



**EDUCATIONAL OBJECTIVE:** Readers will consider typical as well as atypical organisms in patients with human immunodeficiency virus who present with lung infection

**SANDEEP M. PATEL, MD**

Department of Internal Medicine,  
Mayo Clinic, Rochester, MN

**SHEENA S. PATEL, BA**

Boonshoft School of Medicine,  
Wright State University, Dayton, OH

**ROBERT MYERS, MD**

Consultant, Department of Internal  
Medicine, Maricopa Medical Center,  
Phoenix, AZ

# A 37-year-old man with a chronic cough

**A** 37-YEAR-OLD MAN presented to the emergency department with an 8-week history of a mildly productive cough and shortness of breath accompanied by high fevers, chills, and night sweats. He also had some nausea but no vomiting.

Four days earlier, he had been evaluated by his primary care physician, who prescribed a 14-day course of one double-strength trimethoprim-sulfamethoxazole tablet (Bactrim DS) every 12 hours for presumed acute bronchitis, but his symptoms did not improve.

He was unemployed, living in Arizona, married with children. He denied any use of tobacco, alcohol, or injection drugs. On further questioning, he disclosed that he had unintentionally lost 30 pounds over the past 2 to 3 months and had been feeling tired.

When asked about his medical history, he revealed that he had been diagnosed with human immunodeficiency virus (HIV) infection in 2008 and that recently he had not been taking his antiretroviral medication, a once-daily combination pill containing efavirenz, emtricitabine, and tenofovir (Atripla). He had no other significant medical history, and the only medication he was currently taking was the trimethoprim-sulfamethoxazole.

On examination, his temperature was 38.7°C (101.7°F), blood pressure 109/68 mm Hg, heart rate 60 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 100% while breathing supplemental oxygen via nasal cannula at 2 L/min. He did not appear seriously ill.

His mucous membranes were moist, and he did not have oral candidiasis. He had a palpable 1-cm nontender lymph node above his left

clavicle. His heart and lungs were normal on physical examination. He had normal bowel sounds and no signs of peritonitis. His liver and spleen did not seem enlarged. Neurologic examination demonstrated normal cranial nerves, strength, reflexes, and sensation in all four limbs.

Initial blood tests (TABLE 1) showed a normal white blood cell count, normal results on a complete metabolic panel, and a lactate dehydrogenase level of 539 IU/L (reference range 313–618). His serum lactate level was within normal limits.

A chest radiograph showed multiple pulmonary nodules and a cavity in the lingula (FIGURE 1). In view of these findings, the patient was admitted to the hospital for further evaluation and testing.

HIV-specific tests performed on the second day of hospitalization showed extreme immunosuppression, with a CD4 count of 5 cells/μL (normal 326–1,404 cells/μL).

## ■ WHICH ORGANISM IS CAUSING HIS LUNG INFECTION?

**1** Which of the following organisms is the least likely to be associated with this patient's condition?

- Mycobacterium tuberculosis*
- Pneumocystis jirovecii*
- Coccidioides immitis*
- Candida albicans*
- Streptococcus pneumoniae*
- Cytomegalovirus

Bacterial, fungal, and viral lung infections are common in HIV-infected patients, especially if they are not on antiretroviral therapy and

**In severely immunocompromised hosts, diagnoses should not be excluded without firm evidence**

**TABLE 1**  
**The patient's laboratory values**

TEST	RESULTS	REFERENCE RANGE
<b>Complete cell blood count</b>		
Hemoglobin	11.4 g/dL	13.5–17.5
Mean corpuscular volume	86.2 fL	80–100
Leukocytes	4.6 × 10 <sup>9</sup> /L	5.0–10.0
Neutrophils	82%	50–86
Lymphocytes	11%	20–50
Monocytes	7%	0–9
Eosinophils	0%	0–7
Basophils	0%	0–2
Platelets	136 × 10 <sup>9</sup> /L	140–440
<b>Complete metabolic panel</b>		
Sodium	137 mmol/L	137–145
Potassium	4.4 mmol/L	3.5–5.1
Chloride	99 mmol/L	98–107
Bicarbonate	28 mmol/L	22–30
Blood urea nitrogen	13 mg/dL	9–20
Creatinine	0.87 mg/dL	0.66–1.25
Glucose	81 mg/dL	74–106
Alanine aminotransferase	17 U/L	21–72
Aspartate aminotransferase	26 U/L	17–59
Alkaline phosphatase	75 U/L	38–126
Bilirubin, total	0.8 mg/dL	0.2–1.3
<b>HIV-specific tests</b>		
CD3+ count	222 cells/μL	380–2,099
CD3+, %	50%	60–86
CD4+ count	5 cells/μL	326–1,404
CD4+, %	1%	35–63
CD8+ count	176 cells/μL	21–772
CD8+, %	40 %	9–35
CD4+/CD8+ ratio	< 0.1	1–4.4
HIV RNA	220,012 copies/mL	0–75
<b>Other</b>		
Hepatitis C antibody	Negative	
Rapid plasma reagin	Nonreactive	
QuantiFERON	Negative	
Lactate dehydrogenase	539 IU/L	313–681
Lactic acid	1.0 mmol/L	0.7–2.1
<i>Toxoplasma gondii</i> IgG	Positive	

their CD4 lymphocyte counts are low. Clues to the cause can be derived from the history, physical examination, and general laboratory studies. For instance, knowing where the patient lives and where he has travelled recently provides insight into exposure to endemic infectious agents.

The complete blood cell count with differential white blood cell count can help narrow the differential diagnosis but rarely helps exclude a possibility. Neutrophilia is common in bacterial infections. Lymphocytosis can be seen in tuberculosis, in fungal and viral infections, and, rarely, in hematologic malignancies. Eosinophilia can be seen in acute retroviral syndrome, fungal and helminthic infections, adrenal insufficiency, autoimmune disease, and lymphoma.

A caveat to these clues is that in severely immunocompromised hosts, like this man, diagnoses should not be excluded without firm evidence. This patient has severe, active immunosuppression, and only one of the six answer choices above is not a possible causative agent: *C albicans* rarely causes lung infection, even in immunocompromised people.

***Mycobacterium tuberculosis***

Tuberculosis can be the first manifestation of HIV infection. It can occur at any CD4 count, but as the count decreases, the risk of dissemination increases.<sup>1</sup> Classic symptoms are fever, night sweats, hemoptysis, and weight loss.

The CD4 count also affects the radiographic presentation. If the count is higher than 350 cells/μL, then infiltration of the upper lobe is likely; if it is lower than 200 cells/μL, then middle, lower, miliary, and extrapulmonary manifestations are likely.<sup>1,2</sup> Cavitation is less common in HIV-infected patients, but mediastinal adenopathy is more common.<sup>1</sup>

Definitive diagnosis is via sputum examination, blood culture, nucleic acid amplification, or microscopic study of biopsy specimens of affected tissues to look for acid-fast bacilli.<sup>1</sup>

Interferon-gamma-release assays such as the QuantiFERON test (Cellestis, Valencia, CA) or a tuberculin skin test can be used to check for latent tuberculosis infection. These tests can also provide evidence of active infection in the appropriate clinical context.<sup>3</sup>

Interferon-gamma-release assays have sev-

eral advantages over skin testing: they are more sensitive (76% to 80%) and specific (97%); they do not give false-positive results in people who previously received bacille Calmette-Guérin vaccine; they react only minimally to previous exposure to nontuberculous mycobacteria; and interpretation is not subject to interreader variability.<sup>4,5</sup> However, concordance between skin testing and interferon-gamma-release assays is low. Therefore, either or both tests can be used if tuberculosis is strongly suspected, and a positive result on either test should prompt further workup.<sup>6,7</sup>

Of note, both tests may be affected by immunosuppression, making both susceptible to false-negative results as the CD4 count declines.<sup>3</sup>

In any case, a positive acid-fast bacillus smear, radiographic evidence of latent infection, or pulmonary symptoms should be presumed to represent active tuberculosis. In such a situation, directly observed treatment with the typical four-drug regimen—rifampin (Rifadin), isoniazid, pyrazinamide, and ethambutol (Myambutol)—is recommended while awaiting definitive results from culture or polymerase chain reaction (PCR) testing.<sup>1</sup>

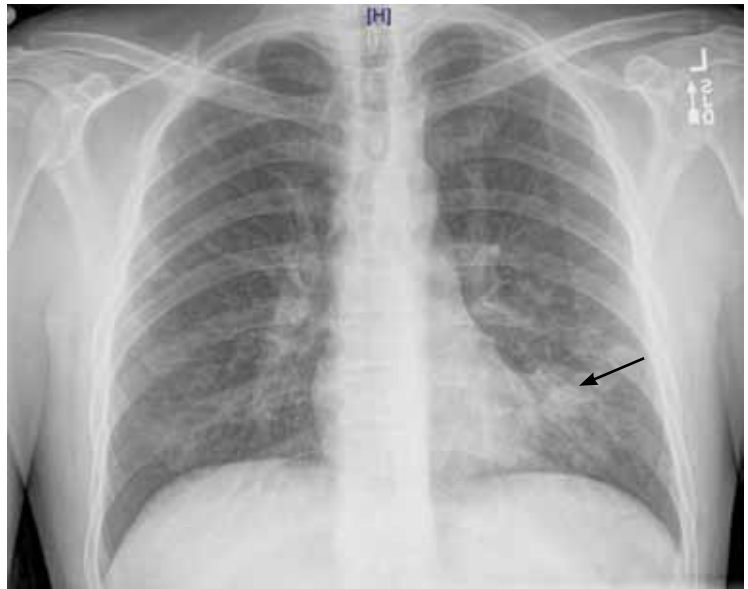
***Pneumocystis jirovecii***

*P jirovecii* was previously known as *P carinii*, and *P jirovecii* pneumonia is an AIDS-defining illness. Most cases occur when the CD4 count falls below 200 cells/ $\mu$ L.<sup>1</sup> Symptoms, including a nonproductive cough, develop insidiously over days to weeks.

Physical examination may reveal inspiratory crackles; however, half of the time the physical examination is nondiagnostic. Oral candidiasis is a common coinfection. The lactate dehydrogenase level may be elevated.<sup>1,8</sup> Radiographs show bilateral interstitial infiltrates, and in 10% to 20% of patients lung cysts develop—hence the name of the organism.<sup>1</sup> Pneumothorax in a patient with HIV should prompt a workup for *P jirovecii* pneumonia.<sup>9,10</sup>

No consensus exists for the diagnosis. However, if sputum examination is unrevealing but suspicion is high, then bronchoalveolar lavage can help.<sup>11-13</sup>

Trimethoprim-sulfamethoxazole for 21 days is the first-line treatment, with glucocorticoids



**FIGURE 1.** The chest radiograph at the time of admission shows findings consistent with a diffuse interstitial process with a lingular consolidation (arrow).

added if the Pao<sub>2</sub> is less than 70 mm Hg or if the alveolar-arterial oxygen gradient is greater than 35 mm Hg.<sup>1</sup>

***Coccidioides* species**

*Coccidioides* infection is typically due to either *C immitis* or *C posadasii*.<sup>14</sup> People living in or travelling to areas where it is endemic, such as the southwestern United States, Mexico, and Central and South America, are at higher risk.<sup>14</sup>

Typical signs and symptoms of this fungal infection include an influenza-like illness with fever, cough, adenopathy, and wasting, and when combined with erythema nodosum, erythema multiforme, arthralgia, or ocular involvement, this constellation is colloquially termed “valley fever.”<sup>15</sup> Most HIV-infected patients who have CD4 counts higher than 250 cells/ $\mu$ L present with focal pneumonia, while lower counts predispose to disseminated disease.<sup>1,2,16</sup>

Findings on examination are nonspecific and depend on the various pulmonary manifestations, which include acute, chronic progressive, or diffuse pneumonia, nodules, or cavities.<sup>14</sup> Eosinophilia may accompany the infection.<sup>15</sup>

The diagnosis can be made by finding the organisms on direct microscopic examination

**Tests for tuberculosis may be falsely negative if the CD4 count is low**

of involved tissues or secretions or on culture of clinical specimens.<sup>1,2,14</sup> Serologic tests, antigen detection tests, or culture can be helpful if positive, but negative results do not rule out the diagnosis.<sup>1,2,14</sup>

A caveat about testing: if the pretest probability of infection is low, positive tests for immunoglobulin M (IgM) do not necessarily equal infection, and the IgM test should be followed up with confirmatory testing. Along the same lines, a high pretest probability should not be ignored if initial tests are negative, and patients in this situation should also undergo further evaluation.<sup>17</sup>

Therapy with an azole drug such as fluconazole (Diflucan) or one of the amphotericin B preparations should be started, depending on the severity of the disease.<sup>1,2,14,18</sup>

### ***Candida albicans***

*C albicans* is a rare cause of lung infection.<sup>19,20</sup> It is, however, a common inhabitant of the upper airway tract, and pulmonary infection is usually the result of aspiration or hematogenous spread from either the gastrointestinal tract or an infected central venous catheter.<sup>20</sup>

The presentation is relatively nonspecific. Fever despite broad-spectrum antibacterial therapy is a major clue. Radiographic abnormalities usually are due to other causes, such as superimposed infections or pulmonary hemorrhage.<sup>21</sup> Sputum culture is unreliable because of colonization. The definitive diagnosis is based on lung biopsy demonstrating organisms within the tissue.<sup>19,20,22</sup>

Therapy with a systemic antifungal agent is recommended.

### ***Streptococcus pneumoniae***

*S pneumoniae* is one of the most common bacterial causes of community-acquired pneumonia in people with or without HIV.<sup>23–25</sup> Moreover, two or more episodes of bacterial pneumonia in 12 months can be an AIDS-defining condition in patients with a positive serologic test for HIV.<sup>16</sup> Therefore, in patients with fever, cough, and pulmonary infiltrates on chest radiography, *S pneumoniae* must always be considered.

Urinary antigen testing has a relatively high positive predictive value (> 89%) and specificity (96%) for diagnosing *S pneumoni-*

*ae pneumoniae*.<sup>26</sup> Blood and sputum cultures should be done not only to confirm the diagnosis, but also because the rates of bacteremia and drug resistance are higher with *S pneumoniae* infection in the HIV-infected.<sup>1</sup>

A combination of a beta-lactam and a macrolide or respiratory fluoroquinolone is the treatment of choice.<sup>1</sup>

### **Cytomegalovirus**

Although influenza is the most common cause of viral pneumonia in HIV-infected people, cytomegalovirus is an opportunistic cause.<sup>2</sup> This is usually a reactivation of latent infection rather than new infection.<sup>27</sup> Typically, infections occur at CD4 counts lower than 50 cells/ $\mu$ L, with cough, dyspnea, and fever that last for 2 to 4 weeks.<sup>2</sup>

Crackles may be heard on lung examination. The lactate dehydrogenase level can be elevated, as in *P jirovecii* pneumonia.<sup>2</sup> Radiography can show a wide range of nonspecific findings, from reticular and ground-glass opacities to alveolar or interstitial infiltrates to nodules.

The diagnosis of cytomegalovirus pneumonia is not always clear. Since HIV-infected patients typically shed the virus in their airways, bronchoalveolar lavage is not adequate because a positive finding does not necessarily mean the patient has active viral pneumonitis.<sup>27</sup> For this reason, infection should be confirmed by biopsy demonstrating characteristic cytomegalovirus inclusions in lung tissue.<sup>2</sup>

Importantly, once cytomegalovirus pneumonia is confirmed, the patient should be screened for cytomegalovirus retinitis even if he or she has no visual symptoms, as cytomegalovirus pneumonitis is typically a part of a disseminated infection.<sup>1</sup>

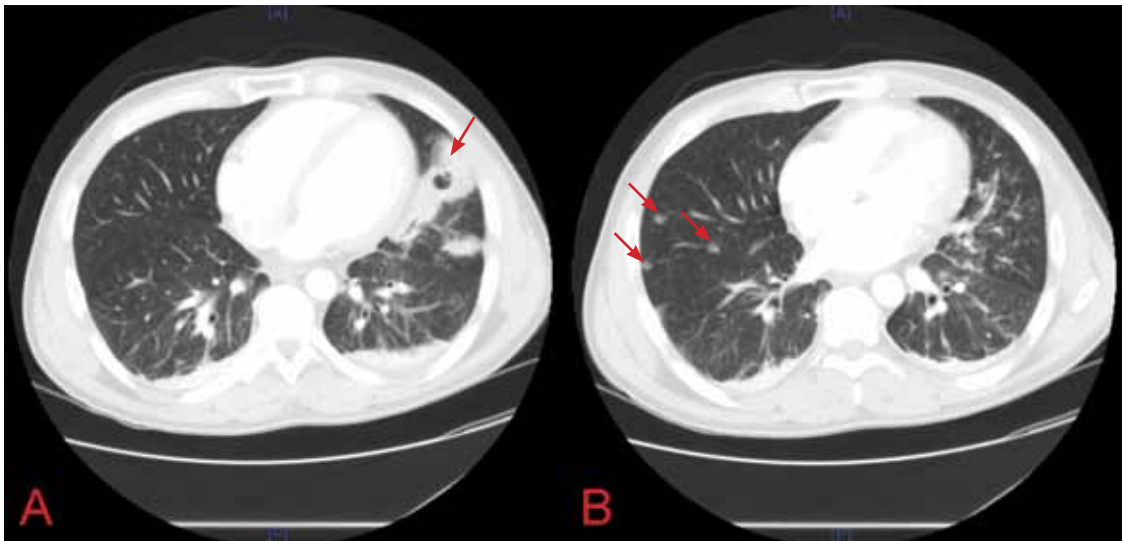
Treatment with intravenous ganciclovir (Cytovene) is required.<sup>1</sup>

### **■ CASE CONTINUED: POSITIVE TESTS FOR COCCIDIOIDES**

Our patient began empiric treatment for community-acquired pneumonia with intravenous ceftriaxone (Rocephin) and azithromycin (Zithromax).

He underwent computed tomography (CT) with contrast to further characterize the

***S pneumoniae* is one of the most common causes of community-acquired pneumonia in people with or without HIV**



**FIGURE 2.** Computed tomography of the chest with contrast shows cavitary lingular infiltrate (A, arrow) and diffuse pulmonary nodules (B, arrows) of about 1 mm. Note the “tree-in-bud” findings indicative of an infectious process.

abnormal findings on chest radiography. This revealed a lingular cavitary airspace consolidation, 1- to 1.2-cm pulmonary nodules scattered throughout both lungs, and mediastinal lymphadenopathy (FIGURE 2).

On the basis of these findings, the patient was immediately placed in negative pressure respiratory isolation and underwent induced sputum examinations for tuberculosis. Further tests for *S pneumoniae*, *S aureus*, *Mycoplasma*, *Legionella*, influenza, *Pneumocystis*, *Cryptococcus*, *Histoplasma*, and *Coccidioides* species were performed.

QuantiFERON testing was negative, and blood cultures were sterile. The first induced sputum examination was negative for acid-fast bacilli. PCR testing for mycobacterial DNA in the sputum was also negative.

Both silver and direct fluorescent antibody staining of the sputum were negative for *Pneumocystis*. On the basis of these findings and the patient’s lack of clinical improvement with trimethoprim-sulfamethoxazole, *Pneumocystis* infection was excluded.

PCR testing of nasopharyngeal samples for influenza A and B was negative. Tests for *S pneumoniae*, *S aureus*, *Mycoplasma*, *Legionella*, influenza, *Cryptococcus*, and *Histoplasma* were also negative. However, sputum cytology revealed characteristic spherules consistent with coccidioidomycosis (FIGURE 3). The pa-

tient’s coccidioidal serologic tests with immunodiffusion and complement fixation returned negative, presumably because of his immunocompromised state. However, an enzyme-linked immunoassay for urinary coccidioidal antigen (MiraVista Diagnostics, Indianapolis, IN), with a sensitivity of 71% and a specificity of 99%, was elevated at 5.15 ng/mL (reference range 0.07–2.0). Based on these findings and those on chest CT, the diagnosis of coccidioidomycosis was confirmed. Treatment needed to be started.

■ **THE PATIENT BEGINS TREATMENT**

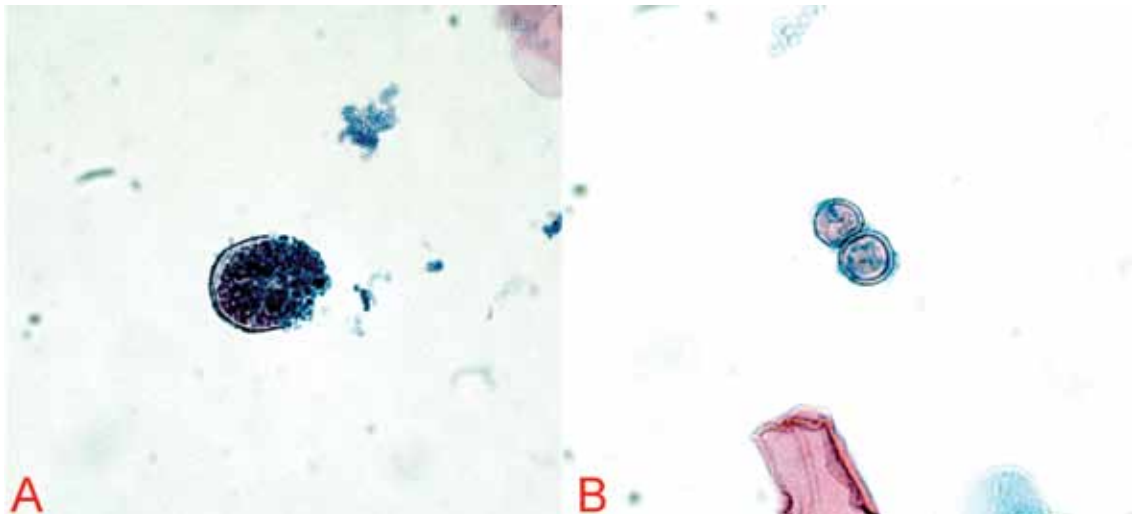
**2** Which treatment is most appropriate for this patient?

- Posaconazole (Noxafil)
- Caspofungin (Cancidas) and surgery
- Fluconazole
- Voriconazole (Vfend) and surgery
- Amphotericin B

Asymptomatic pulmonary coccidioidomycosis in an immunocompetent patient requires only supportive care. However, if the infection is symptomatic, severe (TABLE 2), or in an immunocompromised host, antifungal treatment is indicated.<sup>1,18</sup>

Solitary pulmonary cavities tend to be asymptomatic and do not require treatment,

**Pulmonary coccidioidomycosis requires antifungal treatment if it is symptomatic, severe, or in an immunocompromised host**



**FIGURE 3.** Microscopic study of sputum reveals a spherule (A) with multiple endospores, diagnostic of coccidioidal infection. The double-walled structure of *Coccidioides* is seen in B. In B, the organisms are adjacent to each other and are not to be confused with “budding,” as the reproductive cycle of *Coccidioides* is through endospore formation and propagation (Papanicolaou, × 400).

**After discussion, our patient said he was willing to comply with treatment**

even if coccidioidal infection is microbiologically confirmed.

However, if there is pain, hemoptysis, or bacterial superinfection, antifungal therapy may result in improvement but not closure of the cavity.<sup>18</sup> Therefore, in all cases of symptomatic coccidioidal pulmonary cavities, surgical resection is the only definitive treatment.

Coccidioidal cavities may rupture and cause pyopneumothorax, but this is an infrequent complication, and antifungal therapy combined with surgical decortication is the treatment of choice.<sup>18</sup>

Commonly prescribed antifungals include fluconazole and amphotericin B, the latter usually reserved for patients with significant hypoxia or rapid clinical deterioration.<sup>18</sup> At this time, there are not enough clinical data to show that voriconazole or posaconazole is effective, and thus neither is approved for the treatment of coccidioidomycosis. Likewise, there have been no human trials of the efficacy of caspofungin against *Coccidioides* infection, although it has been shown to be active in mouse models.<sup>18</sup>

Our patient was started on oral fluconazole and observed for clinical improvement or, conversely, for signs of dissemination. After 2 days, he had markedly improved, and within 1 week he was almost back to his baseline level

of health. Testing for all other infectious etiologies was unrevealing, and he was removed from negative pressure isolation.

However, as we mentioned above, his CD4 count was 5 cells/ $\mu$ L. We discussed the issue with the patient, and he said he was willing to comply with his treatment for both his *Coccidioides* and his HIV infection. After much deliberation, he said he was also willing to start and comply with prophylactic treatment for opportunistic infections.

**■ PREVENTING OPPORTUNISTIC INFECTIONS IN HIV PATIENTS**

**3** Which of the following prophylactic regimens is most appropriate for this patient?

- Trimethoprim-sulfamethoxazole, atovaquone (Mepron), and azithromycin
- Trimethoprim-sulfamethoxazole and azithromycin
- Pentamidine (Nebupent), dapsone, and clarithromycin (Biaxin)
- Dapsone and clarithromycin
- Trimethoprim-sulfamethoxazole by itself

According to guidelines for the prevention of opportunistic diseases in patients with HIV, he needs primary prophylaxis against the following organisms: *P jirovecii*, *Toxoplasma gon-*

*dii*, and *Mycobacterium avium* complex.<sup>1</sup>

The CD4 count dictates the appropriate time to start therapy. If the count is lower than 200 cells/ $\mu$ L or if the patient has oropharyngeal candidiasis regardless of the CD4 count, trimethoprim-sulfamethoxazole is indicated to prevent *P jirovecii* pneumonia. In those who cannot tolerate trimethoprim-sulfamethoxazole or who are allergic to it, dapsone, pentamidine, or atovaquone can be substituted.<sup>1</sup>

In patients seropositive for *T gondii*, a CD4 count lower than 100/ $\mu$ L indicates the need for prophylaxis.<sup>1</sup> Prophylactic measures are similar to those for *Pneumocystis*. However, if the patient cannot tolerate trimethoprim-sulfamethoxazole, the recommended alternative is dapsone-pyrimethamine with leucovorin, which is also effective against *Pneumocystis*.<sup>1</sup>

Finally, if the CD4 count is lower than 50 cells/ $\mu$ L, prophylaxis against *M avium* complex is mandatory, with either azithromycin weekly or clarithromycin daily.<sup>1</sup>

Given our patient's degree of immunosuppression, trimethoprim-sulfamethoxazole plus azithromycin is his most appropriate option.

Trimethoprim-sulfamethoxazole and azithromycin were added to his antimicrobial regimen before he was discharged. Two weeks later, he noted no side effects from any of the medications, he had no new symptoms, he was feeling well, and his cough had improved greatly. He did not have any signs of dissemination of his coccidioidal infection, and we concluded that the primary and only infection was located in the lungs.

**DISSEMINATED COCCIDIOIDOMYCOSIS**

**4** Which of the following extrapulmonary sites is *Coccidioides* least likely to infect?

- Brain
- Skin
- Meninges
- Lymph nodes
- Bones
- Joints

Extrapulmonary coccidioidomycosis can involve almost any site. However, the most common sites of dissemination are the skin, lymph nodes, bones, and joints.<sup>14</sup> The least likely site is the brain.

**TABLE 2**

**Conditions associated with severe pulmonary coccidioidomycosis**

**Patient factors**

- Age greater than 55 years
- Filipino or African descent
- Preexisting cardiopulmonary condition
- Diabetes mellitus
- Human immunodeficiency virus infection
- Recipient of organ transplant
- Therapy with high-dose steroids
- Therapy with tumor necrosis factor-alpha inhibitors

**Disease factors**

- Symptoms lasting more than 2 weeks
- Night sweats for more than 3 weeks
- More than 10% weight loss
- Inability to work
- Infiltrates involving more than half of one lung or portions of both lungs
- Prominent or persistent hilar adenopathy
- Anticoccidioidal complement-fixing antibody titer higher than 1:16

INFORMATION FROM GALGIANI JN, AMPEL NM, BLAIR JE, ET AL; INFECTIOUS DISEASES SOCIETY OF AMERICA. COCCIDIOIDOMYCOSIS. CLIN INFECT DIS 2005; 41:1217-1223.

**Central nervous system involvement**

In the central nervous system, involvement is typically with the meninges, rather than frank involvement of the brain parenchyma.<sup>18,28,29</sup> Although patients with HIV or those who are otherwise severely immunocompromised are at higher risk for coccidioidal meningitis, it is rare even in this population.<sup>30,31</sup> Meningitis most commonly presents as headache, vomiting, meningismus, confusion, or diplopia.<sup>32,33</sup>

If neurologic findings are absent, experts do not generally recommend lumbar puncture because the incidence of meningeal involvement is low. When cerebrospinal fluid is obtained in an active case of coccidioidal meningitis, fluid analysis typically finds elevated protein, low glucose, and lymphocytic pleocytosis.<sup>1,32</sup>

Meningeal enhancement on CT or magnetic resonance imaging is common.<sup>34</sup> The diagnosis is established by culture or serologic testing of cerebrospinal fluid (IgM titer, IgG titer, immunodiffusion, or complement fixation).<sup>14</sup>

Of note, cerebral infarction and hydrocephalus are feared complications and pose a serious risk of death in any patient.<sup>32,35</sup> In these cases, treatment with antifungals is life-long, regardless of immune system status.<sup>18</sup>

**The CD4 count dictates the time to start prophylaxis against *P jirovecii*, *T gondii*, and *M avium* complex**

### Skin involvement

Skin involvement is variable, consisting of nodules, verrucae, abscesses, or ulcerations.<sup>15,16</sup> Hemorrhage from the skin is relatively common.<sup>36</sup> From the skin, the infection can spread to the lymph nodes, leading to regional lymphadenopathy.<sup>14,15</sup> Nodes can ulcerate, drain, or even become necrotic.

### Bone and joint involvement

Once integrity of the blood vessels is disrupted, *Coccidioides* can spread via the blood to the bones or joints,<sup>14,15</sup> causing osteomyelitis, septic arthritis, or synovitis. Subcutaneous abscesses or sinus tracts may subsequently develop.<sup>14,15</sup>

### ■ HOW LONG MUST HE BE TREATED?

On follow-up, the patient asked how long he needed to continue his antifungal regimen and if any other testing for his coccidioidal infection was necessary, since he was feeling better.

**5** Which is the most appropriate response to the patient's question?

- He can discontinue his antifungal drugs; no further testing is necessary
- He needs 14 more days of antifungal therapy and periodic serologic tests
- He needs 2.5 more months of antifungal therapy and monthly blood cultures
- He needs lifelong antifungal therapy and periodic urinary antigen levels
- He needs 5.5 more months of antifungal therapy; bronchoscopy with bronchoalveolar lavage at 1 year

How long to treat and how to monitor for coccidioidomycosis vary by patient.

### Duration of therapy depends on symptoms and immune status

The severity of infection (TABLE 2) and the immune status are important factors that must be considered when tailoring a therapeutic regimen.

**Immunocompetent patients without symptoms** or with mild symptoms usually do not need therapy and are followed periodically for signs of improvement.<sup>14,18,29</sup>

**Immunocompetent patients with severe**

**symptoms** typically receive 3 to 6 months of antifungal therapy.<sup>18</sup>

**Immunocompromised patients** (especially HIV-infected patients with CD4 counts < 250 cells/ $\mu$ L) need antifungal treatment, regardless of the severity of infection.<sup>14,18,29</sup> In many cases, the type of infection will dictate the duration of therapy.

Diffuse pneumonia or extrapulmonary dissemination typically requires treatment for at least 1 year regardless of immune status.<sup>14,18</sup> For those with HIV and diffuse pneumonia, dissemination, or meningitis, guidelines dictate that secondary prophylaxis be started after at least 1 year of therapy and improvement in clinical status; it should be continued indefinitely to prevent reactivation of latent infection.<sup>18</sup>

The guidelines say that in patients with higher CD4 counts (presumably > 250 cells/ $\mu$ L) and nonmeningeal coccidioidomycosis, providers *may consider* discontinuing secondary prophylaxis, as long as there is clinical evidence of improvement and control of the primary infection.<sup>18</sup> However, many experts advocate continuing secondary prophylaxis regardless of the CD4 count, as the rates of relapse and dissemination are high.<sup>1,16,37</sup>

### Monitoring

Regardless of the therapy chosen, disease monitoring every 2 to 4 months with clinical history and examination, radiography, and coccidioidal-specific testing is recommended for at least 1 year, and perhaps longer, to ensure complete resolution and to monitor for signs of dissemination.<sup>14,18</sup>

Which test to use is not clear. Serologic testing identifies antibodies (IgM or IgG) to coccidioidal antigens. IgM appears during the acute infection, and tests include immunodiffusion, latex agglutination, and enzyme-linked immunoassays. The last two are highly sensitive but have a significant false-positive rate, and should be confirmed with the former if found to be positive.<sup>17,18</sup> IgG appears weeks after the acute infection and can be evaluated with immunodiffusion or enzyme-linked immunoassay as well.

Keep in mind that these tests provide only qualitative results on the presence of these antibodies, not quantitative information. Fur-

How long to treat and how to monitor for coccidioidomycosis vary by patient



thermore, enzyme-linked immunoassay is not as accurate as immunodiffusion, which has a sensitivity in immunocompromised patients of only approximately 50%.<sup>38,39</sup>

For that reason, complement fixation titers are extremely helpful because they reflect the severity of infection, can be used to monitor the response to treatment, and can even provide insight into the prognosis.<sup>18</sup> The sensitivity of this test in immunocompromised hosts is 60% to 70%.<sup>38</sup> Titers can be checked to confirm the diagnosis and can be periodically monitored throughout the treatment course to ensure efficacy of therapy and to watch for reactivation of the infection.<sup>1</sup> In fact, an initial complement fixation titer of 1:2 or 1:4 is associated with favorable outcomes, while a titer greater than 1:16 portends dissemination.<sup>18</sup>

The caveat to any serologic test (immunodiffusion, enzyme-linked immunoassay, and complement fixation) is that severely immunocompromised patients (as in our case) may not mount an immune response and may have falsely low titers even in the face of a severe infection, and therefore these tests may not be reliable.<sup>38</sup> In these situations, urinary coccidioidal antigen detection assay (sensitivity 71%) or nucleic acid amplification of coccidioidal DNA (sensitivity 75%) may be of more help.<sup>40,41</sup>

Therefore, in the setting of HIV infection, an asymptomatic pulmonary cavity, and diffuse pulmonary involvement secondary to coccidioidal infection, lifelong antibiotics (treatment plus secondary prophylaxis) with periodic testing of urinary coccidioidal antigen levels is the best response to the patient's question, given that his complement fixation titers were initially negative and antigen levels were positive.

### ■ CASE CONCLUDED

The patient continues to be followed for his HIV infection. He is undergoing serologic and urinary antigen testing for *Coccidioides* infection every 3 months in addition to his maintenance HIV testing. He is on chronic suppressive therapy with fluconazole. He has not had a recurrence of his *Coccidioides* infection, nor have there been any signs of dissemination.

### ■ CAVITARY LUNG LESIONS IN HIV PATIENTS

In patients with HIV, cavitory lung lesions on chest radiography can be due to a wide variety of etiologies that range from infection to malignancy. Historical clues, including environmental exposure, occupation, geographic residence, sick contacts, travel, or animal contact can be helpful in ordering subsequent confirmatory testing, especially in the case of infection.

Tuberculosis should be suspected, and appropriate isolation precautions should be taken until it is ruled out.

Laboratory testing, including the complete blood cell count with differential and CD4 count, provide ancillary data to narrow the differential diagnosis. For example, if the CD4 count is greater than 200 cells/ $\mu$ L, mycobacterial infection should be strongly suspected; however, lower CD4 counts should also prompt a search for opportunistic infections. In the appropriate clinical scenario, malignancies including Kaposi sarcoma, non-Hodgkin lymphoma, and bronchogenic carcinoma can be seen and should also be considered.

Nevertheless, the evaluation hinges on the sputum examination and CT scan of the chest to further characterize the cavity, surrounding lung parenchyma, lymph nodes, and potential fluid collections. Usually, further serologic tests and even bronchoscopy with bronchoalveolar lavage and transbronchial biopsy are required. Treatment should begin once the most likely diagnosis is established.

Coccidioidal pneumonia should be considered in all patients with immunodeficiency, including HIV patients, transplant recipients, those undergoing chemotherapy, and those with intrinsic immune system defects, especially if they have a history of exposure or if they are from an endemic region. Antifungal therapy should be initiated early, and dissemination must be ruled out. Suppressive therapy is mandatory for those with a severely compromised immune system, and serologic testing to ensure remission of the infection is needed. Patients who were previously exposed to *Coccidioides* or who vacationed or live in the southwestern United States (where it is prevalent) are at risk and may present with any number of symptoms. ■

**Our patient has not had any recurrence of his *Coccidioides* infection or signs of dissemination**

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ADDRESS: Robert Myers, MD, Department of Internal Medicine, Maricopa Medical Center, 2601 East Roosevelt Street, Phoenix, AZ 85008; e-mail myersmmc@cox.net.