyme in *P. carinii* (ornithine decarboxylase [ODC]) and activity against polyamine biosynthesis in vitro have been demonstrated (50). Because humans and *P. carinii* share the target enzyme ODC, the differential sensitivity of the organism to DFMO with rapid depletion of polyamines in *P. carinii* in vitro suggests a mechanism of action beyond ODC inhibition (38). Clinical experience with DFMO as primary therapy for *Pneumocystis* pneumonia has not been encouraging.

Newer agents. Newer agents under study include the echinocandins (glucan synthase inhibitors), which block the formation of cysts (2, 40); the 8-aminoquinolines, which have entered clinical trials (44); the dicationic substituted bis-benzimidazoles (antimicrotubule pentamidine derivatives) (6, 46, 54); terbinafine (17); isoprinosine; bilobalide (a sesquiterpene from *Ginkgo biloba* leaves); biguanide inhibitors (PS-15) of dyhydrofolate reductase (24); quinghaosu; albendazole (4, 16); proguanil; terbinafine; guanylhydrazones (58); and some nonquinolone topoisomerase inhibitors (18, 20).

BREAKTHROUGH INFECTIONS AND ADJUNCTIVE THERAPIES

Choice of antimicrobial agents in the treatment of breakthrough infections. The choice of antimicrobial agents in the treatment of breakthrough infections occurring in patients receiving prophylaxis has not been carefully studied and is guided by the reasons for failure of prophylaxis. Evidence from recent trials (ACTG protocol 108) with small numbers of patients suggests that treatment with the same agent used for prophylaxis (other than aerosolized pentamidine) is likely to be successful, despite the failure of prophylaxis (48). The possible emergence of resistance of *P. carinii* to antimicrobial agents is discussed in a previous review of prophylactic strategies (19a).

Adjunctive therapies. Adjunctive therapies to the treatment of *Pneumocystis* pneumonia include corticosteroids and, potentially, growth factors (colony-stimulating factors [CSFs]). Delayed response to therapy and/or the inability to reduce immune suppressive therapy may allow progressive disease, despite appropriate therapy for *Pneumocystis* pneumonia. Given the risks of nosocomial superinfection associated with intubation for assisted ventilation, the use of adjunctive corticosteroids was developed to prevent the early deterioration of AIDS patients with documented *Pneumocystis* pneumonia (12, 21, 37, 39). The use of corticosteroids (prednisone at 40 to 60 mg given once to three times a day orally or intravenously) in the first 72 h after admission may reduce pulmonary inflammation to a degree sufficient to avoid intubation. When studied in AIDS patients, the use of corticosteroids in patients with a partial arterial O_2 pressure (p_aO_2) of 35 to 72 mm Hg or with a hypoxemia ratio (p_aO_2/F_IO_2 [inspired O_2 fraction]) of 75 to 350 was of significant benefit in terms of preventing deterioration in oxygenation in the first 7 days of therapy, mortality, and intubation (50% reduction). Adverse reactions to antimicrobial therapies are decreased in patients receiving adjunctive corticosteroid therapy (13). After such therapy, the exercise tolerance and survival of patients were also improved. A gradual corticosteroid taper (usually over 2 weeks) is necessary to avoid relapse of pulmonary inflammation. Patients experience an increase in oral thrush and herpes simplex virus infections following 2 to 3 weeks of therapy with a taper. However, an increase in other opportunistic infections has not been observed, with a few exceptions (e.g., cryptococcosis) (8, 13, 36). The impact of corticosteroids in the compromised host without AIDS appears to be similar to that in patients with AIDS.

However, the utility of additional steroids in the transplant or cancer patient has not been subjected to a controlled clinical trial.

In the presence of *P. carinii*, cytokine production and phagocytosis by alveolar macrophages are abnormal (31). Surfactant proteins A and D, members of the collectin family, are increased during *Pneumocystis* pneumonia in patients and in animal models, while surfactant lipids are reduced (23, 43). These changes may contribute to a diminished uptake of organisms by resident macrophages. One mechanism proposed for the acute, beneficial effect of corticosteroids in the treatment of *Pneumocystis* pneumonia has been the release of preformed surfactant in the lungs with a resultant improvement in respiratory mechanics. The benefits of exogenous surfactant therapy in this disease have, however, not been fully studied.

Cytokines including gamma interferon have been shown to reduce the amount of *Pneumocystis* found in animal models of disease without greatly increasing the inflammatory response (7, 22). The CSFs, including those for the monocyte/macrophage (M-CSF), granulocytes (G-CSF), and granulocyte/macrophage (GM-CSF) lineages, have come into use to supplement immunity in the immunocompromised host. G-CSF has been used successfully in neutropenic cancer patients and in organ transplant recipients at the Massachusetts General Hospital without adversely affecting the transplanted organs while cell counts are within normal range. GM-CSF has been used with systemic antifungal therapy in patients with acute fungal infections with some success. Preliminary data suggest that M-CSF and GM-CSF may be useful in enhancing the clearance of *P. carinii* by resident alveolar macrophages in animal models. Some investigators have endorsed the use of aerosolized pentamidine in addition to standard anti-*Pneumocystis* therapy. Similarly, administration of antimicrobial agents in surfactant is under study. Some theoretical advantage may accrue to local administration, but the efficacy of this approach has not been proved.

Response to therapy. The response to therapy is generally excellent in patients whose infection is diagnosed prior to respiratory failure. The ability to reduce immune suppression or to supplement the immune response (see above) improves the rapidity of clearance of infection. The failure to observe clinical improvement by day 4 or 5 (for those receiving TMP-SMX) or days 5 to 7 (for those receiving pentamidine) should suggest the presence of another process: fibrosis, adult respiratory distress syndrome, dual infection (especially CMV), abscess, bronchial obstruction, drug allergy, or carcinoma. Bronchocsopic lavage and biopsy for microbiology and pathology or chest tomography may be revealing in these patients.

Isolation precautions. As was noted previously in a review of prophylaxis (19a), both reinfection and the reactivation of latent infection appear to be significant factors in the development of disease. Furthermore, multiple examples of clusters of *Pneumocystis* infection have been observed at a number of medical centers. Thus, while the isolation of patients infected or potentially infected with *P. carinii* from immunologically normal patients (who are likely to be seropositive for *Pneumocystis* antigens) is not essential (53), it seems advisable that uninfected, immunocompromised patients should not be exposed to individuals with active *P. carinii* infection.

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