Smith Seminars
Online Continuing Education
AARC-Approved for 2 CRCE
Pneumocystis Carinii Pneumonia in HIV

Objectives

Become familiar with the current diagnosis and treatment modalities used in human immunodeficiency virus.

Have a working knowledge of the clinical presentation, diagnosis, and treatment of the opportunistic infection pneumocystis carinii pneumonia (PCP) in HIV infected patients.

Know the prevention strategies for pneumocystis carinii pneumonia (PCP) in HIV and non-HIV infected patients.

Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus (HIV) is a blood-borne, sexually transmissible virus. The virus is typically transmitted via sexual intercourse, shared intravenous drug paraphernalia, and mother-to-child transmission (MTCT), which can occur during the birth process or during breastfeeding.

The most common route of infection varies from country to country and even among cities, reflecting the population in which HIV was introduced initially and local practices. Co-infection with other viruses that share similar routes of transmission, such as hepatitis B, hepatitis C, and human herpes virus 8, also known as Kaposi sarcoma herpes virus, is common.

Two distinct species of HIV (HIV-1 and HIV-2) have been identified, and each is composed of multiple subtypes, or clades. All clades of HIV-1 tend to cause similar disease, but the global distribution of the clades differs. This may have implications on any future vaccine, as the B clade, which is predominant in the developed world (where the large pharmaceutical companies are located), is rarely found in the developing countries that are more severely affected by the disease.

HIV-1 probably originated from one or more cross-species transfers from chimpanzees in central Africa. HIV-2 is closely related to viruses that infect sooty mangabeys in western Africa. Genetically, HIV-1 and HIV-2 are superficially similar, but each contains unique genes and its own distinct replication process.

HIV-2 carries a slightly lower risk of transmission, and HIV-2 infection tends to progress more slowly to acquired immune deficiency syndrome (AIDS). This may be due to a less-aggressive infection rather than a specific property of the virus itself. Persons infected with HIV-2 tend to have a lower viral load than people with HIV-1, and a greater viral load is associated with more rapid progression to AIDS in HIV-1 infections.

HIV-2 is rare in the developed world. Consequently, most of the research and vaccine and drug development has been focused on HIV-1.

HIV produces cellular immune deficiency characterized by the depletion of helper T lymphocytes ($CD4^+$ cells). The loss of $CD4^+$ cells results in the development of opportunistic infections and neoplastic processes.

Risk factors for possible exposures to human immunodeficiency virus (HIV) include:

- Unprotected sexual intercourse, especially receptive anal intercourse (8-fold higher risk of transmission)
- A large number of sexual partners
- Prior or current sexually transmitted diseases (STDs): Gonorrhea and chlamydia infections increase the HIV transmission risk 3-fold, syphilis raises the transmission risk 7-fold, and herpes genitalis raises the transmission risk up to 25-fold during an outbreak
- Sharing of intravenous drug paraphernalia
- Receipt of blood products (before 1985 in the United States)
- Mucosal contact with infected blood or needle-stick injuries
- Maternal HIV infection (for newborns, infants, and children): Steps taken to reduce the risk of transmission at birth include cesarean delivery and prenatal antiretroviral therapy in the mother and antiretroviral therapy in the newborn immediately after birth.

The patient may present with signs and symptoms of any of the stages of HIV infection. Acute seroconversion manifests as a flulike illness, consisting of fever, malaise, and a generalized rash. The asymptomatic phase is generally benign. Generalized lymphadenopathy is common and may be a presenting symptom.

AIDS manifests as recurrent, severe, and occasionally life-threatening infections and/or opportunistic malignancies. The signs and symptoms are those of the presenting illness, meaning that HIV infection should be suspected as an underlying illness when unusual infections present in apparently healthy individuals.

HIV infection itself does cause some sequelae, including AIDS-associated dementia/encephalopathy and HIV wasting syndrome (chronic diarrhea and weight loss with no identifiable cause).

Screening for human immunodeficiency virus (HIV) infection is paramount, since infected individuals may remain asymptomatic for years while the infection progresses. Serologic tests are the most important studies in the evaluation for HIV infection.

Secondary testing that may be performed to assist with diagnosis or staging includes the following: viral culture, lymph node biopsy, proviral DNA polymerase chain reaction (PCR), and genotyping of viral DNA/RNA.

Staging of HIV disease is based partially on clinical presentation, but other laboratory tests can help in deciding whether to initiate or modify treatment.

Baseline laboratory studies for other infections (such as tuberculosis) are important in the initial workup of a patient with newly diagnosed HIV infection. In addition, baseline levels of factors that may be affected by antiretroviral therapy (such as lipids) should be measured.

Early detection using combination screens may be more effective than simply using serology. The additional detection of p24 antigen or viral RNA may detect a greater number of very recent

infections before seroconversion occurs. This would likely result in significant reductions in transmission as well as overall health costs and healthcare burden.

D4+ T-cell Count

The CD4 T-cell count is a reliable indicator of the current risk of acquiring opportunistic infections. CD4 counts vary, and serial counts are generally a better measure of any significant changes. The reference range for CD4 counts is 500-2000 cells/μL. After seroconversion, CD4 counts tend to decrease (around 700/μL on average) and continue to decline over time. For surveillance purposes, a CD4 count under 200/μL is considered AIDS-defining in the United States owing to the increased risk of opportunistic infections at this level. The magnitude of discordance between absolute CD4 T-cell numbers and CD4 T-cell percentages is greatest in those with active hepatitis C virus and more advanced liver disease.

In children under five years of age, the CD4 T-cell percentage is considered more important than the absolute count. (Less than 25% is considered worthy of starting therapy, regardless of the total CD4 count). In adults with chronic hepatitis C and low absolute CD4 T-cells, the CD4 percentage may also be more useful, due to probable T-cell sequestration in the liver.

Viral Load

Viral load in peripheral blood is used as a surrogate marker of viral replication rate. This is a surrogate because most of the viral replication occurs in the lymph nodes rather than in the peripheral blood.

The rate of progression to AIDS and death is related to the viral load, although, on an individual level, it is poorly predictive of the absolute rate of CD4 T-cell loss. Patients with viral loads greater than 30,000/μL are 18.5 times more likely to die of AIDS than those with undetectable viral loads.

With therapy, viral loads can often be suppressed to an undetectable level (< 20-75 copies/mL, depending on the assay used); this is considered optimal viral suppression. At the same time, the CD4 count rises and the risk of opportunistic infections and death is reduced. Complete inhibition of viral replication appears impossible and may be unnecessary.

Not uncommonly, successfully treated patients will demonstrate intermittent viremia, with viral loads transiently detectable at low levels (typically, < 400 copies/mL); this appears to occur more commonly with some viral load assays than others. Such “blips” are not thought to represent viral replication or to predict virologic failure. Virologic failure is defined as a confirmed viral load of more than 200 copies/mL; although this is a research definition, it may be useful in clinical practice.

Secondary HIV Testing

Viral culture is expensive and time-consuming and is less sensitive in patients with low viral loads. Viral culture may be performed as part of phenotypic drug-resistance testing.

Lymph node architecture is disrupted during HIV infection. HIV DNA, RNA, and proteins may be detected with molecular techniques, and electron microscopy may reveal virions.

Proviral DNA PCR is usually performed only in newborns because conventional serologic testing is useless in these patients (maternal antibodies may persist for 9 months or longer). Two or more negative results separated by at least one month is considered a negative result. Genotyping of viral DNA/RNA can guide therapy. Because patterns of mutations that lead to resistance to specific drugs or drug classes are now well-recognized, sequencing of the viral genome allows for the selection of specific antivirals that are more likely to elicit a response.

Staging

The CDC classifies HIV infection into 3 categories, according to the presence of certain infections or diseases. These conditions may be exacerbated by the HIV infection or represent true opportunistic infections.

Category A is asymptomatic HIV infection without a history of symptoms or AIDS-defining conditions.

Category B is HIV infection with symptoms that are directly attributable to HIV infection (or a defect in T-cell–mediated immunity) or that are complicated by HIV infection. These include, but are not limited to bacillary angiomatosis; oropharyngeal candidiasis (thrush); vulvovaginal candidiasis, persistent or resistant; pelvic inflammatory disease (PID); cervical dysplasia (moderate or severe)/cervical carcinoma in situ; oral hairy leukoplakia; idiopathic thrombocytopenic purpura; constitutional symptoms, such as fever (>38.5°C) or diarrhea lasting more than 1 month; peripheral neuropathy; herpes zoster (shingles), involving 2 or more episodes or 1 or more dermatomes.

Category C is HIV infection with AIDS-defining opportunistic infections.

These 3 categories are further subdivided based on the CD4+ T-cell count. Categories A1, B1, and C1 are characterized by CD4+ T-cell counts greater than 500/µL. Categories A2, B2, and C2 are characterized by CD4+ T-cell counts between 200/µL and 400/µL. HIV infections in patient with CD4+ T-cell counts under 200/µL are designated as A3, B3, or C3.

Importantly, once an HIV infection has been staged into a higher clinical category, it remains in that category permanently. In addition, the infection is classified based on the lowest CD4+ T-cell count in that patient.

For example, if a given HIV-positive patient recovers from a bout of Pneumocystis pneumonia (PCP) and the CD4+ T-cell count improves from 50/µL to 250/µL, that patient's HIV infection remains classified as C3. Persons with A3, B3, and C1-3 HIV infection are considered to have AIDS. This is important to recognize, as this designation is not based solely on the previous occurrence of opportunistic infections but rather on the current risk of infection based on a reduced CD4+ T-cell count.

Pneumocystis carinii pneumonia (PCP)

Pneumocystis carinii pneumonia (PCP) is the most common opportunistic infection in persons with HIV infection. The causative organism has been renamed Pneumocystis jiroveci (pronounced "yee-row-vet-zee").

Pneumocystis first came to attention as a cause of interstitial pneumonia in severely malnourished and premature infants during World War II in Central and Eastern Europe. Before the 1980s, fewer than 100 cases of PCP were reported annually in the United States, occurring in patients who were immunosuppressed (such as cancer patients receiving chemotherapy and solid-organ transplant recipients receiving immunosuppressants). In 1981, the Centers for Disease Control and Prevention reported PCP in 5 previously healthy homosexual men residing in the Los Angeles area.

P jiroveci is now one of several organisms known to cause life-threatening opportunistic infections in patients with advanced HIV infection worldwide. Well over 100,000 cases of PCP were reported in the first decade of the HIV epidemic in the United States in people with no other cause for immunosuppression.

While officially classified as a fungal pneumonia, PCP does not respond to antifungal treatment. Although a histopathologic demonstration of the organism is required for a definitive diagnosis, treatment should not be delayed. Treatment of PCP may be initiated before the workup is complete in severely ill high-risk patients. Treatment of PCP depends on the degree of illness at diagnosis, determined on the basis of the alveolar-arterial gradient.

Antibiotics are primarily recommended for treatment of mild, moderate, or severe PCP. Trimethoprim-sulfamethoxazole (TMP-SMX) has been shown to be as effective as intravenous pentamidine and more effective than other alternative treatment regimens. Corticosteroids are used as adjunctive initial therapy only in patients with HIV infection who have severe PCP. Preventive measures (such as smoking cessation and chemoprophylaxis) can play an important role in disease management.

Microbiology of PCP

Pneumocystis is a genus of unicellular fungi found in the respiratory tracts of many mammals and humans. Distinct genomic variability exists between host-specific members of the genus. The organism was first described in 1909 by Chagas and then a few years later by Delanoes, who ultimately named the organism in honor of Dr. Carini after isolating it from infected rats. Years later, Dr. Otto Jirovec and his group isolated the organism from humans, and the organism responsible for PCP was renamed after him.

The taxonomic classification of the Pneumocystis genus was debated for some time. It was initially mistaken for a trypanosome and then later for a protozoan. In the 1980s, biochemical analysis of the nucleic acid composition of Pneumocystis rRNA and mitochondrial DNA identified the organism as a unicellular fungus rather than a protozoan. Subsequent genomic sequence analysis of multiple genes including elongation factor 3, a component of fungi protein synthesis not found in protozoa, further supported this notion.

The organism is found in 3 distinct morphologic stages:

- The trophozoite (trophic form), in which it often exists in clusters
- The sporozoite (precystic form)
- The cyst, which contains several intracystic bodies (spores)

Pathophysiology and Etiology of PCP

Pneumocystis organisms are commonly found in the lungs of healthy individuals. Most children are believed to have been exposed to the organism by age 3 or 4 years, and its occurrence is worldwide.

Transmission of Pneumocystis

Animal studies have suggested that Pneumocystis organisms are communicable; airborne transmission has been reported. Human evidence of this is provided by molecular analysis of Pneumocystis isolates obtained from groups of patients involved in hospital outbreaks. Further evidence of human transmission has been found in cases of recurrent pneumonia in which the genotype of Pneumocystis organisms in the same person differed in prior episodes. Despite this, barrier precautions are not required for patients hospitalized with P carinii pneumonia (PCP) except to protect other patients with depressed immunity.

Development of PCP

Disease occurs when both cellular immunity and humoral immunity are defective. Once inhaled, the trophic form of Pneumocystis organisms attach to the alveoli. Multiple host immune defects allow for uncontrolled replication of Pneumocystis organisms and development of illness. Activated alveolar macrophages without $CD4^+$ cells are unable to eradicate Pneumocystis organisms. Increased alveolar-capillary permeability is visible on electron microscopy. Physiologic changes include: hypoxemia with an increased alveolar-arterial oxygen gradient; respiratory alkalosis; impaired diffusing capacity; and changes in total lung capacity and vital capacity. There have been reports of PCP occurring as part of the immune reconstitution syndrome.

Risk Factors for PCP

PCP is caused by infection with P jiroveci. Groups are at risk for PCP include persons with HIV infection whose $CD4^+$ cells fall below 200/μL, who are not receiving PCP prophylaxis; patients with HIV infection with other opportunistic infections (such as oral thrush) increases the risk of PCP, regardless of $CD4^+$ count; and persons with primary immune deficiencies, including hypogammaglobulinemia and severe combined immunodeficiency (SCID). Other groups at risk for PCP include persons receiving long-term immunosuppressive regimens for connective-tissue disorders, vasculitides, or solid-organ transplantation (such as heart, lung, liver, kidney); persons with hematologic and nonhematologic malignancies, including solid tumors and lymphomas; and persons with severe malnutrition.

Epidemiology of PCP

Before the widespread use of prophylaxis for P carinii pneumonia (PCP), the frequency of Pneumocystis infection in lung transplant patients alone was as high as 88%. Now, with the routine use of prophylaxis, PCP is very rare in solid-organ transplant patients and has significantly decreased in patients infected with HIV.

Prior to the widespread use of highly active antiretroviral therapy (HAART), PCP occurred in 70-80% of patients with HIV infection. The frequency of PCP is decreasing with the use of PCP prophylaxis and HAART. PCP is still the most common opportunistic infection in patients with HIV infection. Patients with HIV infection are more prone to PCP recurrence than patients not infected with HIV.

In developing regions of the world, the prevalence of PCP was once thought to be much lower, but studies have shown that the lower reported incidence is likely a failure to accurately diagnose PCP. An accurate diagnosis requires access to modern medical care, which is not available worldwide.

Currently, the frequency of documented Pneumocystis infection is increasing in Africa, with Pneumocystis organisms found in up to 80% of infants with pneumonia who have HIV infection. In sub-Saharan Africa, tuberculosis is a common co-infection in persons with PCP.

Prognosis for PCP

In patients with HIV infection, PCP once carried a mortality rate of 20-40%, depending on disease severity at presentation. Currently, mortality rates of 10-20% are reported. PCP is still a major cause of death in patients with AIDS in the United States.

In persons without HIV infection, PCP carries a worse prognosis; this has not changed significantly in the past 20 years. Mortality rates of 30-50% have been documented in several large studies.

The prognosis of PCP is worse in patients who present with concurrent pulmonary disease, in patients who develop pneumothorax, and in patients who require mechanical ventilation. The higher mortality rate is likely a result of delayed diagnoses and delayed initiation of appropriate treatment.

Clinical Presentation of PCP

Patient History

The symptoms of P carinii pneumonia (PCP) are nonspecific. PCP in patients with HIV infection tends to run a more subacute indolent course and tends to present much later, often after several weeks of symptoms, compared with PCP associated with other immunocompromising conditions. Symptoms of PCP include progressive exertional dyspnea, fever, nonproductive cough, chest discomfort, weight loss, chills, and hemoptysis (rare).

Physical Examination

The physical examination findings of PCP are nonspecific and include tachypnea, fever, and tachycardia. Also a pulmonary examination may reveal mild crackles and rhonchi but may yield normal findings in up to half of patients. Additional findings in children with severe disease include cyanosis, nasal flaring, and intercostal retractions.

Extrapulmonary Manifestations

Although Pneumocystis infection rarely causes extrapulmonary manifestations, such findings may be present in patients receiving aerosolized pentamidine for prophylaxis or in patients with advanced HIV infection who are not taking any prophylaxis. They may also occur in the absence of lung involvement.

On the basis of most well-documented findings, Pneumocystis infection may present in almost any organ system including the central nervous system, bone marrow (may have necrosis with resultant pancytopenia), lymphadenopathy, eyes (may have retinal cotton-wool spots), thyroid (may present as a rapidly enlarging thyroid mass), and gastrointestinal tract.

Complications

A pathophysiologic process similar to acute respiratory distress syndrome (ARDS) may occur in patients with severe PCP. These patients may require intubation. This greatly diminishes the prognosis.

Laboratory Studies

A lactic dehydrogenase (LDH) study is performed as part of the initial workup. LDH levels are usually elevated (>220 U/L) in patients with P carinii pneumonia (PCP). They are elevated in 90% of patients with PCP who are infected with HIV. The study has a high sensitivity (78-100%); its specificity is much lower because other disease processes can result in an elevated LDH level.

LDH levels appear to reflect the degree of lung injury. They should decline with successful treatment. Consistently elevated LDH levels during treatment may indicate therapy failure and a worse prognosis.

β-D-Glucan (BDG) is a cell-wall component of many fungi, including candida, aspergillus, and pneumocystis (but not the zygomycetes). It has been shown to be a sensitive test to detect PCP in a meta-analysis of 12 studies assessing the sensitivity, specificity and overall accuracy of the test.

Chest Radiography

Chest radiography should be obtained in any immunocompromised patient with fever and/or respiratory signs or symptoms. The chest radiographic findings may be normal in patients with early mild disease. Diffuse bilateral infiltrates extending from the perihilar region are visible in most patients with P carinii pneumonia (PCP). Less common findings include patchy asymmetric infiltrates and pneumatoceles. Pleural effusions and intrathoracic adenopathy are rare.

Pneumothorax may develop in patients using aerosolized pentamidine. Apical disease may also be found in patients using aerosolized pentamidine for prophylaxis.

Computed Tomography

High-resolution computed tomography (HRCT) scanning of chest is helpful when the chest radiography findings are equivocal. HRCT yields a high sensitivity for P carinii pneumonia (PCP) in patients with HIV infection.

The typical appearance is patchy areas of ground-glass attenuation with a background of interlobular septal thickening. Negative (normal or unchanged) CT scan findings alone do not rule out PCP.

Gallium 67 Scanning

Gallium 67 scanning demonstrates an increased diffuse symmetrical pulmonary uptake in patients with P carinii pneumonia (PCP). Its sensitivity is high (nearly 100%). However, its specificity is low (some studies report as low as 20%). The high cost and 2-day time delay in obtaining results have limited its use.

A gallium 67 scan is potentially more useful in patients with suspected relapse, as bronchoalveolar lavage may be less diagnostic in such cases.

Pulmonary Function Tests

Pulmonary function tests should be obtained as part of the initial noninvasive workup in patients with suspected P carinii pneumonia (PCP). Results may demonstrate a decreased diffusion capacity of carbon monoxide (DLCO) of less than 75% predicted. Decreased DLCO has a high sensitivity (89-100%) but poor specificity (53%). PCP is unlikely if DLCO is normal.

When combined with normal or unchanged high-resolution computed tomography (HRCT) findings, pulmonary function tests may be used to identify patients unlikely to have PCP; such patients may be managed with observation alone.

Pulse Oximetry

Pulse oximetry on room air should be measured in all patients. The oxygen saturation should be measured both at rest and with exertion. If any hypoxemia is found (O_2 saturation < 90%), then an arterial blood gas (ABG) level should be obtained to evaluate the need for possible adjunctive corticosteroids.

HIV Testing

The diagnosis of PCP should prompt consideration for HIV testing. If HIV testing is performed, appropriate pretest and posttest counseling guidelines must be followed.

Sputum Induction

If P carinii pneumonia (PCP) is strongly suspected, obtain a sputum sample by sputum induction for histopathologic testing. Pneumocystis organisms are frequently found in sputum induced by inhalation of a hypertonic saline solution. Sputum induction is the quickest and least-invasive method for definitively diagnosing PCP. Expectorated sputum has a very low sensitivity and should not be submitted for diagnosis.

The sensitivity of sputum induction varies widely (< 50% to >90%) and depends on proficiency in using the technique and the experience of the laboratory. Specificity is high (99-100%). This study may be less sensitive in patients without HIV infection, as the immunodeficiency caused by HIV infection typically leads to a greater alveolar load of Pneumocystis organisms. It may also be less sensitive in patients receiving aerosolized pentamidine for prophylaxis.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) is the most common invasive procedure used to diagnose P carinii pneumonia (PCP). It has a diagnostic yield that exceeds 90% (and may be higher if multiple lobes are sampled). BAL yields a lower sensitivity in patients receiving aerosolized pentamidine, in which case a transbronchial biopsy may be performed in conjunction with BAL. Obtain BAL if PCP is strongly suspected and the induced sputum sample findings are negative. BAL may be used in patients who are unable to cooperate with an induced sputum sample (such as altered mental status). BAL may be less useful in cases of suspected PCP relapse.

Lung Biopsy

Open lung biopsy is the most invasive procedure and yields 100% sensitivity and specificity because it provides the greatest amount of tissue for diagnosis. However, this procedure is reserved for rare cases when bronchoscopy findings are nondiagnostic.

Histologic Findings

Because clinical and radiologic findings are not specific for PCP and because P jiroveci cannot be grown in vitro, histopathologic demonstration is necessary before a definitive diagnosis is established. Histologic staining techniques are available for respiratory tract secretions. Some facilities prefer to use direct immunofluorescence using monoclonal antibodies to detect Pneumocystis organisms because it may be more sensitive than histologic staining.

Treatment of PCP

While officially classified as a fungal pneumonia, P carinii pneumonia (PCP) does not respond to antifungal treatment. However, there are a few reports of successful caspofungin administration in PCP. Echinocandins such as caspofungin may be active against pneumocystis based on their activity against the inclusion of (1-3)beta-D glucan into the fungal cell wall. Case reports suggest it may be worthy of consideration as a treatment option in non-responsive cases, and further research is clearly warranted.

Although a histopathologic demonstration of the organism is required for a definitive diagnosis, treatment should not be delayed. Treatment of PCP may be initiated before the workup is complete in severely ill high-risk patients.

Appropriate histopathologic testing may still be used to confirm a diagnosis of PCP after treatment is initiated. Endotracheal tube aspirates from severely ill patients on mechanical

ventilation may be submitted for diagnosis. Pneumocystis organisms persist in the host for days to weeks after therapy is started, allowing time for completion of the appropriate workup.
Treatment of PCP depends on the degree of illness at diagnosis. Degree of illness is determined on the basis of the alveolar-arterial gradient: mild (< 35 mm Hg), moderate/severe (35-45 mm Hg), or severe (>45 mm Hg). Severe disease is also indicated by a room air partial pressure of oxygen lower than 70 mm Hg. Treatment of extrapulmonary manifestations of PCP is the same as that for other pneumonias.
In patients without HIV infection, response to treatment should begin in 4-5 days. In patients infected with HIV, the treatment response typically takes longer but should occur within the first 8 days. If no response occurs within the expected time, an appropriate alternative regimen should be used. Adding additional PCP medications to a current regimen only increases the risk of adverse drug reactions without improving the likelihood of a good outcome. Up to 10% of mild-to-moderate PCP cases fail to respond to antibiotic treatment because of lack of drug efficacy.
All patients who require corticosteroids should be admitted to the hospital because of the risk of progressive respiratory compromise.
Because of increasing evidence of possible human transmission, the CDC Hospital Infection Control Practice Advisory Committee has recommended that patients with PCP not have direct contact with other immunocompromised patients.

Antibiotic Therapy

Antibiotics are primarily recommended for treatment of mild, moderate, or severe P carinii pneumonia (PCP). Trimethoprim-sulfamethoxazole (TMP-SMX) has been shown to be as effective as intravenous pentamidine and more effective than other alternative treatment regimens.javascript:showrefcontent('refrenceslayer'); The parenteral route may be considered in patients who present with serious illness or in those with gastrointestinal side effects.
TMP-SMX is the preferred initial therapy during pregnancy according to consensus guidelines. The patient's neonatologist should be informed if the medication is used near delivery because of potential for hyperbilirubinemia and kernicterus. For the treatment of infections that are resistant to TMP-SMX, the combination of clindamycin and primaquine is likely to be more effective than intravenous pentamidine.
The recommended duration of treatment for PCP is 21 days in patients with HIV infection and 14 days for all other patients. Patients infected with HIV tend to have a higher organism burden and respond to treatment slower than patients without HIV infection and therefore require a longer duration of therapy.

Adjunctive Corticosteroid Therapy

Corticosteroids are used as adjunctive initial therapy only in patients with HIV infection who have severe P carinii pneumonia (PCP) as defined by a room air arterial oxygen pressure of less than 70 mm Hg or an arterial-alveolar O_2 gradient that exceeds 35 mm Hg. Adjunctive steroids are not recommended in patients without HIV infection.

Microbial degradation and clearance may trigger further inflammation, which can provoke a severe inflammatory response in the lungs that often worsens after therapy is begun. Adjunctive corticosteroid therapy can blunt this inflammatory response, reduce deterioration of oxygenation, and reduce the incidence of respiratory failure.

Outpatient Care

Close medical follow-up with a primary care provider upon hospital discharge is essential to monitor resolution of disease and to initiate prophylactic medication.

Oral therapy with trimethoprim-sulfamethoxazole (TMP-SMX) has been shown to be very effective in the outpatient setting. However, oral therapy should be considered only in patients with mild-to-moderate P carinii pneumonia (PCP) who have reliable outpatient follow-up care.

Prevention of PCP

Smoking Cessation

Smoking cessation is strongly recommended in patients with HIV infection, as studies have shown that, in addition to the common deleterious effects of tobacco use, smokers are at an increased risk of P carinii pneumonia (PCP) and have a more complicated treatment course.

Chemoprophylaxis in Patients with HIV Infection

Two types of outpatient chemoprophylactic therapies exist. Primary prophylaxis is used in immunocompromised patients without a history of PCP. Secondary prophylaxis is used in patients with a prior bout of PCP.

An expert panel overseen by the US Public Health Service and Infectious Disease Society of America has published guidelines on prophylaxis against P carinii pneumonia (PCP) in adult and pediatric patients with HIV infection. Chemoprophylaxis is recommended for the following groups:

> Adults, adolescents, and pregnant patients with a CD4 count of less than 200/µL, oropharyngeal candidiasis, unexplained fever exceeding 100°F (37.7° C) for more than 2 weeks, and a prior episode of PCP regardless of CD4 count should receive prophylaxis.
>
> Children born to mothers with HIV infection should receive prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) beginning at age 4-6 weeks. The drug should be discontinued if they are subsequently determined not to be infected with HIV. Children who are determined to be HIV positive through the first year of life, then as determined by age-specific CD4 levels, should receive prophylaxis.

Prophylaxis may be discontinued in patients with HIV infection whose CD4 count exceeds 200/µL for 3 consecutive months while on highly active antiretroviral therapy (HAART). Prophylaxis should be restarted if the CD4 count drops below 200/µL. Prophylaxis should be continued for life in patients who developed PCP while their CD4 level exceeded 200/µL.

One study suggests that discontinuation of prophylaxis may be safe in patients with HIV and CD4 counts of 101-200 cells/µL and suppressed viral load.

Chemoprophylaxis in Patients without HIV Infection

Unlike in patients with HIV infection, no specific PCP prophylaxis guidelines exist for immunocompromised patients without HIV infection. In general, chemoprophylaxis should be considered in any of the following patients:

- Patients with an underlying primary immune deficiency (severe combined immunodeficiency or hypogammaglobulinemia)
- Patients with a persistent CD4 count less than 200/µL
- Solid organ transplant recipients
- Hematopoietic stem cell transplant (HSCT) recipients, with prophylaxis administered (1) for 6 months after engraftment months or (2) for more than 6 months after HSCT in those who are still receiving immunosuppressive therapy (prednisone, cyclosporine) or who have chronic graft versus host disease
- Patients receiving daily systemic corticosteroid therapy (at least 20 mg daily for at least 1 month)
- Patients with cancer, vasculitides, or collagen vascular disorders and others receiving cytotoxic or immunosuppressive treatments such as cyclosporine or the purine analogs fludarabine or cladribine

Chemoprophylactic Regimens

TMP-SMX is the agent of choice for PCP prophylaxis in the absence of a contraindication. In patients who cannot tolerate TMP-SMX, other options include dapsone, dapsone plus pyrimethamine, atovaquone, and aerosolized pentamidine. Commonly used prophylactic regimens are:

For TMP-SMX, the normal dosage is one double-strength tablet (160 mg TMP to 800 mg SMX) daily. One single-strength tablet (80 mg TMP to 400 mg SMX) daily is also effective. Another alternative is one double-strength tablet 3 times per week. However, a daily-dosing regimen provides an additional benefit of cross protection against Toxoplasma gondii infection and other bacterial infections.

The use of TMP-SMX for long-term PCP prophylaxis does not seem to affect the rates of infection by drug-resistant organisms such as pneumococcus or Staphylococcus aureus. TMP-SMX resistance has been reported among some isolates of Pneumocystis.

For dapsone, the dosage is 100 mg daily by mouth if it is administered alone. If dapsone is given with pyrimethamine (plus leucovorin), the dosage is 50 mg of dapsone daily by mouth with 50 mg of pyrimethamine weekly and 25 mg of leucovorin weekly. Dapsone with pyrimethamine (plus leucovorin) provides protection against T gondii infection but not other bacterial infections.

For atovaquone, the dosage is 1500 mg by mouth once daily given with food. This agent has a low toxicity profile and is an alternative if the patient cannot tolerate TMP-SMX or dapsone. However, atovaquone is very expensive.

For aerosolized pentamidine, the normal dosage is 300 mg in 6 mL sterile water via Respirgard nebulizer every 4 weeks. This agent is better tolerated than dapsone or TMP-SMX. However, it is much more expensive and less effective than other prophylactic agents. Side effects include

cough and bronchospasm. The potential for extrapulmonary Pneumocystis manifestations and apical lung disease exists. In addition, aerosolized pentamidine may diminish the diagnostic sensitivity of sputum induction and bronchoalveolar lavage.

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