Treatment and Prophylaxis of *Pneumocystis carinii* Pneumonia in HIV-Infected Patients

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**PROLOGUE**

This article discusses the management of *Pneumocystis carinii* pneumonia (PCP) taught to the third-year PharmD students enrolled in the Therapeutics V course (required) at the University of Tennessee College of Pharmacy. Both pathophysiology and treatment are taught in concert in the Therapeutics I-V courses. Approximately one hour is devoted to PCP, which is part of a four hour lecture sequence allocated to the management of opportunistic infections in people with AIDS. Students had lectures on the pharmacology of the drugs used in the treatment and prophylaxis of PCP in the proceeding academic year. However, reinforcement of pharmacologic data with the clinical application of this knowledge is emphasized during the lecture. A separate one hour recitation of AIDS-related cases is done in an accompanying course titled, Applied Therapeutics.

The lecture weaves basic drug facts with various clinical scenarios to facilitate the student’s thought process of how best to manage PCP in patients with AIDS. Utilization of a table containing pertinent pharmacologic information coupled with therapeutic algorithms help students develop a systemic approach to provide pharmaceutical care to patients with *P. carinii* infection. The algorithms, originally constructed for teaching purposes, were developed from results from clinical trials published in the medical literature.

**INTRODUCTION**

*Pneumocystis carinii* is an ubiquitous organism of low virulence in healthy persons. Most people in the United States are infected with *P. carinii* by the age of four years but do not develop pneumonia due to an intact host-defense system(1). Improved measures for prevention and alternatives for treatment of acute PCP infection have occurred since the AIDS epidemic was first reported. Adherence to drugs for PCP prophylaxis and potent antiretroviral regimens, coupled with a decrease in the number of individuals acquiring human immunodeficiency virus (HIV) infection, should have pronounced effects on reducing PCP.

**Pathophysiology**

*P. carinii* is a slow-growing, unicellular eucaryote whose genetic sequence is associated to the fungal kingdom, but its susceptibility to antiprotozoal agents links it to a parasite despite the molecular evidence for it being a fungus(1). Transmission is likely to require inhalation of an infectious inoculum. Once inhaled, the organism resides in the alveoli generating large numbers of organisms in the setting of T-lymphocyte depletion caused by HIV. Significant production of *P. carinii* alters the alveolar-capillary permeability resulting in impairment of gas exchange. Poor distribution of inspired air into alveoli that are obstructed with the organism, fluid, and inflammatory mediators leads to ventilation-perfusion mismatch. This clinical description is similar to the pathogenesis of the adult respiratory distress syndrome.

**Clinical Manifestations**

Over 90 percent of patients will have pulmonary complaints, primarily cough, shortness of breath, and tachypnea. Nonspecific constitutional symptoms such as fever, night sweats, fatigue, or weight loss are also observed. Since *P. carinii* is a much slower-growing organism compared to pyogenic bacteria, there is an indolent onset of pulmonary symp-
Fig. 1. Algorithm for acute therapy of Pneumocystis carinii pneumonia (PCP). The schema is divided into therapies for mild to moderate pneumonia and severe pneumonia. Duration of therapy is for 21 days, followed by lifelong secondary prophylaxis (see Figure 2). Doses are provided in Table I. Atovaquone is the suspension formulation. TMP-SMX= trimethoprim-sulfamethoxazole; TMP-DAP = trimethoprim-dapsone; Clinda-Prima = clindamycin-primaquine; PaO₂ = arterial partial pressure of oxygen; A-a gradient = alveolar-arterial oxygen difference; MAC = Mycobacterium avium complex; CMV = cytomegalovirus. Reproduced with permission from the American College of Clinical Pharmacy. Stevens, R.C., Opportunistic infections in AIDS due to Protozoa! and Mycobacterium avium complex, in Carter BL, Lake KD, Rabeel MA, et al, eds: Pharmacotherapy Self-Assessment Program, 3rd ed. Kansas City, MO, American College of Clinical Pharmacy, 1998, p 131

toms in HIV-infected persons. These patients may have fever and complain of lethargy and progressive onset of dyspnea on exertion over two to four weeks prior to seeking medical attention. The chest radiograph reveals the characteristic bilateral patchy infiltrates. Recover of P. carinii cysts from sputum or lungs is the definitive diagnosis.

Patients with AIDS who develop PCP often have an elevation of serum lactate dehydrogenase (LDH). Although serum LDH is nonspecific for PCP, a strong correlation exists between degree of LDH elevation and survival. A high or rising LDH while on antipneumocystis therapy correlates with a worse prognosis, a failure of therapy, and increased mortality, whereas a low or a declining serum LDH value suggests the opposite trend.

GOALS OF PHARMACOTHERAPY

- Identify HIV-infected persons at risk of developing PCP and initiate prophylaxis therapy.
- Determine if the acute PCP is mild to moderate or severe prior to initiation of drug therapy.

- Select the appropriate treatment regimen based on the patient’s severity of pneumonia and history of drug tolerance.
- After successful completion of therapy for acute PCP, counsel patients of the need for secondary prophylaxis to prevent further episodes of pneumonia.

TREATMENT

Acute Therapy

The selection of appropriate antipneumocystis agents for patient-specific conditions requires an understanding of the subtleties in drug selection and monitoring. The first process in drug selection involves categorizing the pneumonia either as mild to moderate PCP or severe PCP. Mild to moderate PCP is defined as PaO₂ on room air ≥ 70 mm Hg or an alveolar-arterial oxygen difference [(A-a) DO₂] < 35 mm Hg. Severe PCP is defined as PaO₂ on room air < 70 mm Hg or A-a gradient ≥ 35 mm Hg. (The A-a gradient is the difference between the ideal alveolar partial pressure of oxygen [ideal PAO₂] less the measured arterial partial pressure of oxygen [measured PaO₂].)
Table 1 lists the first-line and alternative treatment modalities for PCP.

**Mild to Moderate PCP**

The schema for therapy of mild to moderate PCP is depicted on the left side of the algorithm in Figure 1. Trimethoprim-sulfamethoxazole (TMP-SMX) is widely considered as the drug of choice(2,3,4). However, adverse events are common with TMP-SMX and modifications in therapy or selection of alternative regimens often are needed(5). Typically, toxicities manifest within the first one to two weeks of therapy.

Morbilliform rash, the most frequent adverse event with TMP-SMX, is commonly self-limiting; rarely have HIV-infected patients developed severe skin reactions. There is no absolute contraindication to an HIV-infected person with a prior nonmucous membrane involving, nondesquamating dermatological reaction to TMP-SMX to receive the drug in the future should the individual present with acute PCP or need prophylaxis treatment. In patients with AIDS who develop a rash while on TMP-SMX, it is acceptable to continue treatment provided no mucous membranes are involved and no skin has vesiculated. The mild rash or pruritus can be alleviated with antihistamines if needed.

Neutropenia is a concentration-dependent toxicity of TMP-SMX and can be minimized with appropriate dose modification. Dosing TMP-SMX at 15 mg/kg/day instead of 20 mg/kg/day or adjusting the dose to obtain TMP concentrations of 5-8 µg/ml 1.5 hours after intravenous infusion or oral ingestion was shown to lower the incidence of neutropenia(6). Attempts to ameliorate the bone marrow suppression with folinic acid (analogous to the “leucovorin rescue” practiced with methotrexate in treatment of leukemia) was associated with higher rates of therapeutic failure and death compared to placebo in AIDS patients with PCP treated with TMP-SMX(7).

Clinicians should be sensitive to the central nervous system (CNS) adverse effects associated with TMP-SMX, including fine tremors, headache, nervousness, light-headedness, insomnia, drowsiness, and acute psychosis. These toxicities can be concentration dependent and appear to be more intense at daily doses of 20 mg/kg based on the trimethoprim component(8). Doses ranging from 12 to 15 mg/kg/day is appropriate if CNS toxicity occurs. Careful review of patients’ medication profiles should be done to avoid, if possible, concurrent use of other drugs that may have additive CNS effects.

Clearly, toxicities (rash, neutropenia, CNS effects, elevation of hepatic transaminases) associated with TMP-SMX require the need for alternative therapies (Figure 1). TMP-dapsone can be used as an alternative in HIV-infected subjects intolerant to TMP-SMX. Patients who develop a mild rash from TMP-SMX and are subsequently changed to TMP-dapsone can also develop a rash from dapsone in up to 22 percent of cases(9). Dapsone is a sulfonamide moiety and cross-sensitivity is observed. A TMP-SMX rash, presumably due to the sulfila entity, does not, however, preclude the use of dapsone.

Dapsone-induced methemoglobinemia can occur in up to two-thirds of HIV-infected patients, but most individuals are asymptomatic. The manifestations of methemoglobinemia include cyanosis, headache, dizziness, drowsiness, stupor, fatigue, ataxia, dyspnea, tachycardia, nausea and vomiting. Severe methemoglobinemia can lead to hemolysis due to a change in iron oxidation state with impairment of oxygen transport. Dapsone and other potential hemolysing agents should be discontinued, and methylene blue (1-2 mg/kg in a one percent saline solution given once intravenously over 10-15 minutes) should be administered as an antidote if methemoglobin concentrations exceed 20 percent, or at lower concentrations of methemoglobin if patients are severely symptomatic. Dapsone can also cause hemolysis, especially in patients who are deficient in the enzyme glucose-6-phosphate dehydrogenase.

Rash, diarrhea, bone marrow suppression, hemolysis, and methemoglobinemia have been reported with clindamycin-primaquine(2). It seems sensible to avoid this combination if possible in patients with underlying diarrhea due to HIV-associated gastroenteropathy or invasion of the gastrointestinal tract by some other diarrhea-causing opportunistic infection (e.g., cytomegalovirus, Cryptosporidium, Mycobacterium avium complex).

Atovaquone has been shown to be better tolerated than TMP-SMX and pentamidine in mild to moderate PCP, but it is associated with a higher therapeutic failure(10,11). This may possibly be due to reduced bioavailability of the drug when the drug is not administered with a high-fat meal. Atovaquone absorption is enhanced with fatty foods. HIV-infected persons should be instructed to take atovaquone with fatty foods because poor absorption is considered to be the most likely explanation for its inferior therapeutic response compared to TMP-SMX. Macular rash is the most common adverse effect. Hematologic toxicity from atovaquone is rare. The lower therapeutic response necessitates restricting atovaquone to patients with mild to moderate PCP.

**Severe PCP**

Severe PCP requires parenteral antipneumocystis therapy, adjunctive glucocorticoids, and aggressive supportive care (e.g., supplemental oxygen, nutrition support-low albumin is a risk factor for a poor prognosis). A patient can be switched to oral therapy once clinically stable. TMP-SMX is the first-line therapy and intravenous pentamidine is an alternate for treatment of severe PCP (Figure 1).

Intravenous pentamidine is the most frequently prescribed alternative for TMP-SMX in patients with severe PCP who do not tolerate or do not benefit from TMP-SMX. In general, patients should not be labeled as TMP-SMX therapeutic failures until a minimum of five days of therapy are completed. Patients with severe infection often deteriorate during the first few days of therapy because of worsening oxygen desaturation. This is most likely due to release of cytokines from alveolar macrophages during the acute inflammatory process and lysis of P. carinii cysts after exposure to appropriate therapy. Thus, switching to alternative therapy would be premature during this transient decompensation period.

Common side effects of parenteral pentamidine are nephrotoxicity, hypotension, and hypoglycemia. A five year retrospective review of the incidence of parenteral pentamidine-associated adverse effects at San Francisco General Hospital in HIV-infected patients who received at least five days of pentamidine therapy found 72 percent of the patients experienced an adverse effect(12). Nephrotoxicity occurred in 45 percent, hypoglycemia in 24 percent, and pancreatitis in 9 percent of patients receiving pentamidine.

Nephrotoxicity caused by pentamidine is related to cumulative exposure, making renal damage unlikely in the first 5-7 days of therapy. Dosage reduction (3 mg/kg/day) has been used in mild to moderate PCP when azotemia has developed(13), but the efficacy of this dose has not been established in severe PCP. The concurrent use of other nephrotoxic drugs may increase the risk of renal injury.
Hypoglycemia due to pentamidine, which occurs in 10-50 percent of patients with AIDS, is potentially the most dangerous toxicity because of its insidious onset. This side effect has been associated with use of higher doses, prolonged therapy, and repeated courses of intravenous pentamidine. Pentamidine exerts a lytic effect on pancreatic β-cells, causing a sudden influx of insulin into the systemic circulation. No guidelines have been established for monitoring blood glucose, but daily assessment seems advisable. In hypoglycemic patients, it would be prudent to determine blood glucose Accu-checks every 4-6 hours for the first 24-48 hours, 2-3 times daily for the following 10-14 days, then daily for the remainder of therapy. Patient-specific monitoring programs would need to be structured dependent upon the individual’s baseline glucose control.

The role of adjunctive corticosteroids in patients with AIDS who have severe PCP is incontrovertible. Several well-controlled studies showed reduced mortality in patients with AIDS randomized to receive corticosteroids within 72 hours of initiating antipneumocystis therapy(14, 15). Dosage guidelines for prednisone, including a tapering schedule, are listed in Table I. Methylprednisolone, with appropriate dose adjustment for potency differences, can be used when patients are unable to ingest oral prednisone.

At this juncture in the lecture, approximately five minutes is allocated for discussion of several brief cases of acute PCP. This exercise is not in depth since the purpose of this component is to reinforce the main principles of appropriate drug selection and pertinent monitoring parameters through interactive discussion with the students. Detailed case presentations are done in a separate one hour recitation in the Applied Therapeutics course.

Table I. Treatment of Pneumocystis carinii Pneumonia in Patients with AIDS

<table>
<thead>
<tr>
<th>Condition</th>
<th>First-line therapy</th>
<th>Alternative therapy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Infection</td>
<td>TMP (15 mg/kg/day) + SMX (75 mg/kg/day) po or iv x 21 days in 3-4 daily doses</td>
<td>Pentamidine (4 mg/kg/day iv or im) x 21 days</td>
<td>TMP-SMX is the preferred regimen</td>
</tr>
<tr>
<td></td>
<td>TMP (15 mg/kg/day po or iv) + dapsone (100 mg/day po x 21 days)</td>
<td>Atovaquone suspension (750 mg po bid with food) x 21 days</td>
<td>See text and Figure 1 for appropriate selection of other regimens</td>
</tr>
<tr>
<td></td>
<td>Clindamycin (600 mg every 6-8 hr po or iv) + primaquine (30 mg bse po/day) x 21 days</td>
<td>Alternative considerations for refractory infections</td>
<td>Adverse events to sulfonamides (rash fever, leukopenia, hepatitis, etc.)</td>
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<tr>
<td></td>
<td></td>
<td>or side effects with standard agents: trimetrexate (45 mg/m² iv/day) x 21 days + leucovorin (20 mg/m² iv or po every 6 hr) x 24 days</td>
<td>most common at 1-2 wk</td>
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<td></td>
<td></td>
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<td>Patients with severe pneumonia (PaO₂ &lt; 70 mm Hg) should receive corticosteroids</td>
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Prophylaxis

<table>
<thead>
<tr>
<th>First-line therapy</th>
<th>Alternative therapy</th>
<th>Comment</th>
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<tbody>
<tr>
<td>TMP-SMX (1 SS/day, 1 DS/day, or 1 DS 3 times/week)</td>
<td>Dapsone (50 mg bid or 100 mg/day)</td>
<td>Prophylaxis is indicated for any HIV-infected patient with a history of Pneumocystis carinii pneumonia, CD4⁺ count &lt; 200/mm³, unexplained fever (&gt; 100°F) for ≥ 2 weeks, or a history of oropharyngeal candidiasis</td>
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<tr>
<td></td>
<td>Dapsone (50 mg/day) + pyrimethamine (50 mg/week) + leucovorin (25 mg/week)</td>
<td>Efficacy shown in controlled studies only for TMP-SMX, dapsone (+ pyrimethamine), and aerosolized pentamidine</td>
</tr>
<tr>
<td></td>
<td>Dapsone (200 mg/week) + pyrimethamine (75 mg/week) + leucovorin (25 mg/week)</td>
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<tr>
<td></td>
<td>Aerosolized pentamidine (300 mg) q month</td>
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<td></td>
<td>via Respirgard II™ nebulizer + β₂</td>
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<td></td>
<td>agonist (albueterol, 2 puffs)</td>
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<tr>
<td></td>
<td>Pentamidine (4 mg/kg) im or iv every 2 weeks</td>
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</table>

PREVENTION

Chemoprophylaxis is either primary (directed against the initial episode) or secondary (directed against relapses or recurrences following treatment of an acute infection). The United States Public Health Service (USPHS) recommends that adults and adolescents with HIV infection should receive prophylaxis against PCP if they have a CD4⁺ lymphocyte count of < 200 cells/mm³, unexplained fever (> 100°F) for > two weeks, or a history of oropharyngeal candidiasis (Figure 2)(16). Some clinicians may use a set point of 225-250 cells/mm³ if the patient has a pattern of rapidly declining CD4⁺ cells over the preceding months. Patients who have recovered from a documented episode of acute PCP should receive prophylaxis (i.e., secondary prophylaxis).

The potent effect of highly active antiretroviral treatment (HAART) with triple-drug combinations on suppressing the HIV RNA viral load, often below the limits of detection, with the subsequent restoration of CD4⁺ cells above 200/mm³ have led some clinicians to withdraw secondary PCP prophylaxis. An early report provided results from 78 patients (n=62 primary and n=16 secondary prophylaxis) who discontinued pneumocystis prophylaxis when the patients' CD4⁺ cell counts rose above 200/mm³ following initiation of HAART(17). No episodes of PCP occurred during a median follow-up of 12.7 months. These early findings appear promising but clinicians should wait until long-term follow-up data are available that establish the efficacy of this intervention before deviating from the USPHS guidelines(16). However, it is reasonable to consider discontinuation of PCP prophylaxis if desired by a patient who is informed of the potential risks.
TMP-SMX, dapsone with or without pyrimethamine, and aerosolized pentamidine are common agents used to prevent PCP (Figure 2). No single agent or combination has been shown to be superior to TMP-SMX(18,19).

Use of aerosolized pentamidine for prophylaxis has some limitations, including the following: (i) less efficacy compared to TMP-SMX in controlled trials, especially in HIV-infected persons with CD4+ < 100 cells/mm³ (18); (ii) increased rates of extrapulmonary foci of *P. carinii* infection and pneumothorax; (iii) increased risk of PCP manifesting as an upper lobe disease due to poor distribution of the aerosolized drug to this region; (iv) lack of prophylaxis against toxoplasmosis and bacterial infections; and (v) high cost.

Aerosolized pentamidine’s clear advantage, however, is its minor toxicity. Side effects (primarily cough, wheezing, and dyspnea during inhalation administration) are mild and infrequent causes of drug discontinuation. These bronchoconstrictive reactions can be diminished or prevented by administration of an inhaled β₂-agonist (e.g., albuterol, two 100 µg puffs) before aerosolized pentamidine. Also, an inhaled β₂-agonist can be used as needed for bronchoconstriction during or after aerosolized pentamidine.

**IMPROVING OUTCOMES**

If the desired outcomes of therapy or prophylaxis of PCP are not achieved, then a detailed review of the patient’s therapy is needed. Is the patient receiving the best treatment option? Refer to Figure 1 to assure the most appropriate drug selection was made. Is the patient receiving his or her medication according to schedule? Have drug dosages been adjusted for weight and renal function? Refer to product labeling for appropriate dosing regimens. Is the patient receiving adjunctive corticosteroids if indicated? Refer to Figure 1 for indications for steroids. Does the patient have nausea/vomiting or diarrhea? If so, avoid clindamycin-primaquine and atovaquone or consider intravenous therapy. Has adequate time elapsed to enable initial regimen to be effective (minimum of five days)?

Without question, widespread prophylaxis has had a profound effect; the percentage of new PCP cases categorized as an AIDS-defining illness has decreased. As health systems continue to be taxed and further constrain valuable resources, it is conceivable that patients may inadvertently lose access to care or pharmaceuticals. Pharmacists are in a unique position to remain at the forefront of assuring that HIV-infected persons receive optimal prophylaxis for PCP. This is achieved through close monitoring of the patient’s CD4+ lymphocytes, selection of chemoprophylaxis based on the individual’s medication history, and, perhaps most important, constant support and motivation to enhance adherence. These activities probably do more to extend the quality of life than any other intervention short of behavioral modifications and strict adherence to antiretroviral therapy.

**KEY POINTS OF EMPHASIS**

- TMP-SMX is the drug of choice for acute therapy and prophylaxis of PCP.
- Macular rash is a common adverse effect of sulfonamides in patients with AIDS, but should not necessarily preclude future use of these drugs.
- Adjunctive corticosteroids should be administered within 72 hours of starting antipneumocystis therapy for severe PCP defined as a PaO₂ < 70 mm Hg or A-a gradient ≥ 35 mm Hg.
- Atovaquone is an alternative for treatment of mild to moderate PCP in patients having no diarrhea and are able to ingest the oral suspension with fatty foods.
- Prophylaxis with systemic agents (TMP-SMX or dapsone) is recommended in HIV-infected persons with a CD4+ count of < 200 cells/mm³. Aerosolized pentamidine is an alternate in patients with CD4+ counts between 100 to 200 cells/mm³.

**SUMMARY**

*This presentation on prevention and treatment of PCP in patients with AIDS is designed to facilitate the third-year PharmD student to effectively rationalize appropriate drug selection. This patient population is susceptible to numerous adverse events and potential drug interactions because of polypharmacy regimens. As such, close monitoring of patient drug tolerance is essential and selection of alternative therapy is often indicated. Furthermore, this lecture utilizes algorithms to enhance student understanding of the complexities associated with the prophylaxis and management of *P. carinii* infection.*

References


