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Other HIV-Associated Pneumonias

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INTRODUCTION

The incidence and mortality of human immunodeficiency virus (HIV)-related opportunistic infections has decreased significantly from the era before antiretroviral therapy (ART).^{1,2} However, HIV infection and its attendant risk for infectious complications remains one of the most important health care problems worldwide. Among infectious complications in patients with AIDS, the lung is the most frequently affected site.^{3–5} Effective prophylaxis and antimicrobial therapy has made a significant impact on the incidence of common opportunistic infections such as *Pneumocystis jirovecii* pneumonia.⁶ However, pulmonary infections from uncommon pathogens, and organisms not classically related to AIDS, as well as organisms without effective antimicrobial prophylaxis or those without established recommendations for primary prophylaxis have also been reported.

The differential diagnosis of pulmonary infections in patients with HIV is broad. The diagnostic approach should be individualized for each patient based on a detailed history of symptoms and environmental exposures, the physical examination, previous use of any antimicrobial prophylaxis, as well as the intensity and persistence of immune deficiency, which can be assessed by the CD4 cell count. These factors must be taken into account to determine the likelihood of any particular organism as the cause of pneumonia when developing the differential diagnosis for an individual patient.

The diagnosis and treatment of pneumonia in patients with AIDS can also be complicated by atypical presentation of the clinical manifestations of disease, unusual radiographic findings, the presence of multiple infections with different organisms,^{7–12} noninfectious pulmonary complications,¹³ immune reconstitution inflammatory syndrome (IRIS), drug-drug interactions, and adverse drug reactions. Furthermore, the availability of definitive diagnostic tests, especially bronchoscopy, can be challenging in resource-poor areas.¹⁴ Currently, there is no single comprehensive algorithm to serve as a guideline for determining the diagnosis of pneumonia in patients with HIV infection.

This review summarizes some of the major pulmonary infections from organisms other than *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, and *Streptococcus pneumoniae* in patients infected with HIV.

NONTUBERCULOUS MYCOBACTERIAL PNEUMONIA

The Organisms

Nontuberculous mycobacteria (NTM) can be isolated from water and soil. Unlike *M tuberculosis*, there are no known latent NTM infections. The mode of transmission of NTM is from recent acquisition through inhalation and ingestion. No isolation is required for patients hospitalized with pneumonia from NTM because there have been no documented cases of person-to-person transmission. Given that these organisms are ubiquitous in the environment, a positive respiratory sample culture must be interpreted with caution because a positive finding may represent either environmental contamination or transient airway colonization.¹⁵ However, it is thought that colonization with NTM could precede disseminated infection.¹⁶ Patients with advanced HIV infection with CD4 cell counts less than 50 cells/ μ L are at particular risk of developing infections from NTM.¹⁷

The diagnosis of pneumonia from NTM requires at least 2 positive expectorated sputum cultures or at least 1 positive bronchial wash/lavage sample. If granulomatous inflammation or acid-fast bacilli (AFB) are found on histopathology of a lung biopsy, only 1 positive culture from either sputum or lung biopsy or bronchial wash/lavage is required for a definitive diagnosis. However, in addition, appropriate pulmonary symptoms and radiographic abnormalities, as well as exclusion of other diagnoses, are required to fulfill the diagnostic criteria provided by the recommendations of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA).¹⁸

Clinical Manifestations

The incidence of infections related to *Mycobacterium avium* complex (MAC), which consists of *M avium* and *M intracellulare*, has decreased substantially in the post-ART era.¹⁹ However, MAC infections are still the most common NTM infection and the most common infection from NTM associated with IRIS in patients infected with HIV.^{19,20} MAC rarely occurs as a cause of pneumonia in patients infected with HIV, especially as an isolated pulmonary infection without disseminated disease (Fig. 1).²¹ *M kansasii* is the second most common NTM infection in patients infected with HIV.²² Another NTM infection that exhibits clinical manifestations similar to those of MAC is *M simiae*.^{8,23}

Most other NTM infections commonly manifest as disseminated infections with or without pulmonary involvement, except for *M kansasii* and *M xenopi*, which commonly present as localized pulmonary infection.^{17,24,25} Disseminated disease and mycobacteremia from *M kansasii* is more common in patients infected with HIV compared with individuals without HIV.²⁶ Clinical manifestations of *M kansasii* infection are similar to those present during *M tuberculosis* infection except for the occurrence of meningitis, which is fairly uncommon in *M kansasii* infection.^{27,28}

Constitutional symptoms, including fever, night sweats, decreased appetite, and weight loss are common among all NTM infections. Extrapulmonary manifestations should trigger clinicians to consider certain species of NTM more than the others. For instance, clinical features that may suggest infections from MAC and *M genavense* include diarrhea, intra-abdominal adenopathy, and hepatosplenomegaly,^{29–31} whereas skin, soft tissue, bone, and joint involvement suggest infections from rapid-growing mycobacteria (*M abscessus*, *M fortuitum*, *M chelonae*), and other NTMs such as *M malmoense*, *M szulgai*, and *M hemophilum*.^{17,32,33}

Radiographic Findings

Typical radiographic findings of MAC pulmonary infection in immunocompetent hosts include upper lobe involvement with or without cavitation in men, and right middle lobe or lingular involvement in elderly women. In patients infected with HIV, no differences in radiographic findings by patient sex have been described. Multifocal bronchiectasis is the most common radiographic feature of MAC in HIV populations.¹⁵

In NTM infections other than MAC, pulmonary involvement as part of disseminated NTM disease presents more commonly compared with localized pulmonary infection in patients infected with HIV. Consequently, bilateral interstitial infiltrates are the most common radiographic features.^{16,25} However, bilateral patchy infiltrates, cavitary lesions, pleural effusions, mediastinal adenopathy, or a normal chest radiograph can also be found. Although there are some differential radiographic features of pulmonary infection from *M kansasii* and *M tuberculosis*, they cannot be used to reliably distinguish one from another from the radiographic features alone.³⁴ Moreover, there are no specific radiographic features that can be used to distinguish among NTM pulmonary infections in patients infected with HIV.¹⁶

Treatment

Azithromycin or clarithromycin is recommended for primary prophylaxis in patients infected with HIV with CD4 cell counts less than 50 cells/ μ L.³⁵ No primary antimicrobial prophylaxis is currently recommended to prevent infections from NTM other than MAC.

The combination of clarithromycin or azithromycin, rifampin or rifabutin, and ethambutol, with or without the addition of amikacin or streptomycin is the usual antimicrobial regimen for effective treatment of MAC pulmonary disease. For pulmonary disease involving *M kansasii*, the regimen includes isoniazid, rifampin, and ethambutol. Besides MAC and *M kansasii*, there are no standard regimens to treat infections from infrequently encountered NTMs because of limited clinical evidence and published experience.¹⁸

In general, combinations of 3 or 4 antimicrobial agents to which the organism is susceptible are required. Four-drug regimens are used for patients with extensive pulmonary disease, disseminated infection, and mycobacteremia. Most NTMs are susceptible to the newer macrolides (clarithromycin or azithromycin) and fluoroquinolones (moxifloxacin, ciprofloxacin); these are the primary drugs used in most regimens to treat NTM infections. The third and fourth drugs can be chosen among isoniazid, rifampin, ethambutol, amikacin, doxycycline, and trimethoprim-sulfamethoxazole. Other antimicrobial agents to which the organism is susceptible can also be used. The regimen may also be guided by antibiograms reflecting organism sensitivities. However, the clinician must be aware of limitations because the exact correlation of in vitro susceptibility testing of certain drugs and clinical responses for MAC and uncommon NTMs are not always parallel or are still unknown. Consequently, in vitro susceptibility testing for infrequently encountered NTMs is not routinely recommended.¹⁸

Obtaining respiratory samples for cultures is essential in all patients (with or without HIV infection) suspected to have a pulmonary infection from NTM. It not only helps to guide antimicrobial therapy but also helps to determine the duration of treatment. At least 12 months of therapy after a negative respiratory sample culture is generally used as a guideline for treatment duration. In patients infected with HIV with AIDS, the treatment should also be continued until the CD4 cell count is more than 100 cells/ μ L for at least 6 months.³⁵

FUNGAL PNEUMONIAS

Organisms

Medically important fungi that cause pulmonary infections in patients infected with HIV are categorized into 3 different groups in this review: *Aspergillus* species, *Cryptococcus neoformans*, and dimorphic fungi.

Aspergillus species are ubiquitous hyaline molds that can be isolated from air and soil. *A. fumigatus* is the most common species that causes infections in patients infected with HIV.^{36,37} Other common species include *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans*. The mode of pulmonary infection is usually from recent acquisition through inhalation. There is currently believed to be no latent state of infection. However, these fungi can colonize the respiratory tract in patients with preexisting pulmonary diseases and architectural distortion of the lung. In addition to neutropenia and corticosteroid use, which are the well-established major risk factors for infection, a CD4 cell count less than 50 cells/ μ L also represents a significant risk factor for invasive aspergillosis.^{36–38}

Cryptococcus neoformans is a ubiquitous encapsulated yeast that is found worldwide. It can be isolated from aged pigeon droppings. *Cryptococcus gattii*, another *Cryptococcus* species that is found in tropical and subtropical climates, is not discussed in this review because it is typically a pathogen in individuals with an apparently healthy immune system. Infection with *Cryptococcus* is caused by inhaling spores or yeast cells.³⁹ The organism initially forms a primary pulmonary lymph node complex in a manner similar to tuberculosis.⁴⁰ Cryptococcal infection in patients infected with HIV is caused by either reactivation of latent infection or primary infection. Most cases of cryptococcal infection occur in patients with a CD4 cell count less than 200 cells/ μ L.⁴¹

The dimorphic fungi (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides* species, *Paracoccidioides brasiliensis*, *Penicillium marneffei*) are endemic fungi that can be isolated from particular regions of the United States or certain parts of the world (Table 1). Thus, determining the patient's geographic and travel histories is helpful to exclude or suggest infections from certain organisms. The pathogenesis of infection is via inhalation of spores. These infections can be caused by either recent acquisition or reactivation of the latent state.

Clinical Manifestations

Invasive aspergillosis in patients infected with HIV most commonly presents as pneumonia, although disseminated infections involving multiple organs have also been reported.^{36,38} The clinical symptoms are often nonspecific. Cough, dyspnea, and fever are the most common presenting symptoms; chest pain and hemoptysis present less commonly.^{38,42} Tracheobronchial aspergillosis is another manifestation of invasive disease in patients infected with HIV.^{36,38,42} Three forms of tracheobronchial aspergillosis have been described: the obstructive form, the ulcerative form, and the pseudomembranous form. Other well-known manifestations of *Aspergillus* pulmonary syndromes, such as aspergillomas, allergic bronchopulmonary aspergillosis, and chronic necrotizing pulmonary aspergillosis, are rarely reported in patients infected with HIV.^{43–45} According to definitions from the European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG),⁴⁶ histopathologic evidence of tissue invasion by hyphal elements and culture isolation of *Aspergillus* are required to make a diagnosis of proven invasive aspergillosis. Galactomannan in serum and bronchoalveolar lavage (BAL) fluid can support a probable diagnosis of infection.

The most common manifestation of cryptococcal infection in patients infected with HIV is disseminated infection with meningitis.⁴⁷ Patients with localized pulmonary infection generally have a higher CD4 cell count than those with disseminated disease.⁴⁸ However, all patients infected with HIV with cryptococcal pneumonia should undergo a lumbar puncture examination to rule out central nervous system involvement.⁴⁹ Serum and cerebrospinal fluid cryptococcal antigen and fungal blood cultures should also be obtained to exclude disseminated disease. Serum cryptococcal antigen is an excellent screening test for disseminated disease in this population.⁴⁸

Most patients infected with HIV with pneumonia from endemic fungi present with disseminated disease. Molluscum-like skin lesions, hepatosplenomegaly, lymphadenopathy, and fungal isolation from blood and bone marrow cultures are present in disseminated histoplasmosis and penicilliosis.^{50–55} Thus, skin scraping, lymph node aspiration, blood and bone marrow cultures can be used as alternatives to bronchoscopy to establish a definitive diagnosis. Cutaneous manifestations are relatively less common in disseminated blastomycosis, coccidioidomycosis, and paracoccidioidomycosis. Serology, serum antigen, and urine antigen are also useful in the diagnosis. However, definitive identification of organisms by smears and/or polymerase chain reaction (PCR) and isolation of organisms from respiratory samples are strongly encouraged because mixed infections can occur in the advanced stages of HIV infection.

Radiographic Findings

In a case series of pulmonary aspergillosis,⁴² cavitory upper lobe lesions were the most common radiographic pattern, followed by bilateral alveolar or interstitial infiltrates, which were associated with disseminated infection, and focal alveolar infiltrates. The air crescent sign was not found. Respiratory sample cultures and tissue biopsy are necessary to confirm the diagnosis of invasive aspergillosis because there are no absolutely specific radiographic findings.

Radiographic findings in pulmonary cryptococcosis are varied. Bilateral diffuse interstitial infiltrates are the most common finding. Other findings include focal alveolar infiltrates, cavitory lesions, pleural effusions, and lymphadenopathy.^{48,56–58} Ground-glass opacities similar to *Pneumocystis* pneumonia and miliary nodules similar to miliary tuberculosis have also been reported in patients infected with HIV.⁵⁹

Bilateral nodular opacities or interstitial infiltrates are the most common radiographic findings in pneumonia from the endemic fungi.^{50,60–65} Hilar adenopathy can be observed in histoplasmosis and coccidioidomycosis. However, the radiographic findings are varied and nonspecific in these infections.

Treatment

Primary antimicrobial prophylaxis regimens are not generally recommended for fungal infections in patients infected with HIV with a low CD4 cell count, with the exception of histoplasmosis, for which itraconazole is recommended when the CD4 cell count is less than 150 cells/ μ L for patients living in endemic areas where the incidence of histoplasmosis is more than 10 cases per 100 patient-years.^{35,66} Fluconazole or itraconazole can also be considered for primary prophylaxis for patients living in endemic areas of coccidioidomycosis if the CD4 cell count is less than 250 cells/mL.³⁵

The primary antifungal agent for invasive aspergillosis is voriconazole.⁶⁷ It has been shown to have more favorable outcomes compared with amphotericin B deoxycholate.⁶⁸ When required, the lipid formulations of amphotericin B are recommended over amphotericin B

deoxycholate. Caspofungin, micafungin, and posaconazole are alternative agents for patients who are refractory to or intolerant of previous antifungal therapy.^{67,69–71} Treatment can be discontinued when clinical symptoms resolve, there is evidence of resolution or stabilization of radiographic abnormalities, and the CD4 cell count is maintained at more than 200 cell/ μ L.³⁵

The primary antifungal regimen for disseminated cryptococcosis is amphotericin B deoxycholate plus flucytosine for 2 weeks, followed by high-dose fluconazole (400 mg/d) for 8 weeks. For localized pulmonary cryptococcosis with asymptomatic or mild-to-moderate symptoms, fluconazole (400 mg/d) for 6 to 12 months is recommended. Secondary prophylaxis regimens are based on providing fluconazole (200 mg/d) until the CD4 cell count is greater than 100 cells/ μ L for at least 3 to 6 months.^{35,49,71}

Regimens for treatment of endemic fungal pneumonias in patients infected with HIV should generally be designed to treat disseminated infection or at least aimed at treating moderately severe localized disease. The primary antifungal therapy for endemic fungal pulmonary infection with disseminated disease is initial therapy with lipid formulations of amphotericin B for 1 to 2 weeks or until clinical improvement, followed by itraconazole for 12 months, except for penicilliosis for which itraconazole should be provided for only 10 weeks.^{35,66,71–73} Fluconazole can be used instead of itraconazole for coccidioidomycosis and paracoccidioidomycosis. Ketoconazole and sulfadiazine can be used for paracoccidioidomycosis after a favorable clinical response to initial therapy with amphotericin B.

Secondary prophylaxis is required until the CD4 cell count is more than 150 cells/ μ L for 6 months for histoplasmosis and blastomycosis, more than 250 cells/ μ L for 6 months for coccidioidomycosis, and more than 100 cells/ μ L for 6 months for penicilliosis. Secondary prophylaxis for paracoccidioidomycosis has not been well established and was not included in the latest guidelines.

VIRAL PNEUMONIA

Organisms

This review focuses only on cytomegalovirus (CMV) pneumonitis although other respiratory viruses such as influenza virus, parainfluenza virus, respiratory syncytial virus, adenovirus, and meta-pneumovirus can also cause pneumonia in patients infected with HIV. CMV and herpes simplex virus (HSV) cause pneumonitis relatively rarely in patients infected with HIV.

Human CMV or Human herpesvirus 5 (HHV-5) is a double-stranded DNA virus that commonly infects most individuals early in life, and subsequently remains in a latent state in the individual throughout life. Most infections are caused by viral reactivation in patients with advanced immunocompromise. For patients infected with HIV, the infection typically occurs when the CD4 cell count decreases to less than 50 cells/ μ L.

Clinical Manifestations

The most common end-organ disease caused by CMV infection in patients infected with HIV is CMV retinitis. Other end-organ manifestations of CMV diseases include infections of the gastrointestinal tract (colitis, esophagitis) and central nervous system (ventriculitis, encephalitis, myelitis, radiculitis). Although CMV is one of the major pulmonary infections found in HIV-negative immunocompromised patients, such as solid organ and bone marrow transplant recipients, CMV pneumonitis occurs rarely in patients infected with HIV.

However, it is not uncommon to detect CMV in BAL fluid in the presence of other infectious agents, particularly in coexistence with *Pneumocystis jirovecii*.

The significance of CMV in BAL fluid as a cause of pneumonia in patients infected with HIV remains controversial. The methods available to detect CMV in BAL fluid include cytologic examination, viral culture, and PCR. PCR detection of CMV in blood specimens does not help with the diagnosis of CMV pneumonitis. The diagnosis of CMV pneumonitis is more definitive when transbronchial or lung biopsy is performed and CMV cytopathic effects or inclusion bodies are identified within the tissue.⁷⁴

Extrapulmonary manifestations of CMV are not associated with the detection of CMV in BAL fluid.^{75,76} However, CMV pneumonitis should be suspected in patients infected with HIV who exhibit extrapulmonary CMV disease along with bilateral pulmonary infiltrates, and when other organisms responsible for pneumonia cannot be identified from BAL sampling.⁷⁴ The clinical manifestations of CMV pneumonitis are similar to those of *Pneumocystis* pneumonia except for the occasional presence of pleural effusions, which are only rarely found in *Pneumocystis* pneumonia.⁷⁶

Radiographic Findings

Diffuse bilateral interstitial infiltrates or ground-glass opacities are characteristic radiographic features of pneumonia from many organisms in patients infected with HIV, including CMV pneumonitis and *Pneumocystis* pneumonia.^{58,77}

Treatment

When CMV is identified in BAL fluid together with *P jirovecii*, this finding may simply represent viral shedding, reflecting the degree of low immunity in the HIV-infected host,⁷⁸ rather than coinfection with CMV. The coinfection of CMV along with *P jirovecii* is not significantly associated with increased mortality or severity of *Pneumocystis* pneumonia.^{79–82}

For patients infected with HIV with bilateral interstitial pneumonia who have CMV in BAL fluid, anti-CMV treatment might be considered in the absence of other pathogens in the BAL fluid,⁸¹ if CMV is found in BAL fluid in the presence of high levels of CMV viremia,⁷⁵ or if the patient has a poor response to anti-*Pneumocystis* therapy alone. There is also no strong evidence to support initiation of anti-CMV therapy for patients infected with HIV with positive CMV in BAL fluid who have *Pneumocystis* pneumonia requiring adjunctive corticosteroids.

If CMV is considered to be the cause of pulmonary infection, intravenous ganciclovir should be initiated. Alternative anti-CMV agents include foscarnet and cidofovir. Therapy can be switched to oral valganciclovir after at least 2 weeks of intravenous agents and clinic improvement, as well as stabilization of the observed radiologic findings. The treatment also should be continued until the CD4 cell count is greater than 100 cells/ μ L for 3 to 6 months.³⁵ ART should be instituted as soon as possible.

UNCOMMON BACTERIAL PNEUMONIA (NOCARDIOSIS, RHODOCOCOCCOSIS)

Organisms

Uncommon bacteria that can cause pulmonary infection in patients infected with HIV with a low CD4 cell count are discussed in this section, focusing on bacteria in the genera *Nocardia* and *Rhodococcus*. These organisms belong to the same family, Nocardiaceae.

Bacteria in the genus *Nocardia* are gram-positive with partially acid-fast beading branching filaments, which can be isolated in soil worldwide. The most common species causing pulmonary infection is *N asteroides*, whereas *N brasiliensis* is the most common species causing lymphocutaneous infection.⁸³ *Rhodococcus equi* is a gram-positive, weak acid-fast coccibacilli, which can be isolated from the stools of foals. Rhodococcosis is a rare zoonotic infection that occurs in immunocompromised patients, such as transplant recipients and individuals infected with HIV. Pulmonary nocardiosis and rhodococcosis are caused by recent acquisition of organisms through inhalation. Most patients have advanced AIDS with a CD4 cell count less than 50 cells/ μ L.^{84,85}

Clinical Manifestations

Nonspecific symptoms including fever, cough, expectoration, and chest pain are common clinical symptoms in patients presenting with pulmonary nocardiosis or rhodococcosis. The lungs are usually the primary site of infection although direct inoculation through trauma and skin breakdown is possible. In immunocompromised patients, the infection progresses to disseminated disease with extrapulmonary involvement. Hematogenous spreading to the central nervous system and subcutaneous tissues causes brain and subcutaneous abscesses.

Although disseminated infection with extrapulmonary involvement is believed to be from hematogenous spread, isolation of *Nocardia* from blood is extremely uncommon in patients infected with HIV.^{86,87} Nocardemia has been reported in patients with endovascular foreign bodies without HIV infection.^{88–90} The prevalence of central nervous system involvement is 8.8%.⁸³ In contrast, *R equi* can be isolated from sputum and blood in approximately 50% of patients. The central nervous system is involved in 4.5% of infected individuals.⁸⁵ Extrapulmonary involvement in rhodococcosis is higher during relapse resulting from inadequate initial antimicrobial treatment.⁹¹

Radiographic Findings

Pulmonary consolidation with cavitation with or without mediastinal adenopathy are the most common radiographic findings of pulmonary nocardiosis^{92,93} and rhodococcosis.^{85,94–97}

Treatment

A 2-drug or 3-drug regimen is recommended for the initial treatment of nocardiosis. The regimen depends on in vitro susceptibility testing. Some species such as *N facinica*, *N nova*, and *N otitidiscaviarum* can be resistant to trimethoprim-sulfamethoxazole.^{98,99} Trimethoprim-sulfamethoxazole should be included in the regimen if the organism is susceptible to it and the patient is not allergic to sulfonamide antibiotics. The second and/or third agent(s) during the initial treatment can be chosen among amikacin, imipenem-cilastatin, and cephalosporins (ceftriaxone, cefotaxime, and cefepime).⁹⁹ Linezolid is also an alternative agent, but clinical data are limited. The therapy can be switched to oral trimethoprim-sulfamethoxazole with amoxicillin-clavulanate or minocycline or moxifloxacin after 3 to 6 weeks of intravenous therapy. The duration of treatment is usually in the range of 6 to 12 months, and should be based on radiographic response, clinical improvement, and host immune status.

There is no standard antimicrobial regimen for rhodococcosis. The most active antimicrobial agents include glycopeptides, carbapenems, aminoglycosides, fluoroquinolones, macrolides, trimethoprim-sulfamethoxazole, rifampin, tigecycline, and linezolid.^{85,100,101} A combination of at least 2 intravenous antimicrobial agents based on in vitro susceptibility is recommended for the initial therapy, followed by a prolonged course of combined oral antimicrobial agents. The duration of treatment is also individualized for each patient

depending on clinical and radiologic responses, as well as CD4 cell count measurements.^{85,101}

PARASITIC PNEUMONIA

Organisms

Parasitic pneumonia is uncommon in patients infected with HIV. However, pulmonary infection from *Toxoplasma gondii* is more common compared with MAC, CMV, and HSV infections. Other parasites that have reportedly been implicated as causative agents for pneumonia in this population are cryptosporidia and microsporidia.^{102–109} This review focuses on pulmonary toxoplasmosis.

Cats are the definitive hosts for *T gondii*. The routes of transmission to human are through ingestion of food contaminated with sporulated oocysts originating from cat feces or from the ingestion of undercooked meat of animals (pigs, sheep, birds, rodents) that harbor tissue cysts. Symptomatic infection in humans is generally from the reactivation of latent infection.

Clinical Manifestations

The most common manifestation of toxoplasmosis in patients infected with HIV is encephalitis. The incidence of pulmonary toxoplasmosis in patients infected with HIV has been reported in France,¹¹⁰ but it is unknown in the United States. Many reported cases exhibit pneumonitis without encephalitis. The clinical presentation is nonspecific and includes fever, cough, and dyspnea.¹¹¹ The diagnosis is made by identification of toxoplasma tachyzoites in BAL fluid.^{111,112}

Radiographic Findings

Diffuse bilateral interstitial or reticulonodular infiltrates are common radiographic findings of *Toxoplasma* pneumonitis.^{111,113,114} No hilar or mediastinal adenopathy was observed in a small case series.¹¹³ Because the clinical manifestations and radiographic findings are nonspecific, serology for *Toxoplasma* has a role in establishing the diagnosis of pulmonary toxoplasmosis. The diagnosis of pulmonary toxoplasmosis is much less likely when IgG antibodies are absent.

Treatment

The treatment of pulmonary toxoplasmosis is the same as for cerebral toxoplasmosis. The primary regimen is a combination of pyrimethamine-sulfadiazine. Folinic acid (leucovorin) is also provided to reduce hematologic toxicity from pyrimethamine. The combination of pyrimethamine-clindamycin or pyrimethamine-atovaquone are alternative regimens for patients with sulfa allergy.^{35,115} Duration of therapy is at least 6 weeks if clinical and radiologic improvements are confirmed. Secondary prophylaxis is required to prevent recurrent disease until the CD4 cell count is greater than 200 cells/ μ L for 6 months.³⁵

SUMMARY

The differential diagnosis of pneumonia in patients infected with HIV is broad. The clinical manifestations of pulmonary infections in this population are nonspecific. Radiographic findings are varied and nonpathognomonic for any particular organism and may overlap with noninfectious pulmonary diseases. Given the disseminated nature of many of these infections, the findings of diffuse bilateral interstitial infiltrates or ground-glass opacities are characteristic radiographic features of many of the organisms that cause pulmonary infections in this population, with the exception of pulmonary aspergillosis, nocardiosis, and rhodococcosis, which commonly present with cavitary pulmonary lesions. Bronchoscopy is

required in most cases to establish a definitive diagnosis. It is essential that clinicians include testing for these uncommon HIV-associated pneumonias in the diagnostic evaluation of pulmonary disease in this population. The treatment duration for these infections is often prolonged because of low CD4 cell counts, and must be individualized to the clinical response and immune status of each patient. Primary and secondary prophylaxis depend on the CD4 cell count as well as other risk factors such as geographic location.

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KEY POINTS

- The lung is commonly involved with infectious complications in individuals infected with human immunodeficiency virus (HIV).
- In addition to *Pneumocystis* pneumonia discussed in another article in this issue, pulmonary infections in individuals infected with HIV can be related to nontuberculosis mycobacteria, cytomegalovirus, fungi, parasites, uncommon bacterial pneumonia, and other microorganisms.
- A high index of suspicion is needed, and awareness that the clinical presentation and treatment of pneumonia in patients with AIDS can be different from those in immunocompetent patients.
- Judicious use of invasive and noninvasive testing, as well as molecular biological techniques enhances the diagnosis and the prognosis of pulmonary infections in patients infected with HIV.

Fig. 1. Left upper lobe pneumonitis caused by *Mycobacterium avium* infection in a 32-year-old man infected with HIV presenting with cough, fever, sweats, and weight loss. Bronchoscopy with bronchoalveolar lavage established the infection; no other organisms were found.

Table 1

Endemic regional distribution of dimorphic fungi that cause pulmonary infections in individuals infected with HIV

Endemic Fungi	Endemic Areas
<i>Histoplasma capsulatum</i>	The Ohio, Missouri, and Mississippi River valleys in the United States; Mexico, Central America; certain areas in South American, Africa, and Asia
<i>Blastomyces dermatitidis</i>	Midwestern, southeastern, and south central United States; Canadian border around the Great Lakes and the St. Lawrence Seaway
<i>Coccidioides immitis</i>	Central and southern California (San Joaquin Valley, Mojave Desert), south central Arizona, southern New Mexico, and western Texas in the United States; Northern Mexico
<i>Coccidioides posadasii</i>	Southwest Mexico; Certain areas in Central American and South America
<i>Paracoccidioides brasiliensis</i>	Certain areas in Mexico, Central America, and South American
<i>Penicillium marneffei</i>	Southeast Asia, Southern China, Taiwan, Hong Kong, and South Asia