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AN OVERVIEW OF IMPACT OF OPPORTUNISTIC INFECTION ON MORTALITY IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

MUSTAFA MURTAZA, ROBINSON FREDIE & FA MUHAMMAD SALIH

School of Medicine, University Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia

ABSTRACT

AIDS is caused by human immunodeficiency virus (HIV).HIV is a retrovirus primarily attacks the immune defense system making the body extremely vulnerable to opportunistic infection (Ols). Ols are the leading cause of morbidity in patients with HIV infection. The most common opportunistic infections are *Pneumocystis jirovecii pneumonia* (PCP), *Toxoplasmosis gondii* encephalitis, *Mycobacterium tuberculosis*, *Mycobacterium avium complex* (MAC) disease. *Cytomegalovirus* (CMV)(most often retinitis) and infections from *herpes simplexvirus*(HSV). Early HIV detection and initiation of antiretroviral therapy (ART) are important to maintain cellular immunity before reaching risky CD4 levels and developing Ols. Introduction of ART has marked effect on the clinical manifestations and responses to treatment of 0ls. There is a clear association between specific opportunistic infections and shortened survival in patients with HIV infection. Prevention and treatment of opportunistic infection in HIV patients is significantly reducing the mortality among HIV patients The CD4 cell count remains the most important predictor of risk of 0ls.

Aim of this article is to review and analyze the influence of prophylaxis against opportunistic disease on survival rate of HIV/AIDS patients

KEYWORDS: HIV Infection, Opportunistic Infection. Mortality, HARRT, CD4 Cell Count

INTRODUCTION

Background

First cases of disease caused by HIV-induced immune suppression was reported in Los Angeles, New York, and San Francisco in 1981[1]. Simultaneously, an outbreak of Kaposi's sarcoma (SK), a previously rare malignancy, was reported in young homosexual men from the same three cities. These patients had a selective defect in cell-mediated immunity that was manifested by low numbers of $CD4^+$ T lymphocytes and the development of opportunist infections [2, 3]. The hall mark of infection in immune suppression, marking patients susceptible to opportunist infections (OIs) [4]. HIV -infected individuals developing opportunist disease is influenced by several factors e.g. immuno competence is critical determinant of whether an infected individual can contain a potential pathogen, exposure to potential pathogens is required before disease can result, and the relative virulence of a potential pathogen is a factor that may determine which disease is likely to occur. Morevirulent organisms such as *Mycobacterium tuberculosis or Streptococcuspneumonia* cause disease in patients with less severe immunodeficiency, whereas less virulent organisms *Pneumocystisjirovecii* or Cytomegalovirus (CMV) cause illness in those with more severe immunodeficiency [5-7].

If the patient is taking chemo prophylactic agents with activity against specific pathogens influence the risk of disease [8,9]. The CD4 cell count remains the single most important predictor of risk for OIs.The introduction of highly active antiretroviral therapy (HAART) has exerted a profound effect on the epidemiology, natural history, clinical manifestations and responses to treatment of OIs [10-12].Aim of this article is to review the impact of opportunist infections on survival in patients with HIV disease.

INTRODUCTION TO OPPORTUNISTIC PATHOGENS

Opportunistic infections that characterize HIV-induced immunosuppression occur in patients with HIV infection much more frequently than in most other patient group. For example without prophylaxis or effective antiretroviral therapy (ART), Pneumocystis pneumonia (PCP) ultimately develops in at least 80 % 0f HIV-infected patients in North America [13,14].The annual attack rate for patients $CD4^+$ T-cell counts lower than 100 cells/mm^3 is about twice for patients with severe combined immunodeficiency syndrome and more than 10 times the rate for patients with organ transplantation ,solid tumors, or more hematologic malignant neoplasms [15]. Disseminated *Mycobacterium avium* complex (MAC) was rarely recognized in humans before the advent of HIV infection, yet it occurred in 30 5 to 50 % of patients with advance in North America before ART and specific chemoprophylaxis. Other opportunistic infections like TB, cerebral toxoplasmosis, cryptosporidiosis, micros poridiosisand Kaposi sarcoma (KS) are examples of other processes that cause disease much more commonly in patients with HIV infection than in those with other immuno-deficiencies .Indeed, their presence should strongly suggest HIV testing be performed. If a routine enzyme-linked immune absorbent assay (ELISA) or Western bloc HIV test result is negative but $CD4^+$T cell count is low, and there is no other obvious cause of immunosuppression, consideration should be given to an unusual strain of HIV that might be missed by the assay kit being used or to an immunoglobulin synthetic defect in the host. In such cases which are uncommon with current testing techniques, a plasma viral load assay for HIV should be considered [16-18].

Environmental exposure is an important determinant of the complications of HIV infection [19,20].These exposure may be respiratory (e.g. TB, endemic mycosis or *Peneumocystis*).enteric (e,g. *salmonella*, *cryptosporodia* or *microsporodia*), vector borne(e.g., *leishmania*, *Bartonella*, *tryptosomes*), contact mediated(e.g., methicillin resistant *Staphylococcus aureus*(MRSA) or sexual (e.g.,HSV-2,HHV-8,Treponema pallidum).Some pathogens, such as *Candida*, herpes simplex and CMV, are so ubiquitous worldwide that most patients will acquire infection early in life, regardless of where of where they live, and will have a high likelihood of developing disease later in life if they become sufficiently immunosuppressed. Other pathogens such as the endemic mycoses (his to plasmosis, coccidiomycosis) try panosomiasis, or leishmaniasis will only cause disease if patient has had very specific geographic exposure [13]. A common concept that most HIV-associated opportunistic infections were thought to be caused by reactivation of latent infection, but this conclusion was based primarily on speculation rather than data. Some episodes of opportunistic infection in adults clearly represent primary infection rather than reactivation. For some patients, second episode s of disease such as TB and PCP has been caused by different strains than initial episode, suggesting that acquisition of new strain rather than reactivation. Cases of PCP and TB infection have been well documented [21, 22].

CLINICAL SYNDROME OF OPPORTUNISTIC PATHOGENS

Pneumocystis Jirovecii Pneumonia

PCP continues to be a commonly recognized complication of HIV infection worldwide, although in some areas of the world, it is much less commonly recognized [13]. *Pneumocystis* causes disease almost exclusively in the lungs extra pulmonary disease occurs but is uncommon. Patients may have chest tightness or exercise intolerance as very early symptoms, before chest radiography results are abnormal and before arterial blood gases reveal hypoxemia [23]. If therapy is to have the greater chance to succeed, patients and clinicians must be trained to initiate diagnostic evaluation at this stage, before pulmonary dysfunction id severe [24]. Even with very mild manifestation of disease, organisms can be recovered readily from sputum bronchoalveolar lavage, allowing initiation of therapy on an outpatient basis at a stage when prognosis is excellent [25]. In many cases, PCP can be characteristically be distinguished from bacterial pneumonia or viral pneumonia by the duration of symptoms, the character of sputum, and the radiologic manifestations. PCP can be

especially difficult to reliably distinguish from certain other infectious and non-infectious processes, including TB, his to plasmosis, and non-intestinal pneumonitis[26,27]. Therefore it is important to establish a specific diagnosis to ascertain that correct pathogen is being treated and to avoid the toxicities, cost, and inconvenience of unnecessary drugs. Establishing a specific diagnosis is also has epidemiological implications in terms to ascertaining the isolation precautions and contact tracing that is needed. However, given the cost of a diagnosis evaluation, in some settings it may be necessary to treat cases of presumptive PCP empirically [26].

The likely hood that an AIDS patient will survive an episode of PCP depends on the severity of pulmonary dysfunction at the time of initiation of therapy, patient's ability to tolerate available regimens, the presence of concomitant pathology, and the severity of the patient's immunological dysfunction. A poor prognosis correlates best with an alveolar-arterial gradient greater than 30 mm Hg, a severely abnormal chest radiograph, or a larger number of organisms detected on lavage or biopsy [28].Patients who experience breakthrough while receiving prophylactic therapy are usually those who are not receiving TMP-SMX, who are not adherent, or who have very low $CD4^+$ T-cell count [29].

Toxoplasmosis

Toxoplasmosis gondii causes disease in patients with HIV infection by reactivation rather than by primary infection [30].Patients almost always have immunoglobulin G antibodies against Toxoplasma,(although insensitive ELISA assay may fail to detect such antibodies),have fairly advanced disease($CD4^+$ T-cell count lower than 50 cells/$mm^3$and have not been receiving TMP-SMX prophylaxis[30].Because the seroprevalence of toxoplasmosis is much higher in some areas such as Western Europe (50% to 75 %) and South America than in United States (15 %) (i.e. There is a higher incidence of latent infection),those areas have much higher frequencies of AIDS- associated toxoplasmosis [31]. If HIV infected patient with $CD4^+$ T-cell count of less than 100 cells.mm^3 presents with a space occupying cerebral lesion that involves gray matter, the differential diagnosis should focus on two entities: toxoplasmosis and lymphoma. Progressive multifocal leukoencephalopathy(PML) should manifest differently because it affects primarily white matter. There are increasing reports of solid tumors in HIV-infected patients: thus clinician must be alert to possibility that CNS masses represents metastatic tumor [32].

Cytomegalovirus

CMV infections include: chorioretinitis, CMV colitis, CMV pneumonitis, CMV esophagitis, CMV polyradiculitis and CMV involvement of adrenal glands. Before the era of specific prophylaxis or ART was available, 21 % to 44 % of patients developed CMV associated disease at some point of illness [33]. HIV infected patients with circulating $CD4^+$T-cells counts lower than 50 cells /mm^3 are often viremic and viruric with CMV. The likelihood of development of CMV-associated disease is related to both the degree of immunosuppression and the quantity of circulating CMV. The later can be assessed by a variety of quantitative systems that detect antigen or nucleic acid in circulating blood [34,35].Retinitis is the most commonly recognized disease caused by CMV [36].Most cases occur at $CD4^+$ T- cell counts lower than 50 cells /µL .CMV retinitis has the potential to involve and rapidly damage the macula and optic disk, to cause retinal detachments, and to result in visual impairment and ultimately in blindness[13]. Esophagitis, enteritis, colitis, pneumonitis and encephalitis are life threatening syndromes caused by CMV and have been documented to respond to therapy [37].

Mycobacterium tuberculosis

The clinical manifestations of TB among patients with HIV/AIDS depend on host immune status. For patients who have CD4+ T-lymphocyte counts higher than 350 cells /µmanifestation of pulmonary disease are not substantially different from general population. Extra pulmonary disease is more common. For patients with lower $CD4^+$ T-lymphocyte

counts, lower lobe pulmonary disease, military disease, cavitation, effusions, adenopathy, and extra pulmonary disease are more common [38].When ART is initiated, a variety of clinical manifestations related to tuberculosis may occur. Soon after initiating ART, latent disease may become active, requiring specific chemotherapy.Inaddition, patients who initiate ART at a time when they have low $CD4^+$ T-cells counts and high viral loads may manifest IRIS. IRIS may manifest as clinical exacerbation at sites previously known to be involved by active disease or at sites that had been clinically silent until enhanced immunity caused clinical manifestations in response to viable or nonviable organisms.

All persons with HIV infection should be tested for TB with either with PPD or an interferon-ɣ release assay (IGRA) [13].TB can be diagnosed by smear, culture, or nucleic acid probe of a respiratory sample or some other tissue fluid. A variety of treatment regimens can be used. Drug susceptibility testing should be performed to ensure that adequate therapy isinitiated. The treatment regimens should be modified based on susceptibility results [39].Drug interactions between antituberculous drugs (especially rifamycin and retroviral drugs (especially protease inhibitors and non-nucleoside reverse transcriptase inhibitors) need to be carefully considered and appropriate adjustments made [40].

Mycobacterium avium Complex

MAC has been much less common since the widespread use of ART[41].MAC most often manifests as a systemic process characterized by fever, weight loss, elevated serum alkaline phosphatase levels, and substantial anemia [41]The incidence of MAC declined 39.9 % between 1996 and 1998, compared with 4.7 % per year between 1992 and 1995 [42].The prevalence of disseminated MAC for patients with $CD4^+$ T-cells counts of less than 100 mm^3 is approximately 10 %; at autopsy, prior to HAART and continue us of prophylaxis, the rate was approximately 50 % [43,44].Testing of isolates for clarithromycin or azithromycin resistance is recommended for all clinically significant isolates [rept.13]Patients at high risk include with those with a $CD4^+$ T-cell count lower than 50 cells /mm^3,those with previous opportunistic infection (especially with CMV), and those with a respiratory or gastrointestinal tract that is colonized with MAC [45].Clarithromycin,azithromycin , and rifabutin are each effective chemo prophylactic agents in terms of reducing the incidence of disease and reducing mortality [45].

Cryptospridiosis

Cryptosporidium parvum the parasite that cause human infection is now known to be ubiquitous. Transmission is by the fecal-oral route; numerous USA, waterborne outbreaks in normal hosts have heightened awareness of this parasite's threat to public health. The prevalence of cryptosporidiosis in HIV –infected patients was estimated to be 10% to 15 % prior to advent of HARRT]. AIDS patients have a spectrum of disease ranging from asymptomatic carriage to fulminant, persistent, cholera like diarrhea. Cryptosporidium causes diarrhea, nausea, vomiting, abdominal pain, and weight loss, fever is uncommon. Biliary tract involvement occurs in at least 15 % AIDS patients and results in severe right upper quadrant pain with protracted nausea and vomiting. Ultrasonography demonstrates gallbladder wall thickening and dilated bile duct [46-48]. Prevention of cryptosporidiosis should focus on environmental control because no drugs are known to effective for prevention [13] .Albendazole and fumagillin have activity in vitro and in vivo against some microsporidia.

Candidiasis

Candidiasis is the most common fungal infection in HIV patients. Stomatitis, esophagitis, vaginitis and proctitis caused by *Candida albicans* infection is common and often respond to topical therapy(nyastatin, clotrimazole},and oral therapy((itraconazole, posaconazole, or fluconazole), or intravenous therapy(fluconazole, voriconazole, caspofungin, micafungin, anidulafungin, or one of severe amphotericin B preparations) [49,50].There is usually no urgency to institute antifungal therapy for any of these Candidal mucosal disorders .Stomatis, esophagitis and proctitis, often recur after

therapy is discontinued if $CD4^+$ cell count remain low. Fluconazole administration may have to be continued for life if recurrences are frequent or severe or $CD4^+$ cell counts lower than50 cells /µ and extensive exposure to fluconazole[51].

Cryptococcosis and Histoplasmosis

Cryptococcus neoformans is most frequent cause of meningitis in HIV infected patients [52]. Patients usually present with fever, headache, neck stiffness, or photophobia Most have $CD4^+$ T-cell counts lower than 50 cells/µl. Patients also present with pulmonary or cutaneous manifestations with or without apparent neurological disease. Patients with meningitis CSF that typically demonstrate elevated protein and mononuclear cells and decreased glucose. In some patients one or all parameters may be normal.Baselinefactors predicting a poor therapeutic responses in patients with meningitis include altered mental status (e.g., confusion, lethargy, obtundation), CSF antigen titer greater than 1:32, decreased leukocyte count (fewer than 20 cells /mm^3), age younger than 35 years, positive blood cultures for *Cryptococcus*, and perhaps hyponatremia and positive CNS culture for *Cryptococcus*[53].

Histoplasmosis is a common life threatening opportunist infection in patients with HIV infection in certain geographic areas such as United States, Puerto Rico, and much of Latin America[54]. Patients with low $CD4^+$ T-cells counts lower than 150 cells/ul, are likely to present with extra pulmonarymanifestations such as fever, meningitis, abdominal pain, diarrhea, or shock. Diagnosis is established by direct microscopic, or culture (bronchoalveolar lavage, bone marrow, or blood) or by antigen detection (urine, blood or bronchoalveolar lavage)[55]. Acute for moderate or severe non-meningeal disease should consist of intravenous amphotericin B for at least 14 days, for most patients[55].

Hepatitis C Virus

HCV infects approximately 4 million people in the United States, of whom an estimated 10,000 die each year .HCV is a major pathogen in HIV infected patients reflecting shared epidemiologic risk factors [56]. The natural history of HCV is clearly accelerated among patients with HIVconfection .Cirrhosis is more likely to occur in older patients, males, alcohol users(20 to 50 g/day), and those with lower $CD4^+$ T-cell counts[57]. The goals of therapy are prevention of fibrosis, cirrhosis, hepatocellular carcinoma, and death. The only effective treatment currently is the combination of an interferon product plus ribavirin. Sustained viral responses for type 1 disease are very disappointing [57].

Human Herpes Virus 8 and Kaposi Sarcoma

KS is the most common neoplasm in AIDS.Early in the AIDS epidemic a 20,000-fold increase rate of KS was noted among homosexual men [58]. Seroprevalence of HHV-8 is 1 % to 5 % in the general population, but higher in certain geographic areas among men who have sex with men,HHV-8 associated with Kaposi sarcoma as well as less common neoplastic processes, including primary effusion cell lymphoma and multicentricCastleman disease Serocon version to HHV-8 usually precedes the development of these tumors [59].Seropositive patients with HHV-8 viremia have a markedly elevated likelihood of developingKaposi sarcoma, and all patients with multicentricCastleman disease are viremic[60]. A PCR to quantitate circulating HHV-8 in peripheral blood is useful primarily for diagnosis and management of persons with multicentricCastleman disease [60]. Kaposi sarcoma can cause life threatening disease by obstructing a vital structure such as the larynx, bronchus, biliary duct, or bowl. Kaposi sarcoma can occasionally infiltrate a vital organ such as the lung and cause fatal hypoxemia. In these life threatening situations either radiation therapy or cytotoxic chemotherapy is necessary to produce a rapid and substantial response [61].

EFFECTIVENESS OF ANTIRETROVIRAL THERAPY ON OPPORTUNISTIC INFECTIONS

HAART has exerted profound effect on the epidemiology HIV /AIDS and opportunistic infections The incidence

of nearly all AIDS defining opportunistic infections decreased significantly in the United States between 1992 and 1998 [61].Decreases in most common Ols, including *Pneumocysticarinii* pneumonia (PCP), esophageal candidiasis, and disseminated *Mycobacterium avium* complex (MAC), were most pronounced during this period when HAART was introduced. The incidence of major Ols in eight U. S. cities declined from 21.9/100 person-years in 1994 to 3.7 /100 person-years by mid-1997.Morality declined from 29.4/100 person-years in 1995 to 8.8/100 person-years in 1997, after remaining constant during 1994 and 1995[63, 64].Several reports have described reduction in mortality and in the rate of hospitalization HIV-infected patients. There were reductions in mortality regardless of sex, race, age and risk factors for HIV transmission of HIV[65,42].Overall mortality nationally has declined an estimated 21 % or a rate of 4.6 deaths per 100,000 in 1998,the lowest rate since 1987 [63]

IMPACT OF OPPORTUNISTIC INFECTION ON MORTALITY IN HIV/AIDS PATIENTS & CONCLUSIONS

Opportunistic diseases cause substantial morbidity, results in hospitalization, necessitate toxic and expensive therapies, and shorten the survival of HIV infection [66].Virtually all HIV-related mortality is preceded by opportunistic disease, whether or not it meets the case definition for AIDS. In addition, prophylaxis of several opportunistic infections has shown to prolong overall survival[67].A number of studies have demonstrated increase in HIV viral load in patients with acute opportunistic diseases or inpatients whose immune system has been stimulated by antigenic challenge [68]. Several studies have reported an association between specific opportunistic infections and shortened survival in patients with HIV infection[69].Recent studies have emphasized the importance of viral load in predicting mortality. $CD4^+$ T-cells levels also remain and important prognostic tool [70, 71]. The occurrence of opportunistic diseases was predictive of an increased risk of death, independent of $CD4^+$T-cell count. These data was consistent with other reports in patients with more advance HIV disease in whom $CD4^+$T-cell levels are more predictive of survival than viral load [72].Overall it is opportunistic infections that reduce the survival of HIV/AIDS patients and opportunistic infections that kill not the HIV virus.

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