

HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE HIV-ASSOCIATED OPPORTUNISTIC INFECTIONS Bacterial Infections

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ABSTRACT : Bacterial infections are the most common opportunistic infections in HIV. Since the advent of highly active antiretroviral therapy (HAART), the incidence of these infections is on the decline. However, globally there is a significant lack of access to care among HIV patients because of limited drug availability and cost of treatment. Furthermore, non-compliance and drug resistance can hinder viral suppression, predisposing patients to opportunistic infections. We review the major bacterial opportunistic infections in HIV positive patients including tuberculosis, *Mycobacterium avium* complex infections, syphilis, bacterial enteric disease, bacterial pneumonia and bartonellosis. Epidemiology, clinical presentation, diagnosis, treatment and prophylaxis are also reviewed.

1. MYCOBACTERIUM TUBERCULOSIS

Tuberculosis (TB) is the most common opportunistic infection associated with human immunodeficiency virus (HIV) infection globally. The World Health Organization (WHO) estimates that tuberculosis is the cause of death in 11% of acquired immunodeficiency syndrome (AIDS) patients [1]. It is known that *Mycobacterium tuberculosis* accelerates the course of HIV infection [2]. Tuberculosis is both preventable and treatable, therefore screening for tuberculosis with skin testing is recommended for all cases of HIV [3].

Active tuberculosis occurs at any CD4 lymphocytes count. Typical presentation includes persistent cough, fever, night sweats, weight loss, shortness of breath, hemoptysis and chest pain. With more advanced immunosuppression (i.e. CD4 < 200 cells/ μ L), disseminated and extrapulmonary TB is more likely, with atypical chest X-ray findings and poorly formed or absent granulomas on histopathology [4]. Pleural TB usually presents as unilateral pleural effusion, while tuberculous meningitis is a chronic meningitis. TB disease in HIV-infected

individuals can be primary (directly after exposure in up to 30% of cases) or reactivation disease [5]. The rate of progression from latent infection to active disease is higher in HIV-infected persons (7-10%/year as compared to 5-10% lifetime risk in HIV negative individuals) [6].

The diagnostic workup should include in addition to a tuberculin skin test (TST), a chest X-ray, sputum for acid fast bacilli (AFB) smear and mycobacterial culture, fine needle aspirate or tissue biopsy for extrapulmonary disease and mycobacterial blood cultures for disseminated disease with advanced immunosuppression.

Nucleic acid amplification test can be used for rapid detection of *M. tuberculosis* from AFB smear positive specimens. Any AFB smear positive should be assumed to be *M. tuberculosis* until final identification is done.

Management of tuberculosis in HIV-infected patients follows the principles for non HIV-infected patients. Treatment consists of an initiation phase of two months with isoniazid, a rifamycin, pyrazinamide and ethambutol, followed by a continuation phase of four or seven months with isoniazid and a rifamycin assuming sensitivity to first line agents. A continuation phase of seven months is required for high risk patients (cavitary disease, positive smear or culture at two months, meningitis, bone or joint disease) [7].

Few considerations when treating an HIV patient :

- Rifamycins interact with protease inhibitors and non nucleoside reverse transcriptase inhibitors used to treat HIV by inducing cytochrome P-450 system. Rifabutin is recommended instead of rifampin for most patients on antiretrovirals.
- Directly observed therapy (DOT) is highly recommended.
- When considering intermittent dosing regimens it is recommended to use daily DOT for the first two months and thrice weekly DOT for the rest of treatment at least, to prevent induced rifamycin resistance [8].
- Drug resistance testing for first line agents is recommended for all patients.
- For treating multi-drug resistant TB a specialist should be consulted.
- Paradoxical (immune reconstitution) reactions consisting of worsening clinical and radiographic pictures after beginning anti-tuberculous treatment are more common among HIV patients, especially those on antiretroviral therapy. These can usually be managed by NSAIDs or short course of steroids [9].

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All HIV infected persons with positive TST (≥ 5 mm induration), should be treated for latent tuberculosis infection (LTBI) if active disease is excluded, regardless of age with isoniazid (9 months) or rifampin (4 months). Combination Rifampin/Pyrazinamide for two months is no longer recommended because of reports of fatal hepatotoxicity with it [10].

2. MYCOBACTERIUM AVIUM COMPLEX

Mycobacterium avium complex (MAC) comprises *M. avium* and *M. intracellulare*. These organisms are widespread in nature. In AIDS patients, *M. avium* causes most of the infections. Acquisition is by inhalation or ingestion. Human to human transmission is unlikely [11]. Most cases occur in HIV patients with CD4 count less than 50 cells/ μ L and are thought to be recent infections rather than reactivation.

Disseminated infection usually manifests with fever, night sweats, weight loss, diarrhea and abdominal pain. Localized forms of MAC that have been reported in HIV patients include lymphadenitis, serositis, skin and soft tissue infections and CNS disease. Hepatosplenomegaly and lymphadenopathy can be present on exam ; anemia and elevated alkaline phosphatase are common laboratory findings [12].

Diagnosis is by positive blood culture in disseminated disease or culture/AFB smear of affected tissue [13].

Current treatment recommendation is to use at least two drugs for the MAC infections in HIV patients. Clarithromycin is considered first agent and alternatively azithromycin (preferred in pregnancy), ethambutol is the second agent and rifabutin as third drug is usually recommended with advanced immunosuppression, high mycobacterial load and absence of effective antiretrovirals [14]. A study published in 2003 comparing different treatment regimens for disseminated MAC infections in HIV patients showed decreased relapse and improved survival using the three-drug combination compared to two drugs [15]. Alternatives to rifabutin include a fluoroquinolone or amikacin. Clofazimine should not be used as trials showed lack of efficacy and increased mortality [16]. Patients with disseminated MAC should also have highly active antiretroviral therapy (HAART) initiated or optimized.

Immune reconstitution inflammatory syndrome similar to tuberculosis can occur [17]. Treatment duration depends on the immune status of the patient and varies from 12 months to lifelong. Patients who finish 12 months of therapy, are asymptomatic and have persistent increase in CD4 cell count above 100 cells/ μ L (> 6 months) can stop therapy [14]. Secondary prophylaxis should be restarted when CD4 cell count decreases to less than 100 cells/ μ L.

Primary prophylaxis for MAC is indicated for patients with AIDS when CD4 cell count is less than 50 cells/ μ L. Regimens include azithromycin 1200 mg weekly (preferred), clarithromycin 500 mg twice daily or rifabutin 300 mg daily. Primary prophylaxis can be stopped if CD4 rises persistently above 100 cells/ μ L.

3. SYPHILIS

Syphilis is a spirochetal systemic illness caused by *Treponema pallidum subsp pallidum*. Infection usually occurs via sexual contact or close contact with an active lesion. Transfusion-related infection also occurs. Genital ulcerations caused by syphilis increase the risk of HIV transmission. Both syphilis and HIV are prevalent among individuals with the same risk factors (men who have sex with men, intravenous drug users, and persons with multiple sexual partners).

As with HIV negative persons, primary syphilis in HIV-infected persons presents usually with a painless genital ulcer known as chancre, but atypical chancres or multiple chancres can be seen. Similarly, secondary syphilis usually progresses from primary over two to eight weeks. The symptoms are varied but involve most often a centrifugal skin rash affecting palms and soles, generalized lymphadenopathy with fever, malaise, anorexia, arthralgias and headache [18]. Secondary syphilis symptoms can last several weeks before degenerating to latent state without signs or symptoms. Relapse of secondary syphilis can occur in the first few years of the infection. Late or tertiary syphilis manifests as neurosyphilis, cardiovascular or gummatous syphilis. Symptoms of neurosyphilis are reported to develop earlier, and progress quicker in patients with HIV than in non HIV patients. Even though symptoms are the same in both groups, associated uveitis and meningitis is more frequent in HIV positive persons.

The diagnosis is based on a combination of treponemal and non treponemal tests, the performance of which is similar to non HIV persons [19]. False negative and false positive tests do occur, therefore use of additional testing like dark field microscopy and direct fluorescent antibodies on biopsy might be needed.

Asymptomatic neurosyphilis is well described and defined as abnormal CSF (lymphocytic pleocytosis, elevated protein or positive serologic tests) without symptoms.

CSF-VDRL when positive is used to establish the diagnosis, and CSF-treponemal tests when negative are used to rule out the diagnosis of neurosyphilis. Of note HIV infection by itself can cause mild CSF pleocytosis.

Treatment of syphilis is similar for patient infected with HIV as for HIV negative patients [20]. However patient with HIV infection should in addition :

- have closer follow-up to detect possible treatment failures or disease progression ;
- have evaluation for clinical evidence of CNS or ocular disease. For any symptoms or signs suggestive of neurosyphilis, and for all persons with active tertiary syphilis, those with late-latent disease, and those who are failing treatment for non-neurologic syphilis, a CSF examination is warranted.
- have penicillin-based regimen whenever possible, even if desensitization is needed for allergic patients.

4. BACTERIAL ENTERIC DISEASE

The most common causes of bacterial enteric infections in HIV-1 infected patients include *Salmonella*, *Campylobacter* and *Shigella*.

Patient with HIV infection are about 60 times more likely to get salmonellosis, and are more likely to have invasive and disseminated disease [21]. Acquisition is fecal-oral from undercooked contaminated poultry and eggs [22]. Manifestations include a self-limited diarrhea, protracted diarrhea with fever and weight loss, or sepsis with or without diarrhea. Bacteremia can occur with any of the above manifestations and has a tendency to recur [23]. Therefore, blood cultures should be obtained in addition to stool culture in any HIV-infected patient with diarrhea and fever.

Usually non typhoidal salmonella bacteremia is a rare event in the general population therefore its occurrence in a healthy adult should prompt immunodeficiency workup including HIV testing.

Because of the high risk of bacteremia with salmonellosis in HIV-infected patients treatment is recommended with fluoroquinolones [24] (Ciprofloxacin is preferred) for 1-2 weeks for simple gastroenteritis without bacteremia, and 4-6 weeks for bacteremia or advanced immunosuppression ($CD4^+$ T cells $< 200/\mu L$), followed by chronic suppression (for bacteremia). Alternative therapy is TMP/SMX or a 3rd generation cephalosporin.

Campylobacter jejuni infection is 39 times more common in HIV-infected patients, especially among men who have sex with men (MSM) [25]. Infections tend to be more severe, invasive and diarrhea is more likely to be prolonged and associated with bacteremia and extra intestinal involvement (cellulitis, osteomyelitis, vasculitis and rheumatologic symptoms). On colonoscopic examination ulcers can be found and biopsies are diagnostically useful. For mild to moderate disease a fluoroquinolone (ciprofloxacin) or a macrolide (azithromycin) for one week is adequate. Therapy should be for at least two weeks with bacteremia, and a second agent (aminoglycoside) might be warranted.

Shigellosis also tends to occur more frequently among HIV-infected patients especially MSM [26]. Bacteremias can occur and relapses of diarrhea and/or bacteremia after treatment is reported [27]. Usual presentation is an acute febrile diarrhea with nausea and vomiting. Treatment is a fluoroquinolone for three to seven days ; alternatives are TMP/SMX for three to seven days or azithromycin for five days. Bacteremia should be treated with a longer (2 weeks) course.

5. BACTERIAL PNEUMONIA

Bacterial pneumonia has an incidence of up to 10% per year among HIV-infected persons [28] and serious infections with pneumococcus can occur with relatively normal $CD4^+$ T cells. The common offenders are per decreasing order of frequency *Streptococcus pneumoniae*,

Haemophilus influenzae, and in those with advanced HIV infection, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [29]. Infections are usually acute, tend to be more aggressive, and recurrences after treatment are common (both relapses and re-infections). Atypical agents are much less common. Patient with more indolent course over weeks to months are likely to have fungal or mycobacterial disease [30].

Diagnosis is made based on the clinical presentation, CBC and CXR findings. In addition blood cultures and sputum GS and culture should be obtained if possible before starting antibiotics. Evaluation for *Pneumocystis jiroveci* by induced sputum if patient has risk factors ($CD4^+$ T cells $< 200/\mu L$, oral thrush, diffuse pulmonary infiltrates), and evaluation for tuberculosis if there is exposure history, are warranted.

Additional diagnostic tests might include urine antigen testing for *Legionella*, serology for *Mycoplasma* and *Chlamydia*, CT of the chest, bronchoalveolar lavage and biopsy.

Treatment guidelines for community acquired pneumonia can be followed for HIV-infected patients [31]. Extended spectrum cephalosporins (ceftriaxone, cefotaxime) or a fluoroquinolone (levofloxacin, gatifloxacin, moxifloxacin) can be used. Combining a cephalosporin with a macrolide or a quinolone is usually recommended for severe pneumonia. For patients with severe immunosuppression ($CD4^+$ T cells $< 100/\mu L$), neutropenia, history of bronchiectasis or pseudomonas infections, covering this organism and other gram negatives is recommended.

For prevention of bacterial pneumonia, patients with HIV infection with $CD4^+$ T cells $> 200/\mu L$, should receive the 23-valent pneumococcal vaccine if not received in the past 5 years.

6. BARTONELLOSIS

Bartonella henselae and *Bartonella quintana* cause bacillary angiomatosis (BA) in HIV-infected patients. *B. henselae* causes peliosis hepatis (vascular lesions) and splenitis. It is acquired by cat and flea exposure. *B. quintana* is associated with body lice, and poor personal hygiene (homeless people). BA usually occurs with advanced immunosuppression ($CD4 < 50/\mu L$) [32] and affects the skin in most of the cases. Skin lesions are red vascular papules that can be confused with Kaposi sarcoma. *B. quintana* can cause subcutaneous nodules and lytic painful bone lesions. Other presentations include lymph nodes, mucosal surfaces, central nervous system, bacteremia and endocarditis.

Diagnosis is by histopathology of affected tissues [32], Warthin-Starry silver stain and culture. The organism is fastidious and blood cultures (lysis centrifugation technique) need to be incubated for three weeks. Serology and PCR assays are available. Treatment is with erythromycin or doxycycline for at least three months. Clarithromycin or azithromycin are considered alternative agents.

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