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AIDS Related Opportunistic Infections, Going but not Gone

Rafik Samuel, Robert L. Bettiker, and Byungse Suh

Section of Infectious Diseases, Temple University Hospital, Philadelphia, Pennsylvania, USA

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It is now more than two decades since the AIDS epidemic began with a cluster of *Pneumocystis carinii* pneumonia (PCP) in a community of homosexual men. Since then, many other infections have been characterized as opportunistic infections secondary to HIV infection. These include, but are not limited to, infections with *Toxoplasma gondii*, *Cytomegalovirus* (CMV), *Mycobacterium avium* complex (MAC), and *Cryptococcus neoformans*. Over the last two decades, there have been dramatic improvements in diagnosis, prevention and treatment of all these infections. As a result, in North America and Western Europe, the rates of opportunistic infections secondary to AIDS have decreased substantially. We will review these common opportunistic infections below.

Key words: *Pneumocystis carinii* Pneumonia, *Toxoplasma gondii*, *Mycobacterium avium intracellulare* complex, Cytomegalovirus, *Cryptococcus neoformans*, AIDS

INTRODUCTION

Twenty years ago the acquired immune deficiency syndrome (AIDS) was introduced to the world with the initial reports of *Pneumocystis carinii* pneumonia in men who have sex with men (MSM). Many previously rare infections of humans are encountered at much higher rates in people with human immunodeficiency virus (HIV), spurring significant research into the diagnosis, prevention and treatment of these infections. We will discuss some of the more common opportunistic infection presentations in HIV infected individuals due to *Pneumocystis carinii, Toxoplasma gondii, Mycobacterium avium-intracellulare complex, Cryptococcus neoformans* and Cytomegalovirus.

Pneumocystis carinii Pneumonia (PCP)

PCP was first reported in the United States in 1955 (Lunseth *et al.*, 1955). Initially this disease occurred sporadically in people who had received immunosuppressive therapy such as steroids, or who had hematologic malignancies (Hughes, 1977). The sudden appearance of PCP in clusters of MSM in New York City, Los Angeles and San Francisco (Gottlieb *et al.*, 1981; Masur *et al.*, 1981; Follansbee *et al.*, 1982) soon led to the discovery of AIDS and HIV.

The organism, *P. carinii,* has been difficult to classify. It originally was believed to be a protozoan because it existed in cysts and has sporozoite and trophozoite forms. Recently, however, it has been classified as a fungus based upon its ribosomal and mitochondrial DNA. Interestingly, it does not respond to antifungal drugs, nor does it grow on fungal media (Tietjen, 2000).

P. carinii is acquired by aerosols and is likely transmitted from person to person. Seventy-five percent of children are thought to be infected by the age of four (Pifer *et al.*, 1978). Most infections occurring in AIDS patients are likely reactivation of latent disease, but outbreaks have occurred (Helweg-Larsen *et al.*, 1998). PCP rarely occurs until the CD4 count is below 200 cells/mm^3 (Stansell *et al.*, 1997). Ninety-five percent of PCP cases occurred in patients with CD4 < 200. (Stansell *et al.*, 1997). The annual incidence of PCP in patients with CD4 counts between 200 and 350 is 0.5% (Phair *et al.*, 1990), but rises to 8% over a 6 month period in those with CD4 counts below 200 (Stansell *et al.*, 1997).

PCP is generally gradual in onset compared to bacterial pneumonia and is characterized by fever (79-100%), cough (95%), and progressive dyspnea (95%) (Kales *et al.*, 1987; Stansell *et al.*, 1997). The cough is usually non productive. Other symptoms include fatigue, chills, chest pain, and weight loss. The most common findings on physical examination include fever (84%) and tachypnea

Correspondence to : Rafik Samuel, MD Section of Infectious Diseases Temple University Hospital 3401 N Broad Street, Philadelphia, PA 19140, USA
E-mail rafiksamuel@hotmail.com

Table I. Therapies for *Pneumocystis carinii* pneumonia

AGENTS AND DOSAGES
Trimethoprim/sulfamethoxazole (15-20 mg of trimethoprim/kg/day)
Intravenous pentamadine (3-4 mg/kg/day)
Atovaquone (1500 mg/day)
Dapsone (100 mg/day) + trimethoprim 300 mg daily
Clindamycin 300 mg tid + primaquine 30 mg daily

Table II. Agents for prophylaxis of *Pneumocystis carinii* pneumonia

Trimethoprim/sulfamethoxazole DS or SS once daily
Dapsone 100 mg daily
Aerosolized Pentamadine 300 mg once monthly
Atovaquone 750 mg twice daily
Trimethoprim/sulfamethoxazok DS three times weekly

Table III. Indications for prophylaxis of *Pneumocystis carinii* pneumonia

CD4 < 200 or CD4% < 14
History of PCP
Oropharyngeal candidiasis
Unexplained fever for 2 weeks

(62%) (Kales *et al.*, 1987).

The most common radiographic abnormalities are diffuse, bilateral interstitial or alveolar infiltrates on chest x-ray (De Lorenzo *et al.*, 1987). Other less common radiographic presentations include pneumothoraces, lobar infiltrates, cysts, nodules or effusions (Kales *et al.*, 1987; De Lorenzo *et al.*, 1987; Sepkowitz, 1991). Initially, x-rays may appear normal in symptomatic patients. More recently, high resolution computed tomography has been shown to have a sensitivity of 100% and specificity of 89% when patchy or nodular ground-glass attenuation was used to indicate PCP (Gruden *et al.*, 1997).

Abnormal laboratory values associated with PCP include an elevated LDH and an increased alveolar-arterial oxygen gradient. LDH is elevated in 90% of patients with PCP (Zaman and White, 1988; Stover and Meduri, 1988). PCP also causes an increased alveolar-arterial oxygen gradient which is directly related to severity of the infection.

Although radiographic and laboratory tests can be highly suggestive of PCP, definitive diagnosis can only be made by visualizing the organism in respiratory samples. Sputum or bronchoalveolar lavage fluids have a sensitivity of 55% (Zaman *et al.*, 1988) and 97-100% (Bustamante and Levy, 1994), respectively, when viewed with Giemsa or silver stains. Immunoflourescent staining of sputum and polymerase chain reaction techniques are under investigation (Torres *et al.*, 2000).

Whenever possible, definitive diagnosis of PCP should be made prior to treatment to avoid the toxicities of the drugs used. There are many drug regimens that can be used for the treatment of this pathogen. Trimethoprim-sulfamethoxazole; dapsone and trimethoprim; clindamycin and primaquine; atovaquone; and intravenous pentamadine have all been used in the treatment of PCP (Table I). Multiple studies have shown equivalence of these agents in the treatment of mild to moderate *P. carinii* pneumonia, most often defined as arterial partial oxygen pressure >50 torr or alveolar-arterial oxygen gradients <45 mmHg (Hughes *et al.*, 1993; Safrin *et al.*, 1996; Toma *et al.*, 1998; Dohn *et al.*, 1994). For severe PCP, however, most clinicians would initially use only trimethoprim-sulfamethoxazole (Bozette *et al.*, 1995; Toma *et al.*, 1993; Dohn *et al.*, 1994). Overall, treatment success ranges between 70-85% in all the study groups. The duration of therapy, regardless of the agent or agents used, should be twenty-one days (Bozette *et al.*, 1995; Toma *et al.*, 1993; Dohn *et al.*, 1994; Hughes *et al.*, 1993; Safrin *et al.*, 1996; Toma *et al.*, 1998).

In addition, for moderately severe to severe PCP, multiple studies have shown that the addition of steroids decrease mortality, the need for mechanical ventilation, the length of hospital stay and morbidity (Gagnon *et al.*, 1990; Montaner *et al.*, 1990). In one study, survival was improved dramatically with the addition of steroids to antimicrobial therapy (Gagnon *et al.*, 1990). Steroids are now recommended for any individual with PCP who has an arterial partial oxygen pressure <70 torr or alveolar-arterial gradients >35 mmHg (NIH University of California Panel for corticosteroids as adjunctive therapy for pneumocystis pneumonia, 1990). The dose of steroids should be equivalent to prednisone forty milligrams twice daily for five days followed by forty milligrams once daily for days six to ten, then twenty milligrams daily until day twenty-one (NIH University of California Panel for corticosteroids as adjunctive therapy for pneumocystis pneumonia, 1990)

Prevention may be just as important as treatment, and multiple regimens exist to prevent this opportunistic infection (Table II). There are also multiple indications for prophylaxis of PCP (Table III) (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001). More recently it has been shown to be safe to discontinue prophylaxis if a patient has been on antiretroviral therapy and the CD4 count has climbed to greater than 200 cells/mm^3 for three months (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001).

With the implementation of prophylaxis and the introduction of highly active antiretroviral therapy, the incidence and mortality of PCP have decreased significantly. In one report, the incidence decreased from 2.35/1000 to 0.22/

1000 person days (Ledergerber *et al.*, 1999). In another study, overall mortality secondary to PCP decreased from 28.6% to 3.8% of all AIDS related deaths (Kravcik *et al.*, 1997). These reports support the current recommendations for and the importance of prophylaxis, treatment, and prevention of PCP.

Toxoplasma gondii Encephalitis

Toxoplasma gondii encephalitis was first reported in 1941 in children (Sabin, 1941). Additionally, it was reported in individuals with malignancy and those receiving immunosuppressive medications (Montoya and Remington, 2000). As with PCP, the incidence of central nervous system toxoplasmosis sharply increased in the early 1980s among MSM (Anderson *et al.*, 1983; CDC, 1982; Vilaseca, 1982; Hauser *et al.*, 1982) and yet another previously rare disease became more commonplace with the onset of the AIDS epidemic.

T. gondii is a protozoan that completes its life cycle in felines. Humans acquire *T. gondii* by ingesting infected oocysts from the environment, by ingesting tissue cysts from infected animals, by inhaling cysts from feline excrement or by blood transfusion/ transplantation of infected human tissues. The majority of transmission is through ingestion of undercooked meat (Montoya and Remington, 2000). Once the *T. gondii* oocysts are ingested or inhaled, they invade the intestinal or pulmonary epithelium and disseminate through the body and encyst in many different tissues, including muscle, brain, and heart, where they usually remain dormant for life.

Prevalence of this latent infection in adults varies from ten percent up to as high as eighty five percent in France (Montoya and Remington, 2000). In patients with HIV, clinical reactivation can occur in the central nervous system (CNS) when CD4 counts fall below 100 cells/mm^3. Toxoplasmosis has become the most common CNS opportunistic infection in AIDS patients. Patients with AIDS and a CD4 < 100 that have IgG against *T. gondii* have a thirty percent chance of developing CNS toxoplasmosis during their lifetime if not receiving prophylaxis (Porter and Sande, 1992).

T. gondii can reactivate in multiple sites including the CNS, lungs, retina, gastrointestinal tract, liver, musculoskeletal system, heart, testes, bladder and bone marrow (Rabaud *et al.*, 1994). The most common site of reactivation, however, is the CNS, where reactivation usually takes the form of cerebral abscesses. Symptoms include headache (55%), confusion (52%), and fever (47%) (Porter and Sande, 1992). Focal neurologic deficits and seizures can occur, as well as nausea and vomiting from increased intracranial pressure.

Diagnosis of *T. gondii* infection is usually presumptive. Antibodies to *T. gondii* are unreliable. The best imaging study is gadolinium enhanced magnetic resonance imaging (MRI). The most common finding is multiple, ring enhancing brain lesions with a predilection for the basal ganglia (Levi RM *et al.*, 1990). Unfortunately, many different entities can cause these findings on MRI, including lymphoma, cryptococcoma, aspergilloma, tuberculoma, or nocardia. Other imaging available for the diagnosis of toxoplasmosis includes thallium single photon emission computed tomography (SPECT) (Lorberboym *et al.*, 1998), which may be useful in distinguishing infection from lymphoma. CSF is usually normal in patients with CNS toxoplasmosis, but may show a mild pleocytosis.

The definitive diagnostic test for CNS toxoplasmosis is brain biopsy, but the significant risk of morbidity and mortality associated with this procedure (12%) limits its use (Antinori *et al.*, 1997). The diagnosis is therefore often made presumptively. Empiric treatment should be considered in a symptomatic patient with a typical radiographic appearance on MRI and a low CD4 count, especially if they have not been on prophylactic medications.

Treatment includes pyrimethamine, folinic acid and one of the following: sulfadiazine, clindamycin, azithromycin, or atovaquone for six weeks (Luft *et al.*, 1993; Dannemann *et al.*, 1992; Katlama *et al.*, 1996; Jacobson *et al.*, 2001; Torres *et al.*, 1997), (Table IV), after which suppressive therapy is continued (Table V). Patients without a clinical response within 2-3 weeks should have a repeat MRI. If there is no radiographic improvement, a brain biopsy is warranted.

Prophylaxis of *T. gondii* infection is effective and should be used. Primary prophylaxis should be given to any

Table IV. Therapies for *Toxoplasma gondii* encephalitis

Pyrimethamine 200 mg loading dose followed by 75 mg daily+folinic acid 10-25 mg daily +
Sulfadiazine 1.5-2 g four times daily or
Clindamycin 450 mg four times daily or
Azithromycin 1200 mg daily or
Atovaquone 750 mg four times daily

Table V. Suppressive therapy for *Toxoplasma gondii* encephalitis

Pyrimethamine 25 mg daily+folinic acid 10 mg daily+sulfadiazine 500 mg four times daily **OR**
Pyrimethamine 25 mg daily+folinic acid 10 mg daily+clindamycin 450 mg three times daily

Table VI. Agents for prophylaxis for *Toxoplasma gondii* encephalitis

Trimethoprim/sulfamethoxazole double strength daily or
Trimethoprim/sulfamethoxazole single strength daily or
Atovaquone 750 mg twice daily or
Pyrimethamine 75 mg weekly + dapsone 50 mg daily + folinic acid 25 mg weekly

individual with a CD4 < 100 cells/mm^3 and a positive IgG against *T. gondii*. (Table VI) (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001; Carr *et al.*, 1992; Ribera *et al.*, 1999; Girard *et al.*, 1993). The agent of choice for prophylaxis is trimethoprim-sulfamethoxazole, which happens to be the same agent used for the prevention of PCP. Similar to PCP prophylaxis, both primary and secondary prophylaxis can be stopped when the CD4 count rises above 200 for three months (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001; Furrer *et al.*, 2000).

Results from the multicenter AIDS cohort study show the incidence of CNS toxoplasmosis has declined from 5.4/1000 person years in 1990 to 2.2/1000 person years in 1998 (Sacktor *et al.*, 2001). Mortality from cerebral toxoplasmosis has decreased as well during the mid-1990s, down from 7.1% to 5.7% (Kravcik *et al.*, 1997). These decreases in incidence and mortality demonstrate effectiveness of prevention and treatment of yet another serious opportunistic infection of AIDS.

Cytomegalovirus (CMV)

As reports of other unusual infections were surfacing in 1981 in MSM, CMV infections also increased. Unlike CMV infections that were noted previously in transplant recipients and those on steroids, the majority of CMV infections in AIDS were retinal infections. Unfortunately, these infections caused blindness and debilitated many individuals with AIDS.

CMV is a virus in the herpesviridae family. Humans are the only reservoir for CMV, and transmission occurs by direct contact with saliva, urine, genital secretions, feces or blood (Jacobson, 1999). Following primary infection, persistent infection occurs and CMV can be shed intermittently. Fifty percent of children at age 6 will have CMV antibodies and up to 75-100% of adults have antibodies positive for CMV (Gold and Nankervis, 1982; Collier *et al.*, 1987). In patients with latent infection, recurrent infection is possible secondary to reactivation.

CMV infection in AIDS patients tends to occur when CD4 counts decline to less than 50 cells/mm^3. End organ damage occurs in 21-44% of patients with AIDS (Gallant *et al.*, 1992). When CMV disease occurs, 85% develop retinitis, 10% develop gastrointestinal disease and the remainder develop neurologic or pulmonary manifestations (Gallant *et al.*, 1992).

The most common manifestation of ocular CMV is inflammation involving all layers of the retina, resulting in necrosis and edema. Once damaged, the retina does not recover and, if left untreated, blindness can occur. Retinitis clinically presents as painless blurring, loss of central vision, floaters or flashing lights. Ophthalmologic evaluation reveals a retina with fluffy white lesions that may bleed (Holland *et al.*, 1996; Freeman *et al.*, 1993).

Gastrointestinal CMV disease most commonly involves the esophagus and/or the colon. Patients usually present with localizing symptoms such as odynophagia and substernal pain or bloody, watery diarrhea associated with abdominal pain. On endoscopy, erythema, erosions or ulcerations are observed (Goodgame, 1993).

Neurologic disease can present as encephalitis or polyradiculopathy. Patients with encephalitis have lethargy, confusion and fever. MRI typically shows periventricular enhancement in the brain. Cerebrospinal fluid analysis will have CMV DNA present along with normal values for cell counts, glucose and protein. If left untreated, patients may become obtunded and die within weeks of onset of symptoms (McCutchan, 1995; Fox *et al.*, 1995). CMV polyradiculopathy can present as progressive lower limb weakness and areflexia. Cerebrospinal fluid examination reveals a neutrophilic pleocytosis and the presence of CMV DNA. Without therapy, flaccid paralysis may develop (McCutchan, 1995; Fox *et al.*, 1995).

Diagnosis of CMV end organ disease can be quite difficult. CMV IgG, CMV cultures, CMV PCR, and CMV antigen detection can have low predictive value of disease because many persons are latently infected with this virus. Up to one third of patients who have CMV retinitis have negative blood tests for CMV. On the other hand, many patients who have a positive culture for CMV do not have end organ disease (Studies of ocular complications of AIDS in collaboration with the AIDS clinical trial group, 1997).

Since these culture and isolation techniques are not predictive of disease, diagnosis of end organ disease is recommended as follows. For retinitis, diagnosis is made clinically by an ophthalmologist after ophthalmoscopic examination and visualization of the characteristic changes of CMV disease. CMV gastrointestinal disease is diagnosed by clinical symptoms, direct visualization of the mucosa and mucosal biopsy that demonstrates CMV inclusions (Beaugerie *et al.*, 1997). CMV encephalitis or polyradiculopathy can be diagnosed by both clinical presentation and the presence of CMV DNA by PCR in the CSF (Arribase *et al.*, 1995). CMV pneumonitis may be diagnosed by clinical symptoms, CMV positive sputum cultures and demonstration of CMV inclusion bodies on

Table VII. Treatment of Cytomegalovirus retinitis

Agent	Induction Dose (14 days)	Maintenance Dose
Ganciclovir	5 mg / kg / q 12 hours	5 mg / kg / day
Ganciclovir implants	Lasts 6-8 months	Replace as needed
Valganciclovir	900 mg / q 12 hours	900 mg / day
Foscarnet	90 mg / kg / 12 hours	90 mg / kg / day
Cidofovir	5 mg / kg / week	5 mg / kg / 2 weeks

Table VIII. Agents for CMV disease and their toxicities

Agent	Major Toxicity	Required Monitoring
Ganciclovir	Neutropenia and thrombocytopenia	Complete blood count and serum creatinine
Ganciclovir implants	Retinal detachment, infection	None
Valganciclovir	Neutropenia and thrombocytopenia	Complete blood count and serum creatinine
Foscarnet	Nephrotoxicity, neurotoxicity, genital ulcerations, cation chelation	Complete blood count, serum creatinine, serum cations
Cidofovir	Nephrotoxicity, neutropenia, uveitis, hypotony	Serum creatinine, urinalysis, intraocular pressure measurements

cytology or pathology (Uberi-Foppa *et al.*, 1988). Growing CMV from bronchoscopy specimens is not adequate for diagnosis.

Treatment of CMV end organ disease should be initiated promptly, especially if the CNS or retina is involved. Available therapy includes systemic ganciclovir, ganciclovir ocular implants, valganciclovir, foscarnet and cidofovir (Table VII). Ganciclovir is the first line agent for all CMV disease because of its relatively low toxicity profile. The ganciclovir implants are helpful for retinitis, but they do not address systemic disease or the contralateral eye (Jacobson, 1999). Recently, valganciclovir, a valine ester of ganciclovir that enhances oral absorption, has been approved. Valganciclovir affords a sixty percent bioavailability of ganciclovir compared to less than ten percent for the original oral formulation of ganciclovir. Valganciclovir has been approved only for retinitis secondary to CMV (PDR, 2002). Studies are ongoing for other forms of CMV infection. Please see table VIII for medications and their toxicities.

Unfortunately, the success rate of CMV therapy is not very high. Efficacy for retinitis is measured by progression of retinitis. If untreated, progression occurs in 14-22 days, while therapy with either ganciclovir or foscarnet delays progression to 226 days (Whitley *et al.*, 1998; Studies of Ocular Complications of AIDS Research, 1996). In another study, the efficacy of intraocular implants is better than intravenous ganciclovir: 221 days to progression vs 71 days with intravenous ganciclovir (Musch *et al.*, 1997). Both cidofovir and valganciclovir have been shown to be effective, however, no randomized study comparing them to other agents is available (Lalezari *et al.*, 1997; Studies of Ocular Complications of AIDS Research, 1997; PDR, 2002).

Both ganciclovir and foscarnet have equal efficacy in treatment of gastrointestinal disease (70-80%). Induction therapy with foscarnet or ganciclovir lasts 3-6 weeks, but total duration of maintenance therapy is controversial (Dietrich *et al.*, 1993; Blanshard *et al.*, 1995). There are no randomized trials of treatment for other CMV end organ diseases, although case reports examining ganciclovir and foscarnet show promise for pulmonary and neurological disease. (Arribas *et al.*, 1996; So and Olney, 1994)

In patients with retinitis, maintenance therapy may be stopped after recovery of the immune system. If CD4 counts increase above 100 for 6 months, and retinal examination by an ophthalmologist demonstrates no active disease, therapy may be discontinued (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001).

The poor efficacy of current treatments has led to attempts to prevent CMV disease. In one study, oral ganciclovir decreased the incidence of retinitis, but did not decrease other organ disease (Spector *et al.*, 1996). Unfortunately, the toxicity of ganciclovir and the lack of efficacy in preventing other CMV disease has led to no recommendations for prophylaxis of CMV disease (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001).

One serious feature of CMV disease is the exacerbation of symptoms after the initiation of antiretroviral therapy. This immune reconstitution syndrome seen in patients with retinitis can be vision threatening (Whitcup, 2000). These patients develop substantial intraocular inflammation that results in visual impairment. Anterior uveitis, cataract, vitritis, cystoid macular edema and disc edema may occur if anti-CMV medication is stopped in the presence of antiretroviral therapy or if immune recovery occurs in the presence of CMV infection without anti-CMV medication (Whitcup, 2000).

Decreases in CMV disease have been appreciated since the introduction of antiretroviral therapy. The rates have decreased from 2.24 events per 100 person years to 0.65 events per 100 person years since the introduction of antiretroviral therapy (Ledergerber *et al.*, 1999). These numbers are not as impressive as those for PCP, but nonetheless are an improvement in the lives of persons with AIDS.

Mycobacterium avium complex

The *Mycobacterium avium* complex (MAC), consisting primarily of *M. avium* and *M. intracellulare*, was first described in 1907 by Koch and Rabinowitsch (Havlir and Ellner, 2000). Prior to the 1980's, MAC infections were mostly limited to indolent pneumonitis complicating an underlying severe pulmonary disease. With the onset of

the AIDS epidemic, the incidence of MAC infections exploded (Zakowski *et. al.*, 1982), with as many as 43% of patients becoming infected at some point in the course of their HIV disease (Benson, 1997).

MAC is a ubiquitous mycobacterium, and has been found in soil, natural and municipal water supplies, food, house dust, and as a colonizer and infectious agent in domestic and wild animals. An estimated 7-12% of adults in the United States are believed to have been exposed to *M. avium* (von Reyn *et. al.*, 1993). Infection occurs via inhalation of aerosolized MAC or via oral ingestion. Person-to-person transmission is thought not to occur (Horsburgh *et. al.*, 1994; Arbeit *et al.* 1994).

Prior to highly active antiretroviral therapy and MAC prophylaxis, various authors found a prevalence of MAC disease between 20-40% of AIDS patients with a CD4 count below 100 cells/mm^3 (Havlik *et. al.*, 1992; Nightingale *et. al.*, 1992; Chaisson *et. al.*, 1992), making it the most common cause of bacteremia in AIDS patients (Benson, 1994). MAC infections rarely occur with a CD4 count of greater than 100 cells/mm^3 (Horsburgh, 1997), and in a series of 15 patients with disseminated MAC, 13 of them had CD4 cells less than 50 (Havlik, 1992).

Symptoms of disseminated MAC infection are usually non-specific. Ninety percent of patients have fever, nearly eighty percent have night sweats, and half have diarrhea. Less common symptoms include abdominal pain in one third of patients, and nausea and vomiting in approximately one fourth. Physical findings include weight loss and intraabdominal lymphadenopathy in nearly forty percent, and hepatosplenomegaly in one quarter of patients. Anemia with a hematocrit less than 25% is found in eighty-five percent of patients, and an elevated alkaline phosphatase occurs in a little over half of them (Havlik, 1992; Benson, 1994).

Multiple atypical presentations have been described, including erosive mediastinal lymphadenitis (Peacock *et. al.*, 2000), endobronchial lesions mimicking malignancy (Rigsby, 1994), cervical lymphadenitis (Horsburgh, 1997), and osteomyelitis (Currier, 2000).

Diagnosis is usually made by a positive culture from a normally sterile site, with blood, bone marrow, lymph nodes or liver being some of the more common sites (Kilby, 1998; Grinsztejn, 1997). Although death rarely is attributable to the MAC infection, the severe weight loss that often occurs may contribute further to the weakening of the immune system (Horsburgh, 1991). Without treatment, and prior to antiretroviral therapy, the median survival of an AIDS patient with disseminated MAC was four months, whereas a comparable patient without mycobacteremia had a median survival of nearly one year.

A prospective cohort study of 367 AIDS patients with a CD4 count < 50 cells/mm^3 from 1990 to 1992 showed that MAC bacteremia was an independent risk factor for death (relative hazard [RH]=1.8), and that antimycobacterial treatment could prolong life (263 vs. 139 days, $p < 0.001$) (Chin, 1994).

Table IX. Treatment Recommendations for *Mycobacterium avium* complex

Recommended	Clarithromycin 500 mg q 12 hours and ethambutol 15 mg/kg/day
Alternative	Clarithromycin 500 mg q12 hours and one of the following: rifabutin 300 mg daily, ciprofloxacin 500-750 mg daily, or amikacin 15 mg/kg/day

Table X. Agents for prophylaxis of *Mycobacterium avium* Complex

Azithromycin 1200 mg once weekly
Clarithromycin 500 mg twice daily
Rifabutin 300 mg once daily

Current treatment guidelines recommend clarithromycin 500 mg bid and at least one of the following: ethambutol 15 mg/kg/day (preferred), rifabutin 300 mg/day, ciprofloxacin 500-750 mg/day, or amikacin 15 mg/kg/day (Table IX). Clofazimine has not been found to be efficacious, and some studies suggest that it may be harmful (Koletar, 1997). Symptomatic improvement should occur within two weeks of initiation of therapy (Kemper, 1992). Treatment duration is a minimum of one year, but may need to be continued indefinitely.

One study in the early nineties found that nearly one quarter of patients diagnosed with MAC bacteremia died within one month, suggesting that prophylaxis against this infection is needed (Chin *et. al.*, 1994). Current guidelines for MAC prophylaxis include clarithromycin 500 mg twice daily or azithromycin 1200 mg once weekly in patients with a CD4 count below 50 cells / mm^3. In one study conducted in 1992-1993, MAC infection developed in 19 of 333 patients (6%) receiving clarithromycin prophylaxis versus 53 of 354 (15%) patients receiving placebo. Clarithromycin reduced overall mortality as well: survival at ten months was 68% in the clarithromycin group, as compared with 59% of those in the placebo group (Pierce *et. al.*, 1996). Prior to beginning prophylaxis, disseminated MAC infection should be ruled out, either clinically or by culture, in order to avoid exposure of the mycobacteria to monotherapy. Additionally, rifabutin may cause cross-resistance to rifampin in *M. tuberculosis* and should be used with caution in a patient who may be co-infected (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001) (Table X).

One study of clarithromycin prophylaxis found that 11 of 19 (58%) patients in the treatment arm who developed MAC bacteremia had isolates resistant to the drug. Antibiotic sensitivities should be obtained in mycobacterial isolates from patients who fail treatment or develop MAC

Table XI. Treatment of *Cryptococcus neoformans* meningitis

Initial Treatment	Amphotericin B 0.7 mg/kg/day for two weeks, with or without flucytosine 100 mg/kg/day.
Suppressive Therapy	Fluconazole 400 mg/day for 8 weeks followed by fluconazole 200 mg/day or itraconazole 200-400 mg twice daily.

bacteremia while on prophylaxis (Pierce *et. al.,* 1996).

Prophylaxis may be discontinued in patients on HAART who have maintained a CD4 count greater than 100 cells/mm^3 for at least three months (El-Sadr *et. al.*, 2000; Currier *et. al.*, 2000). Prophylaxis should be resumed in patients who subsequently fall below 50 cells/mm^3. In a patient with a prior episode of disseminated MAC, prophylaxis should be restarted if the CD4 count drops below 100 cells/mm^3 (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001).

The prevalence of MAC, like most other opportunistic infections, appears to be declining with the advent of antiretroviral therapy and the institution of prophylaxis. MAC incidence has decreased from 13.4 per 100 person-years in the eighteen months preceding the introduction to antiretroviral therapy as compared to 2.6 per 100 person-years in the subsequent eighteen months among 839 persons with AIDS (Baril *et. al.*, 2000). Better understanding of prophylaxis and treatments for this disease, coupled with the advent of antiretroviral therapy, have drastically lowered both the morbidity and incidence of this infection (Palella *et al.*, 1998; Kravcik *et al.*, 1997; Detels *et al.*, 1998).

Many studies have shown an acute flare of subclinical MAC infections within two to twelve weeks of beginning antiretroviral therapy (DeSimone *et al.*, 2000; French, 1999; Davaro and Himlan, 1999). These infections may be painful and tend to be focal, such as lymphadenitis, hepatitis, inflammatory skin lesions, or endobronchial lesions. Restoration of T-lymphocyte activity appears to be the cause of the symptoms and the acute inflammation. If at all possible, antiretroviral therapy should be continued with the addition of MAC therapy. Anti-inflammatory agents such as steroids may be used if symptomatic relief is needed.

Cryptococcus neoformans

Prior to the AIDS epidemic, cryptococcal infections occurred half of the time in persons with cell-mediated immune defects such as those caused by transplant immunosuppression, corticosteroid therapy, and lymphomas the remainder had no apparent risk factors. In the early 1980s cryptococcal disease was suddenly noted to develop in MSM with alarming frequency. These patients developed both meningitis and cutaneous manifestations from *C. neoformans.*

C. neoformans is a yeast that is 4-6 μm in diameter that can be found throughout nature, although it has a predilection for pigeon droppings. AIDS now accounts for 80-90% of cryptococcosis, and 10% of advanced AIDS patients are thought to be infected with this organism (Diamond, 2000, Powderly, 1999). Susceptibility to cryptococcosis generally does not occur until the CD4 cell count drops below 100 cells/mm^3 (Cox and Perfect, 2000). In one early series of twenty-six patients, twenty-two of them had meningitis, two had pneumonia, one had pericarditis, and the final patient had fungemia (Zuger *et. al.,* 1986). Cryptococcus can also form small brain abscesses, or infect bone, liver, pancreas, peritoneum, heart, prostate, adrenal glands, or the skin (Powderly, 1999; Saag *et. al.,* 2000).

The lung is thought to be the portal of entry via inhalation of aerosolized organisms. Although pneumonia can occur, meningitis is the presenting problem in 90% of cryptococcosis (Garofano, 1998). Cryptococcal meningitis often has an insidious onset of days to months (Rozenbaum and Goncalves, 1994), with the classic signs of stiff neck, photophobia, and depressed mental status occurring in only 20-30 percent of patients. Far more common are the non-specific symptoms of fever (88%) and headache (81%) (Zugar *et. al.,* 1986). Nausea, dizziness, irritability, somnolence and obtundation are also found (Diamond, 2000). Cranial nerves, especially the optic nerve, are involved in twenty percent of cases, and papilledema in thirty three percent. CSF abnormalities include elevated protein, low glucose, a lymphocyte predominant pleocytosis of approximately 20 leukocytes/mm^3, and, in 70% of patients, an elevated opening pressure > 20 mm H_2O. In patients with advanced AIDS, however, the CSF may be normal. Sensitivity of India ink preparations of CSF range from 25% to 72%, and the organism grows in culture approximately 92% of the time. Detection of cryptococcal polysaccharide capsular antigen, either from serum or CSF, is a highly sensitive test (92%-95%) for cryptococcal disease (Diamond, 2000). Focal cryptococcal lesions (cryptococcomas) or hydrocephalus may be evident on computed tomography or magnetic resonance imaging.

Clinical pulmonary disease occurs in 12% of patients. Symptoms include fever, cough, dyspnea, and pleuritic chest pain. Chest X-ray may show diffuse interstitial infiltrates, but can also show localized infiltrates, cavitary lesions, miliary nodules, mass lesions mimicking tumors, and hilar and mediastinal lymphadenopathy (Diamond, 2000; Garafano, 1998; Powderly, 1999). Fifteen percent of AIDS patients with disseminated cryptococcosis also have a second lung pathogen, such as *P.* carinii, so lung symptoms might not always be attributable solely to cryptococcus. Patients with apparent isolated cryptococcal

pneumonia should also be evaluated for meningitis. If only pulmonary infection exists, rapid treatment with antifungal therapy may lower the risk of dissemination (Powderly, 1999).

Cryptococcal skin disease usually signifies disseminated disease, although it may precede other manifestations by several weeks. Lesions typically resemble those of molluscum contagiosum. Cutaneous cryptococcosis may also present as pustules, vesicles, plaques, abscesses, cellulitis, purpura, draining sinus, or subcutaneous swelling (Fitzpatrick 1992; Powderly, 1999).

Prior to the AIDS epidemic, cryptococcal meningitis was treated and cured with a six week course of low dose amphotericin B combined with flucytosine (Bennett *et. al.,* 1979). Some studies, however, found that flucytosine may be too toxic to the bone marrow for AIDS patients (Chuck and Sande, 1989), and higher doses and longer durations of amphotericin B were shown to be superior for relief of symptoms (Dismukes *et al.,* 1987; Saag *et. al.,* 1992; van der Horst *et. al.,* 1997). Current recommendations for therapy are an initial course of amphotericin B 0.7-1.0 mg/kg/day for two weeks with or without flucytosine 100 mg/kg/day, followed by fluconazole 400 mg/day for eight weeks followed. This treatment regimen is then followed by suppressive therapy with fluconazole 200 mg/day or itraconazole 200-400 mg bid (Bozzette *et. al.,* 1991; Powderly 1999, van der Horst *et. al.,* 1997) (Table XI). An entirely oral regimen with fluconazole or itraconazole is attractive, but no clinical study has been able to show superiority or equivalence with these drugs as compared with initial therapy with amphotericin. Symptoms of obtundation or visual changes secondary to increased intracranial pressure are often not quickly amenable to antifungal therapy, and may require a series of large volume CSF drainage (Graybill *et. al.,* 2000).

Fluconazole has been shown to reduce the incidence of cryptococcosis (Powderly *et. al.,* 1995). Nevertheless, primary prophylaxis is not recommended because mortality is not reduced, and significant morbidity may arise from resistant mucocutaneous candidiasis among AIDS patients previously treated with fluconazole (Powderly 1994; Cameron *et. al.,* 1993). Secondary prophylaxis (i.e. maintenance therapy), however, is necessary to prevent relapse of cryptococcosis. Secondary prophylaxis may be discontinued if the CD4 count rises above 100-200 cells/mm^3 for greater than six months as a result of antiretroviral therapy. It should be reinstituted if the CD4 drops below 100 cells/mm^3 once again. (USPHS/IDSA guidelines for the prevention of opportunistic infections, 2001). Unfortunately, antiretroviral therapy has been documented to precipitate symptomatic cryptococcosis in previously asymptomatic patients (Woods *et. al.,* 1998). If this occurs, therapy should be continued and treatment for cryptococcosis should be instituted.

CONCLUSION

Over the last two decades, HIV has evolved from a fatal condition into what may be considered a chronic disease. In patients who are diagnosed with HIV, there are multiple antiretroviral regimens available for treatment, and if necessary, agents to prevent and treat the opportunistic infections that they may acquire. Despite these facts, there are three major reasons contributing to the fact that AIDS, opportunistic infections, and, death still occur.

First, antiretrovirals and agents to prevent and treat opportunistic infections are not available through out the world. For example, sub-Saharan Africa as a whole has limited health care resources, yet the prevalence of AIDS can be as high as 30-40 percent in certain locales. Second, many individuals are unaware that they are infected, and may be unknowingly spreading this disease. Third, there is no cure for HIV infection, and long-term therapy can cause intolerable side effects or lead to development of antiretroviral-resistant virus. These patients may have no treatment options.

Partly as a result of these three factors, the morbidity and mortality from opportunistic infections has not dropped to zero. Further research is needed to find ways to reach infected persons, to develop newer agents that are more tolerable and effective, and to produce an effective vaccine to prevent the underlying cause of these opportunistic infections : HIV.

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