Pneumocystis Pneumonia

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ABSTRACT

Pneumocystis is an opportunistic fungus that is a major cause of morbidity and mortality in immunocompromised hosts. Despite a decline in incidence with the advent of highly active antiretroviral therapy (HAART), *Pneumocystis* remains the most common opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS) and is an increasing cause of disease in patients with other forms of immunosuppression. Although there have been advances in the prevention and treatment of this infection, the mortality for *Pneumocystis* pneumonia (PCP) in the setting of AIDS remains 10 to 20%. The mortality for patients with other forms of immunosuppression is poorly defined but may actually be higher than that reported in the setting of AIDS. The continued severity of PCP in the AIDS population, its increasing frequency in other immunosuppressed populations, and increasing evidence that normal hosts may serve as a reservoir for the organism merit continued evaluation of the epidemiology, clinical presentation, diagnosis, and treatment of this infection.

KEYWORDS: *Pneumocystis, P. jiroveci, P. carinii,* PCP, pneumocystosis

THE PATHOGEN

Organisms of the genus *Pneumocystis* are nonfilamentous fungi that have been isolated from the lungs of a variety of mammals. The inability to reliably culture this microbe hampered early attempts at its classification and description of its life cycle.[1] Evolution in the understanding of the biology of this organism has led to frequent changes in its taxonomy and nomenclature since it was discovered by Chagas in 1909. At the time of its discovery, the organism was thought to be a morphological variant of *Trypanosoma cruzi*.[2] Subsequent studies revealed that the organism was actually a new species and it was given the name *Pneumocystis carinii*. Morphological similarities between *Pneumocystis* and protozoa led to the misclassification of the organism as a protozoan for many years. This hypothesis was further supported by the fact that antiprotozoal drugs, but not antifungal drugs, exhibited efficacy against the disease.[3,4] That finding is largely due to the fact that the cell wall of the organism is lacking in ergosterol, which renders it resistant to the polyenes and azoles.[5] The protozoan hypothesis was widely accepted until RNA ribosomal sequencing identified the organism as a fungus in 1988.[6]

Once at home in the correct kingdom, further DNA studies revealed the complexity of the genus. Several studies demonstrated that numerous, distinct species of *Pneumocystis* exist and that they exhibit significant host specificity.[3,4] In addition, genetic variation within a given species of the organism has been widely reported.[3,4] As new data were reported, multiple name changes ensued. Changes in established nomenclature tend to generate strong opinions, and resistance to the name change exists. Although controversy persists, *Pneumocystis carinii* is now generally accepted to refer only to the species isolated from rats and

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P. jiroveci (or *P. jirovecii*) refers to the species isolated from humans. To prevent confusion in the medical literature the term *PCP* has been retained but now represents *Pneumocystis* pneumonia rather then *Pneumocystis carinii* pneumonia.

EPIDEMIOLOGY

Seroepidemiological surveys of healthy children have demonstrated that *Pneumocystis* has a worldwide distribution and that most children have been exposed to the organism at a young age.[7,8] Despite its widespread distribution, a reservoir for *Pneumocystis* has not been clearly identified.[5] There are data to support both an environmental and a human reservoir for this organism. *Pneumocystis* DNA has been detected at low levels in the air of hospital corridors and at high levels in the air of rooms occupied by patients with PCP.[7] Rodent forms of *Pneumocystis* have been identified in pond water[9] and water filters[10]; however, it is unclear if the host or the environment serves as the source in these cases. Increasing evidence from human and animal studies suggests that the mammalian host acts as the reservoir for *Pneumocystis* through either transient colonization or long-term occupancy, with the organism residing in a latent state.[8]

Pneumocystis colonization of immunocompetent rats has been reported in the medical literature,[11] and advances in molecular techniques have allowed for similar evaluations for colonization of immunocompetent humans. A recent study by Medrano et al supports the colonization hypothesis.[12] The authors performed nested polymerase chain reaction (PCR) in two independent analyses on oropharyngeal wash samples from 50 healthy patients and found 20% were positive for *Pneumocystis* DNA. Although a small study, it raises the possibility that immunocompetent humans serve as either a sustained or a transient reservoir for this organism. Another recent retrospective study utilized PCR to detect *Pneumocystis* in nasopharyngeal wash samples from immunocompetent children hospitalized with a diagnosis of respiratory tract infection.[13] The investigators detected the organism in 67 of the 422 patients evaluated (16%). Samples were also assessed for the presence of respiratory syncytial virus (RSV), and 30 of the 67 *Pneumocystis* positive samples also tested positive for RSV. The presence of other respiratory pathogens was not assessed. Although it is unclear if the respiratory symptoms can be attributed to *Pneumocystis* alone, this study clearly demonstrates that immunocompetent children are, at the very least, colonized with *Pneumocystis* at a young age.

Much like our knowledge of the reservoir for *Pneumocystis*, the mode of acquisition of this organism is yet unproven. Reactivation of a latent infection has been the prevailing theory; however, there is increasing evidence for airborne transmission in animals and humans. A mouse model of *Pneumocystis* infection supports the theory of airborne transmission.[14] It was observed that immunocompetent mice became colonized with *Pneumocystis* after being housed with infected severe combined immunodeficiency (SCID) mice. It was then demonstrated that the colonized, immunocompetent mice could transmit the organism to previously uninfected SCID mice as well as to a second group of immunocompetent mice. The evidence for airborne transmission is less clear among humans; however, transmission of the organism from patients with active PCP to other immunocompromised persons has been implicated in several nosocomial clusters.[15–21] Although some experts recommend isolating patients with PCP from other immunocompromised patients, consensus guidelines have assessed the data as inconclusive and do not recommended isolation as standard practice at this time.[22]

CLINICAL MANIFESTATIONS

Consistent with the probable mode of acquisition, the predominant organ affected by *Pneumocystis* is the lung. In human immunodeficiency virus (HIV) infected patients, the major presenting symptoms are nonspecific and include shortness of breath, fever, and nonproductive cough. The disease onset is insidious, with patients having symptoms for weeks or months before presentation. Physical examination is also nonspecific but often reveals tachycardia and tachypnea. Lung auscultation is typically normal. Laboratory studies are nondiagnostic, although patients typically have impaired oxygenation with low partial pressure of oxygen ($PaO_{2)}$ or elevated alveolar–arterial (A–a) gradient. The chest radiograph classically reveals bilateral, diffuse infiltrates. The infiltrates commonly originate in the perihilar region, with outward extension as the disease progresses.[23] Thin-walled cysts known as pneumatoceles are seen in 10 to 20% of cases.[24] Pneumatoceles are clinically relevant because they result in a predisposition for pneumothorax, which can be a presenting finding or may develop during therapy.[23] Atypical radiographic presentations such as unilateral disease, nodules, cavities, lymphadenopathy, and pleural effusion have also been described.[25,26]

Prior to the acquired immunodeficiency syndrome (AIDS) epidemic, *Pneumocystis* was a sporadic cause of infection in patients compromised by malignancy, immunosuppressive therapy, and severe malnutrition. *Pneumocystis* pneumonia (PCP) has since become more frequent in this HIV-uninfected population. This is largely due to the fact that the number of patients receiving stem cell and solid organ transplants has increased and the use of immunosuppressive medications for a variety of conditions has become more widespread. These patients typically present with a more acute and severe respiratory illness than that seen in the

HIV-infected population.[27] The differences in clinical presentations between these two groups of immunosuppressed patients were highlighted by Kovacs et al in a retrospective study comparing the clinical features of PCP in 49 HIV-infected patients and 39 patients with other forms of immunosuppression.[28] The study found that in comparison with HIV-infected patients, PCP in HIV-uninfected patients was associated with a decreased duration of symptoms (five vs 28 days, $p = .0001$), a higher respiratory rate (26 vs 24 breaths per minute, $p = .015$), a lower median room air arterial oxygen tension (52 vs 69 mm Hg, $p = .0002$), and a higher room air A–a gradient (59 vs 41 mm Hg, $p = .001$). That study also found no significant difference in mortality between the HIV-uninfected and HIV-infected patients (50% and 57%, respectively). However, other series have described a higher mortality in the HIV-uninfected group. A recent retrospective study spanning a 10-year period found that the mortality was higher in patients without HIV infection compared with patients with HIV infection (63% vs 41%, respectively).[27]

Extrapulmonary manifestations of pneumocystosis have been estimated to occur in only .06 to 2.5% of patients with *Pneumocystis* infection.[29] However, extrapulmonary disease may be underestimated because a series of autopsies in 233 HIV-infected patients revealed extrapulmonary pneumocystosis in 13%.[30] Patients with disease outside the thoracic cavity typically have advanced HIV disease and are either on no prophylaxis or prophylaxis with aerosolized pentamidine.[31] The most common extrapulmonary sites involved are the lymph nodes; but disease may also be located in the spleen, bone marrow, liver, gastrointestinal tract, eyes, ear, thyroid, muscle, adrenal glands, and kidneys.[31] The lungs may or may not be involved in patients with extrapulmonary disease. Disease outside the lungs may present in a local fashion; however, the majority of patients develop disease at multiple sites.[29] Extrapulmonary manifestations have also been described in patients without HIV infection; these patients typically suffer from other forms of immunosuppression and are more likely to have clinically apparent disease.[29,31] The sites of involvement are similar to those reported in the HIV-infected population. Symptoms for all patients vary based on location of disease and can include abdominal pain, hepatitis, anasarca, dysphagia, chest pain, and fever.[29]

DIAGNOSIS

The principal definitive diagnosis for *Pneumocystis* infection remains direct visualization of the pathogen by various staining techniques such as the Grocott-Gomori methenamine silver (GMS), Wright-Giemsa, calcofluor white, and the Papanicolaou stains.[31] Direct and indirect immunofluorescent stains that utilize antibodies directed against the organism are also commonly used.[32] GMS selectively stains the wall of *Pneumocystis* cysts and can be used on smears or tissue (Fig. 1). Wright-Giemsa stains all stages of the parasite and works best with cytologic smears. Calcofluor white is a chemifluorescent agent that nonspecifically binds to the β-linked polymers of the cell wall and can be used with tissue or smears. The Papanicolaou stain highlights the eosinophilic material surrounding the organism known as a "foamy body" but does not stain individual organisms clearly. Specimens can also be tested with immunofluorescent stains with antibodies against *P. jiroveci,* which have higher sensitivity than histological stains but also have higher rates of false positivity.[32] Comparative studies are few, but a study published by Procop et al compared four of the most commonly used staining methods for direct detection in clinical respiratory specimens. Results revealed that the Diff-Quik stain, a commonly used variation on the Wright-Giemsa stain, was the least sensitive technique (48.4%), whereas the immunofluorescent stain was the most sensitive (90.8%) but least specific (94.7%), with a resultant lower positive predictive value (81.9%). The GMS and Calcofluor white stains had intermediate sensitivities of 76.9% and 73.8%, respectively, but very high specificities of 99.2% and 99.6%, respectively.[32] Given these findings, a reasonable approach for some laboratories may be to confirm a positive immunofluorescent test with the more specific GMS or calcofluor stains.

Newer molecular techniques for the diagnosis of *Pneumocystis* involve DNA amplification by PCR. A prospective study of quantitative PCR on oral-wash samples of patients with suspected PCP reported an overall sensitivity of 88% and specificity of 85%. Importantly, both the sensitivity and specificity declined after initiation of therapy.[33] This technique has similar

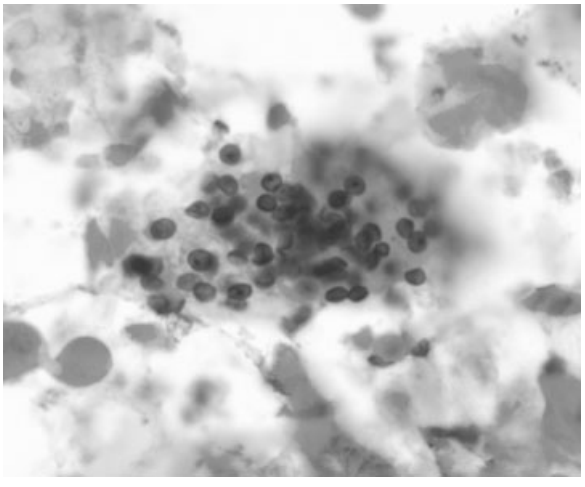

Figure 1 Cysts of *Pneumocystis* seen on Grocott-Gomori methenamine silver (GMS) staining of bronchoalveolar lavage fluid in a patient with human immunodeficiency virus infection.

sensitivity to staining techniques and has potential for use with a wide variety of specimens collected noninvasively; however, at this time it is less available in clinical laboratories. With the improved sensitivity of PCR, there has been identification of an asymptomatic carrier state in patients without an overwhelming immune deficiency such as neonates and pregnant women[34] and, in one study, even in 20% of those that are otherwise healthy.[12]

The clinical specimen tested can often determine the predictive value of a given test. Bronchoscopy with bronchoalveolar lavage (BAL), with reported sensitivities of 89 to 98%, is considered the diagnostic procedure of choice for PCP but has inherent risks related to its invasive nature.[31] A less invasive technique, induced sputum, has sensitivities reported from 74 to 83%.[35] The sensitivity of induced sputum varies between studies and with the staining method utilized.[36] A meta-analysis of studies comparing induced sputum to fiberoptic bronchoscopy with BAL elucidated the utility of induced sputum in conjunction with immunofluorescent staining for the diagnosis of PCP in HIV-infected patients.[36] This utility of induced sputum has not been studied in patients with other forms of immune suppression. The reduced organism burden in patients with immunosuppression due to conditions other then HIV limits the sensitivity of induced sputum for PCP diagnosis in this population.[36] Transbronchial biopsy and open lung biopsy are needed in rare occasions when noninvasive tests and BAL are unrevealing; however, both are associated with a higher rate of complications.

Other clinical, laboratory, and radiological parameters of PCP are nonspecific but can assist in diagnosis. Elevations in serum lactate dehydrogenase (LDH) have been associated with *Pneumocystis* infection.[37–39] However, one study demonstrated that LDH can be elevated in multiple pulmonary infections and that the level was more associated with radiological severity of disease than with microbiological etiology.[40] Concentrations of S-adenosylmethionine were shown to be significantly lower in HIV patients with PCP pneumonia versus other causes of pneumonia, but this has been studied only in limited settings.[41] Chest radiographs were normal or nondiagnostic in almost 30% of patients with PCP pneumonia in one study (Fig. 2). When combined with a reduced diffusion capacity of the lung for carbon monoxide (DLCO) measurement (below 75%), the sensitivity for PCP diagnosis improved to 97.5%.[42] Many diagnostic algorithms suggest the use of high-resolution computed tomography (HRCT) for patients with normal or nonspecific chest radiographs. A prospective study of 35 HIV-infected patients revealed the sensitivity of HRCT to be 100%, with a specificity of 89% and accuracy of 90%, for the diagnosis of PCP pneumonia with normal, equivocal, or nonspecific chest radiographs.[43]

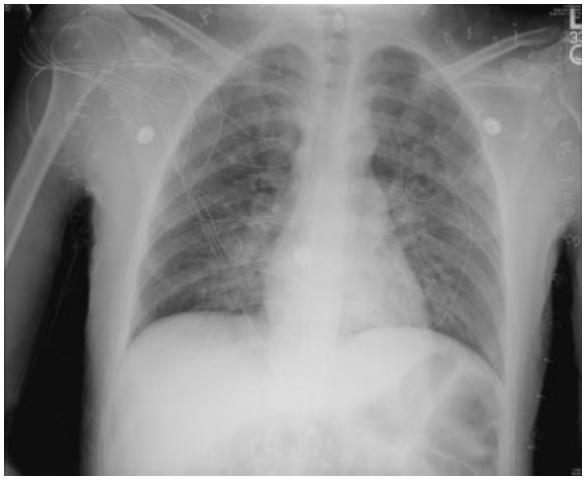

Figure 2 Diffuse bilateral infiltrates on portable chest radiograph. Typical, but not diagnostic of *Pneumocystis* pneumonia.

TREATMENT

The treatment of choice for PCP remains trimethoprim-sulfamethoxazole (TMP-SMX) (Table 1). This fixed drug combination has been shown in clinical trials to be equivalent to intravenous pentamidine and more effective than other regimens.[44–48] Toxicity rates and rates of discontinuation of therapy due to toxicity have also been similar to other regimens (Table 2). Oral formulations of TMP-SMX have also been shown to be effective for mild or moderate disease.[45] With widespread use of TMP-SMX for prophylaxis there has been a rising incidence of infection with *Pneumocystis jiroveci* with mutations in the dihydropteroate synthase (DHPS) gene; however, the clinical significance of this finding remains unclear, and investigations have produced conflicting results. Several studies report no change in outcome with TMP-SMX treatment of patients with DHPS mutations compared with patients with wild-type DHPS genes.[49,50] Others have reported that DHPS mutations are indeed associated with treatment failure,[51,52] and in a single study they are an independent predictor of death.[53] Further studies are needed to clarify the clinical significance of DHPS mutations. Screening for these mutations as part of clinical care is not currently practical.

Intravenous pentamidine is generally considered a second-line agent for severe disease or for patients who fail primary therapy with TMP-SMX (failure defined as lack of improvement after 5 to 7 days of therapy).[47,48,54,55] The regimen of dapsone-TMP was shown in trials to have similar efficacy to TMP-SMX, but it has inconvenient dosing.[46] The combination of primaquine and clindamycin has been shown to be effective in mild and moderate disease and in one series was shown to be the most effective salvage regimen in patients that failed primary therapy with either TMP-SMX or pentamidine, but the combination may have limited use because there is no intravenous formulation of primaquine.[54,56–58]

Table 1 Treatment Regimens for *Pneumocystis* Pneumonia

Disease Severity	Preferred Regimen	Alternative Regimens
Mild or moderate	TMP-SMX DS two tablets PO every 8 hours	Dapsone 100 mg PO daily and TMP 5 mg/kg PO every 8 hours OR Primaquine 15–30 mg base PO daily and clindamycin 300–450 mg PO or 600 mg IV every 6–8 hours OR Atovaquone 750 mg PO every 12 hours OR Trimetrexate 45 mg/m^2 IV daily and leucovorin 20 mg/m^2 IV every 6 hours
Severe ($pO_2 < 70$ mm Hg or A–a gradient > 35)	TMP 15–20 mg/kg/d IV and SMX 75–100 mg/kg/d IV every 6–8 hours and adjunctive corticosteroid therapy	Pentamidine 4 mg/kg/d IV and adjunctive corticosteroid therapy

Data from References 45–48, 54–58.
A–a, alveolar–arterial; DS, double strength (trimethoprim 160 mg and sulfamethoxazole 800 mg); IV, intravenous; PO, by mouth; pO_2, partial pressure of oxygen; TMP-SMX, trimethoprim-sulfamethoxazole.

Atovaquone is less effective than TMP/SMX in trials but has fewer side effects.[43,59] Trimetrexate has also been shown to be less effective in trials but does offer an alternative intravenous anti-*Pneumocystis* agent.[60] Inhaled pentamidine should not be used for treatment of acute PCP because it has been shown in several trials to be inferior to intravenous pentamidine.[61,62] Echinocandins have anti-*Pneumocystis* effect in animal studies, but clinical studies in humans are lacking. Of note, there have been two cases reported in the literature in which patients receiving an echinocandin for a concomitant diagnosis of aspergillosis developed progressive and ultimately fatal PCP.[63]

Patients with severe PCP, defined as a $PaO_2 < 70$ mm Hg or an A–a gradient > 35 mm Hg should receive adjunctive corticosteroid therapy within 24 to 72 hours of anti-*Pneumocystis* therapy.[44,64] Prednisone at an initial dose of 40 mg orally twice a day for days 1 to 5 is followed by a taper; 40 mg orally daily on days 6 to 10; 20 mg orally daily on days 11 to 21.[64] Methylprednisolone at 75% of the prednisone dose can be substituted if an intravenous formulation is required.[44] Several randomized trials in the early 1990s demonstrated the efficacy of corticosteroids in the treatment of PCP. Patients with moderate to severe PCP treated with corticosteroids had less early deterioration and a lower risk of respiratory failure and death at 31 days.[65–67] Rates of death in patients treated with corticosteroids were 11% versus 23% in patients not treated with corticosteroids.[65] A recent meta-analysis has confirmed the benefit of adjunctive corticosteroid therapy, finding that risk ratios for overall mortality were significantly lower at month 1 and months 3 to 4 of follow-up. In addition, the risk ratio for mechanical ventilation was lower in the corticosteroid group.[68] There are no guidelines for management of antiretrovirals (ARVs) in the setting of acute PCP. The fact that ARVs and anti-*Pneumocystis* agents often have overlapping toxicities leads many physicians to delay the onset of ARV therapy in a treatment naive patient. In addition, the risk of drug–drug interactions and the potential for the precipitation of an immune reconstitution inflammatory syndrome (IRIS) are also justifications for delaying therapy until PCP treatment is complete.[44]

Table 2 Adverse Effects of Commonly Used Medications

Drug Regimen	Side Effects
TMP-SMX	Rash, GI upset, bone marrow toxicity
Dapsone	Rash, GI upset, bone marrow toxicity
Dapsone and pyrimethamine	Rash, GI upset, bone marrow toxicity
Primaquine and clindamycin	Rash, GI upset
Atovaquone	Headache, GI upset, anemia, neutropenia
Trimetrexate	Bone marrow toxicity
Pentamidine (intravenous)	Hypotension, hypoglycemia, pancreatitis
Pentamidine (inhaled)	Bronchospasm

GI, gastrointestinal; TMP-SMX, trimethoprim-sulfamethoxazole.

PROPHYLAXIS

The use of chemoprophylaxis as a strategy for decreasing the morbidity and mortality associated with PCP was first evaluated in a randomized, controlled trial of pediatric oncology patients over 20 years ago.[69,70] This study demonstrated a significant decrease in the

incidence of PCP with the use of TMP-SMX prophylaxis. Subsequent studies in patients with solid organ transplant,[71] hematopoietic stem cell transplant (HSCT),[72] connective tissue disease,[73] and AIDS[74] have echoed those findings.

Recommendations for the timing of initiation of prophylaxis in the setting of HIV infection are well defined; CD4 + T-lymphocyte count < 200 cells/mL or the occurrence of oral thrush. PCP prophylaxis can be considered for patients with a CD4 + T-lymphocyte percentage of < 14% or a history of an AIDS-defining illness who do not otherwise qualify. Primary and secondary prophylaxis can be safely discontinued for patients on highly active antiretroviral therapy (HAART) when the CD4 + T-lymphocyte count is sustained > 200 cells/mL for a minimum of 3 months. If prophylaxis is discontinued it is imperative to monitor the CD4 count regularly and reinstitute prophylactic TMP-SMX if the CD4 count drops below 200 cells/mL.[21]

Consensus guidelines for the prevention of opportunistic infections in HSCT recipients were published in 2000. The current recommendation is that PCP prophylaxis be initiated for all allogeneic HSCT recipients from time of engraftment until 6 months post-HSCT.[75] PCP prophylaxis should be continued beyond 6 months in any allogeneic recipients who continue to receive immunosuppressive therapy or who have chronic graft versus host disease (GVHD). The guidelines also recommend that PCP prophylaxis be considered for recipients of autologous HSCT in select circumstances. Specifically noted are patients with an underlying hematologic malignancy, patients undergoing intensive preconditioning therapy, and those who are receiving fludarabine or cladrabine.[75]

There are numerous therapies, such as prednisone and monoclonal antibodies, that have the ability to impair T-cell function, but qualitative impairment is difficult to measure. Guidelines for these patient populations are not defined, and the lack of a clear marker of immunosuppression, such as the CD4 + T-lymphocyte count utilized for HIV-infected patients, has resulted in more generalized recommendations. The general consensus is that PCP prophylaxis be considered for any patients receiving T-cell-depleting therapies or corticosteroids in doses equivalent to ≥ 20 mg of prednisone per day for more than 2 to 3 weeks.[76,77]

TMP-SMX is the chemoprophylactic agent of choice because several studies have shown it to be superior to dapsone,[78] pentamadine,[79] and atovaquone[45] (Table 3). In addition to preventing PCP, daily TMP-SMX provides protection against several community-acquired bacterial pathogens of the respiratory tract, *Toxoplasma gondii, Isospora belli*, and *Cyclospora cayetanensis*.[71,76,80] TMP-SMX is generally well tolerated in the HIV-uninfected population, with adverse reactions reported in only 6 to 8% of patients.[81,82] Much higher rates of adverse reactions (25 to 50%) occur in HIV-infected patients.[83–85] However, several studies in the HIV-infected population have demonstrated that slow, gradual titration of TMP-SMX decreases occurrence of adverse reactions and in some cases may allow for the reintroduction of TMP-SMX therapy in patients who have experienced an adverse reaction in the past.[86,87]

Table 3 Prophylaxis Regimens for *Pneumocystis* Pneumonia

PREFERRED REGIMEN
TMP-SMX, one DS or one SS tablet PO daily
ALTERNATIVE REGIMENS
TMP-SMX, one DS tablet PO three times per week
Dapsone, 50 mg PO twice daily OR 100 mg PO daily
Dapsone 50 mg PO daily and pyrimethamine 50 mg PO weekly and leucovorin 25 mg PO weekly
Dapsone 200 mg PO weekly and pyrimethamine 75 mg PO weekly and leucovorin 25 mg PO weekly
Aerosolized pentamidine 300 mg via Respirgard II (Vital Signs Inc., Totowa, NJ) nebulizer monthly
Atovaquone 1500 mg PO daily

Data from Reference 22.
DS, double strength (trimethoprim 160 mg and sulfamethoxazole 800 mg); PO, by mouth; SS, single strength (trimethoprim 80 mg and sulfamethoxazole 400 mg); TMP-SMX, trimethoprim-sulfamethoxazole.

CONCLUSIONS

Pneumocystis is primarily a cause of pulmonary disease, but in rare instances it may affect virtually any organ in the body. Despite advances in antiretroviral therapy, PCP remains the most common opportunistic infection in patients with HIV infection and remains a risk for other immunocompromised patients and those receiving immunosuppressive medications. Our understanding of the biology of this organism has evolved considerably since its discovery in 1909, but much remains to be determined with regard to the reservoir for the organism, its life cycle, and its mode of transmission. Advances in the use of PCR as a diagnostic modality for this infection may help clarify some of these unanswered questions.

DISCLAIMER

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army, Department of the Air Force, Department of Defense, or US government.

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