TABLE 243-2 SUGGESTED ORAL TREATMENT FOR EXTENSIVE TINEA INFECTIONS AND ONYCHOMYCOSIS

Antifungal Agent	Suggested Dosage	Comments
Extensive Tinea Skin Infection		
Terbinafine	250 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period
Itraconazole[a]	200 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period except for drug interactions
Onychomycosis		
Terbinafine	250 mg/d for 3 months	Slightly superior to itraconazole; monitor for hepatotoxicity
Itraconazole[a]	200 mg/d for 3 months *or* 200 mg bid for 1 week each month for 3 months	Drug interactions frequent; monitor for hepatotoxicity; rarely causes hypokalemia, hypertension, edema; use with caution in patients with congestive heart failure

[a]Itraconazole capsules require food and gastric acid for absorption, whereas itraconazole solution is taken on an empty stomach.

area should be kept as dry as possible. When patients have extensive skin lesions, oral itraconazole or terbinafine can hasten resolution (Table 243-2). Terbinafine interacts with fewer drugs than itraconazole and is generally the first-line agent. Onychomycosis does not respond to topical therapy, although ciclopirox nail lacquer applied daily for a year is occasionally beneficial. Itraconazole and terbinafine both accumulate in the nail plate and can be used to treat onychomycosis (Table 243-2). These agents are more effective and better tolerated than griseofulvin and ketoconazole. The major decision to be made with regard to therapy is whether the extent of nail involvement justifies the use of systemic antifungal agents that have adverse effects, may interact with other drugs, and are costly. Treating for cosmetic reasons alone is discouraged. Relapses of tinea cruris and tinea pedis are common and should be treated early with topical creams to avoid development of more extensive disease. Relapses of onychomycosis follow treatment in 25–30% of cases.

244 *Pneumocystis* Infections

Henry Masur, Alison Morris

DEFINITION AND DESCRIPTION

Pneumocystis is an opportunistic pathogen that is an important cause of pneumonia in immunocompromised hosts, particularly those with HIV infection (Chap. 226), and in individuals with organ transplants, those with hematologic malignancies, and those receiving immunosuppressive therapy. The organism was discovered in rodents in 1906 and was initially believed to be a protozoan. Because *Pneumocystis* cannot be cultured, our understanding of its biology has been limited, but molecular techniques have demonstrated that the organism is actually a fungus. Formerly known as *Pneumocystis carinii*, the species infecting humans has been renamed *Pneumocystis jirovecii*.

EPIDEMIOLOGY

P. jirovecii pneumonia (PCP) came to medical attention when cases were reported in malnourished orphans in Europe during World War II. The disease was later recognized in other immunosuppressed populations but was rare in the era before HIV/AIDS and before intensive immunosuppressive therapy for organ transplantation and autoimmune disorders. In 1981, PCP was first reported in men who had sex with men and in IV drug users who had no obvious cause of immunosuppression. These cases were subsequently recognized as the first cases of what came to be known as the acquired immunodeficiency syndrome (AIDS) (Chap. 226). The incidence of PCP increased dramatically as the AIDS epidemic grew: without chemoprophylaxis or antiretroviral therapy (ART), 80–90% of patients with HIV/AIDS in North America and Western Europe ultimately develop one or more episodes of PCP. While its incidence declined with the introduction of anti-*Pneumocystis* prophylaxis and combination ART, PCP has continued to be a leading cause of AIDS-associated morbidity in the United States and Western Europe, particularly in individuals who do not know they are infected with HIV until they are profoundly immunosuppressed and in HIV-infected patients who are not receiving ART or PCP prophylaxis.

PCP also develops in HIV-uninfected patients who are immunocompromised secondary to hematologic or malignant neoplasms, stem cell or solid organ transplantation, and immunosuppressive medications. The incidence of PCP depends on the degree of immunosuppression. PCP is increasingly reported among individuals receiving tumor necrosis factor α inhibitors and antilymphocyte monoclonal antibodies for rheumatologic or other diseases. While clinical PCP in immunocompetent hosts has not been clearly documented, studies have shown that *Pneumocystis* organisms can colonize the airways of children and adults who are not overtly immunocompromised. The relevance of these organisms to acute or chronic syndromes, such as chronic obstructive pulmonary disease (COPD), in immunocompetent patients is being investigated.

In some developing countries, the incidence of PCP among HIV-infected individuals has been found to be lower than that in industrialized countries. This lower incidence may be due to competing mortality from infectious diseases such as tuberculosis and bacterial pneumonia, which typically occur before patients become immunosuppressed enough to develop PCP. Geographic variations in *Pneumocystis* exposure and underdiagnosis also may explain the apparent lower frequency of PCP in some countries.

PATHOGENESIS AND PATHOLOGY

Life Cycle and Transmission The life cycle of *Pneumocystis* involves both sexual and asexual reproduction, and the organism exists as a trophic form, a cyst, and a precyst at various points. Serologic and molecular studies have demonstrated that most humans are exposed to *Pneumocystis* early in life. It was historically thought that *Pneumocystis* developed from reactivation of latent infection, but *de novo* infections from environmental sources and person-to-person transmission occur as well. Outbreaks of PCP suggest that nosocomial transmission can take place, and studies with rodents show that immunocompetent animals can serve as reservoirs for transmission of *P. carinii* (the infecting species in rodents) to immunocompetent and immunosuppressed animals. However, *Pneumocystis* organisms are species specific, and thus humans are infected only by other humans who transmit *P. jirovecii*; humans cannot be infected with animal species of *Pneumocystis* such as *P. murina* (mice) or *P. oryctolagi* (rabbits). The utility of respiratory isolation in preventing transmission from patients with PCP to other immunosuppressed individuals has been debated; no clear evidence exists, although it seems prudent to isolate patients with active PCP from other immunosuppressed patients.

Role of Immunity Defects in cellular and/or humoral immunity predispose to development of PCP. CD4+ T cells are critical in host defense against *Pneumocystis*. For HIV-infected patients, the incidence is inversely related to the CD4+ T cell count: at least 80% of cases occur at counts of <200 cells/μL, and most of these cases develop at counts of <100 cells/μL. CD4+ T cell counts are less specific and thus less useful in predicting the risk of PCP in HIV-uninfected, immunosuppressed patients.

Lung Pathology *Pneumocystis* has a unique tropism for the lung. It is presumably inhaled into the alveolar space. Clinically apparent pneumonia occurs only if an individual is immunocompromised. *Pneumocystis* proliferates in the lung, provoking a mononuclear cell