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REVIEW ARTICLE

Opportunistic Infections in the Immunocompromised: Hiv Vs Non-HIV Patients - A Narrative Review

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ABSTRACT

Opportunistic infections affect patients with immunocompromised status and are caused by common microorganisms with more severe presentations, or atypical organisms that do not cause disease in the immunocompetent. The type of infection varies with the type of immune dysfunction.

Patients with cell-mediated immune dysfunction tend to be infected with a range of viral infections, intracellular bacteria, and fungi. This contrasts to patients with defects in humoral immunity, where infections with encapsulated bacteria, and enteric organisms such Giardia lamblia and enteroviruses predominate. Patients with phagocytic defects are especially prone to infections with Gram-negative bacteria and fungi, whilst those with complement disorders are prone to recurrent infections with encapsulated bacteria. In contrast to patients with primary immunodeficiencies, which usually present with only one defect of the above, acquired immunodeficiencies present with a variety of those, and clinical presentations are diversified.

The epidemic of HIV and AIDS shed some light into infections that were before extremely rare, by making them frequent, but with the advent of anti-retroviral therapy their clinical presentation has shifted. Also, the emergence of novel immunotherapies for cancer and autoimmune diseases, allied with an increase in organ transplant has increased the pool of immunosuppressed patients without HIV, which present differently regarding opportunist infections.

Rapid and specific microbiologic diagnosis is essential. Newer microbiologic assays have improved the diagnosis and management of opportunistic infections.

Our aim was to revise and summarize the most frequent opportunist infections, and how their presentation and course compares in different immunosuppressed diseases (HIV and non-HIV).

Keywords: Opportunistic infections, HIV, immunosuppression

Introduction

Opportunistic infections (OI) are infections caused by less common microorganisms, or agents that usually do not cause serious disease in an immunocompetent person[1]. They can appear by reactivation of latent infections, community, or nosocomial transmission[2]. The appearance of an OI in a patient should raise suspicion of an underlying immunodeficiency[1]. Besides the already occurring burden associated to infection, with important morbidity and mortality, OI increase the problem by greater diagnostic and management challenge, higher unpredictability, severity, duration and mortality[1,2].

Host defense from infection depends upon a complex integrated system of physical barriers, innate immunity (e.g., phagocytic cells, natural killer cells, complement) and adaptive immunity (B and T lymphocytes).[3]

The type of OI is often suggestive of the kind of defect in the immune system[1,3,4]. Therefore, immunodeficiencies can be categorized by the defect in the immune system[1,3,5]. Patients with cell-mediated immunity dysfunction are more susceptible to infection by virus, or intracellular agents such as *Listeria* or *Mycobacteria*, fungi, or protozoa; humoral immunity dysfunction predisposes to bacterial and protozoa infection, by enabling mucosal barriers breaching; phagocyte dysfunction usually comprises prolonged or recurrent bacterial infections; finally, complement defects favor recurrent infections by specific agents such as *Neisseria* and *Pneumococcus*[1,3,5].

Furthermore, immunodeficiencies (ID) can be classified as primary versus secondary or acquired[3,5]. Even though, some primary immunodeficiencies can be categorized into one specific immune system defect (cell-mediated, humoral, complement), certain are more complex affecting more than one arm of immunity[3,5]. Most acquired immunodeficiencies result from more than one defect in the immune system. Examples of acquired of ID are treatment-related, through the use of immunosuppressive drugs; neoplasia (mainly hematologic malignancies) and its treatment; immunosuppression for organ transplant (solid and hematological) and rejection; Human Immunodeficiency Virus (HIV) infection; metabolic conditions such as diabetes mellitus, protein-losing enteropathy, nephrotic syndrome and asplenia; surgery and trauma; chronic conditions such rheumatologic diseases, chronic hepatitis and cirrhosis and chronic renal disease[3,5].

This narrative review will focus on some of the most frequent opportunist infections and how they differentiate between patients with HIV, and patients immunocompromised from other causes.

Material and methods

We performed a thorough search on MEDLINE/PubMed for reviews, meta-analysis, clinical trials, case series, or guidelines, on opportunistic infections on immunocompromised patients. We used several keywords: "opportunistic infections", "infections in immunocompromised", "infections in HIV patients", "infections in immunossupression non-HIV", and then more specific searches by specific conditions: "bacterial infections", "mycobacterial infections", "viral infections", "protozoa infection", etc. Papers regarding manifestations of diseases could be older (first descriptions of diseases), but comparative studies between HIV and non-HIV immunosuppressed patients were limited to the last 10 years. The selected papers were retrieved and discussed inclusion in the narrative review. The text was organized in the following chapters: 1) disease and pathogen overall description, 2) manifestations and outcomes in the HIV patient, 3) manifestations and outcomes in non-HIV patients and differences towards the HIV patient.

Opportunistic infections

1. Bacteria

Bacterial infections are one of the most common OI, however they remain mostly overlooked[6,7]. These OI are usually seen in immunocompetent patients, but are more frequent in HIV patients and present more severely as CD4 counts decline[7]. The introduction of anti-retroviral therapy correlating with increasing CD4, reduce the risk and morbidity associated with these infections[7,8]. Interestingly, despite the correlation of these OI with CD4, they do not appear to correlate with neutropenia, which can be even lower in other forms of immunossupression[8,9].

In this line, immunosuppressed patients without HIV, also present frequently with bacterial OI. The main risk factors are neutropenia, high dose corticosteroids and antibody deficiencies[4]. The likelihood and type of infection relates to the host immunosuppression, nature and duration of antimicrobial prophylaxis, and local hospital and regional microbiology[10]. Considering solid organ transplant recipients, bacterial infections are the most frequent in the early post-transplant period, arising either from the donor allograft, the recipient or from complications of the surgery and hospitalization[10]. The most common

infections are therefore aspiration pneumonitis, surgical site (wound) infections, catheter-related bloodstream infections, urinary tract infection[10]. Besides the morbidity and mortality associated with these infections, there is also morbidity associated with graft failure[10].

2. Mycobacteria

Mycobacteria tuberculosis

Mycobacteria tuberculosis is an airborne mycobacteria that causes tuberculosis (TB), one of the most common OI, besides a worldwide burden in immunocompetents[11]. Clinically it causes most frequently pulmonary infection but can affect any organ and cause disseminated infection, which depends on the degree of immunity[12]. Primary infection can be followed by elimination from the body, or latent infection which can be later reactivated if immunocompromised. Immunosuppressed patients are also susceptible to reinfection[11,12].

TB presentation in HIV patients follows the degree of immunossupression[13,14]. As the immune system function declines, pulmonary presentations are less frequent, with more frequent extra-pulmonary and disseminated presentations[11,13,14]. Imaging follows a similar evolution with the decline of the immune system and lower CD4 counts, from a non-HIV presentation like, into a more atypical one[11,13–15]. Mortality is also higher in patients with HIV, when compared to immunocompetent patients[16,17].

Considering clinical and radiological presentation correlates with the immune status, it is not surprising, immunosuppressed patients without HIV, also present more frequently with extra pulmonary and disseminated TB, with atypical symptoms and imaging[18]. Interestingly, mortality seems even higher in this subset of patients when comparing to HIV and immunocompetent TB patients[18].

Atypical mycobacteria

Atypical mycobacteria or non-tuberculous mycobacteria (NTM) are species that do not belong to the *Mycobacterium tuberculosis* complex or *Mycobacterium leprae*[19]. They are free-living ubiquitous microorganisms and responsible in 90% of cases for chronic lung infections in immunocompetent patients[19]. Broadly, NTM can cause pulmonary disease, superficial lymphadenitis, skin and soft tissue infection, and finally disseminated disease in the immunocompromised, or associated with indwelling catheters, caused by *Mycobacterium avium* complex (MAC) and rapid growing mycobacteria[20].

In the immunosuppressed, the most frequent NTM associated infectious occur in HIV patients with AIDS, in particular MAC infections, affect 20-25% patients with CD4 counts under 50 cells/mm^3 [21–23]. In HIV patients, MAC infections resemble the immune reconstitution syndrome, and has overall good prognosis with effective response to antibiotic therapy[21,24]. Following MAC, *Mycobacterium kansasii* is the most frequent NTM isolate in HIV patients[25]. It typically affects AIDS patients with low CD4 counts and presents with pulmonary or disseminated infection similar to Mycobacterium tuberculosis[26], but with worser prognosis (around 50% mortality)[27].

MAC infections can also affect other immunocompromised patients without HIV, most commonly patients with leukemia[21]. In solid organ transplant recipients MAC infection usually presents with pulmonary involvement[21,28,29]. However in other immunocompromised patients, other NTM are usually found, such as *Mycobacterium kansasii* and *Mycobacterium haemophilum* usually with soft tissue involvement, but also rapid growth mycobacterium in catheter-associated infections[21,28]. Prognosis is usually good, with effective response to therapy, however in the lung is involved usually there is decline in function[21,28,29].

3. Fungus

Pneumocystis jirovecii

Pneumocystis jirovecci (PCP), previously *Pneumocystis carinii,* was initially classified as a protozoan and recently reclassified as a fungus[1,30]. It causes pneumonia in the immunocompromised, characterized by dyspnea, cough and low grade fever, accompanied by tachycardia, tachypnea and hypoxemia[1,30,31]. Elevation of lactate dehydrogenase are suggestive[30], and imaging varies from diffuse bilateral interstitial infiltrates to cysts, and even pneumothorax[1,30,31]. Diagnosis requires detection by RT-PCR of the fungus in respiratory samples by bronchoalveolar lavage[1,31]. Treatment is with trimethoprim/sulfamethoxazole (TMP/SMX)[31], as well as prophylaxis (in lower dosages)[1,30]. However, prophylaxis has only been established to HIV patients[21,30].

PCP in HIV patients with low CD4 counts, can reach over 50% in incidence, remaining the most common AIDS related OI, when comparing to other causes of immunodepression in which incidence is lower[21]. Furthermore, clinical course in HIV patients is more

insidious with longer prodrome[21], but with more exuberant symptoms and higher LDH, which can help diagnose[30]. However, non-HIV immunocompromised patients, had higher likelihood of hypoxemia, requiring mechanical ventilation, and higher mortality rate[21,30,31]. It remains unanswered whether the bad outcomes in non-HIV patients are related to a more severe disease course, or to a higher difficult in diagnosis secondary to a more subtle presentation[30].

Aspergillus

Aspergillosis has become one of the most common causes of infectious death in severely immunocompromised patients, with mortality rates up to 40% to 50% in patients with acute leukemia and recipients of hematopoietic stem cells transplantation (HSCT) [32]. Aspergillosis encompasses a spectrum of diseases, dependent on host factors and the immunologic response, following inhalation or inoculation with *Aspergillus* conidia (spores). In soil and on other vegetative or moist material, aspergillus species exist as saprobes, digesting dead or dying organic material. *Aspergillus* spp are ubiquitous in the environment and thus unavoidable. The respiratory airways are exposed to its conidia daily and therefore a highly coordinated immune response is needed to eliminate the pathogen and prevent disease. Thereat, aspergillosis principally involves the sinopulmonary tract; other entry sites such as the gastrointestinal tract and skin occur on rare occasions, and the infection can further invade locally or trough hematogenic dissemination and reach the vascular or central nervous system. Aspergillus infection can be divided in noninvasive forms, such as allergic bronchopulmonary aspergillosis and allergic fungal rhinosinusitis, and invasive forms, including chronic pulmonary aspergillosis and invasive pulmonary aspergillosis (IPA)[33,34]. The invasive forms arise almost exclusively in immunocompromised patients and therefore will mainly focus on them in this review. The severity of invasive infection correlates inversely with the immune status of the host, with greater emphasis to the degree and duration of neutropenia.

HIV patients are subject to nearly the whole spectrum of Aspergillus-related diseases due to the varying degrees of immunosuppression, however invasive aspergillosis (IA) remains relatively uncommon[35,36], with fewer than 3% of IA cases occurring in those infected with HIV[37] and being the less common invasive fungal disease in HIV patients discussed in this review[38]. The use of systemic glucocorticoids for the treatment of other pathologies, such as *Pneumocystis jirovecii* pneumonia (PJP), can also contribute to aspergillus infection[36,39,40]. Moreover, prior or concomitant diagnosis of AIDS-opportunistic infections – particularly those involving the lungs, such as PJP and CMV infection, through impairment of pulmonary macrophage function - are also at greater risk for aspergillosis[35,36,41,42].

IA affects patients with advanced AIDS (usually when CD4+ T-cell count <100mm3) or when other immunocompromising conditions (such as neutropenia) are also present. Approximately 80% of IA cases in HIV-infected individuals are pulmonary infections – on par with other immunosuppressive conditions. IPA is the most common form and is characterized by acute to slowly progressive necrotizing pneumonia[43]. Fever, cough, and dyspnoea are frequent although nonspecific and don't differ significantly when compared with other series of immunocompromised patients[44].

The increased risk of aspergillosis is well documented among patients who have undergone HCST, mainly in the initial period of neutropenia and during treatment of graft-versus-host disease (GVHD), and among solid-organ transplant (SOT) recipients – particularly lung transplant, with up to 10% to 15% of patients developing aspergillosis[45] - treated with systemic glucocorticoids or other immunosuppressive agents[46,47]. As a matter of fact, IPA is the most common IFI in HSCT and in SOT recipients (43% and 59% of all IFIs, respectively)[32]. Patients with acute leukaemia, under intensive cytotoxic chemotherapy associated with prolonged neutropenia, are also at greater risk of IA, with a incidence of this pathology around 5%[48]. Chronic granulomatous disease, an inherited disorder of NADPH oxidase, is associated with recurrent bacterial and fungal diseases, and invasive aspergillosis is a major cause of death in these patients[48].

More recently, other non-traditional – or, at least, not usually thought at first as immunocompromised - populations at risk for IA have been identified:

- Intensive care unit (ICU) patients[49,50]
- Severe respiratory viral infections[51–54]
- Novel immunomodulators and immunosuppressive therapies used for the treatment of rheumatological diseases (in particular), malignancies, organ transplant rejection prevention, such as tumor necrosis factor α blockers, tyrosine kinase inhibitors and chimeric antigen receptor T-cell therapy [54–56].

Symptoms are globally like the ones in HIV patients and dependent on the affected anatomical region. Still, in IPA, some clinical differences can be observed

between distinct forms of immunosuppression. In patients with acute leukemia or other causes of bone marrow failure, there is a scant inflammatory response, vascular thrombosis secondary to hyphal angioinvasion and possible evolution to cavitation. In patients submitted to allogenic HCST, IPA manifests as an inflammatory fungal pneumonia and angioinvasion with coagulative necrosis. In post-SOT, patients can present as an acute inflammatory pneumonia, a chronic necrotizing aspergillosis; or, in lung-transplant recipients, a tracheobronchitis affecting the anastomotic site and causing dehiscence. In patients with chronic granulomatous disease, IPA can occur as an acute to slowly progressive pneumonia or as a particular presentation of this disease, known as "mulch pneumonitis"[57], defined as an acute hypersensitivity response to a large, aerosolized exposure.

Candidiasis

Candida spp. are considered the single most important cause of opportunistic fungal infections worldwide, being the most common cause of infectious deaths in the developed world[58]. Candidiasis is a broad term that refers to cutaneous, mucosal, and deep-seated organ infections caused by fungi of the *Candida* genus. Invasive candidiasis (IC) refers to bloodstream infections with *Candida* spp. — referred as candidemia — and deep-seated infection (such as intra-abdominal abscess, peritonitis, or osteomyelitis), with or without candidemia.

Candida spp. colonization is needed for subsequent infection. *Candida* spp. are commensal yeasts making part of the normal human skin and gut microbiota, being found up in around 60% to 75% of healthy individuals[59,60]. IC is usually a consequence of increased or abnormal colonization in a host with a local or generalized immunological deficiency. As so, in immunocompromised patients, Candida spp. can cause an array of disease manifestations ranging from mild oral disease to disseminated candidiasis.

Candida infection in HIV patients is almost exclusively mucosal, and its prevalence increases greatly with CD4 counts < 200 cells/mm3 or a high viral load (>10,000 copies/mL)[61]. Therefore, since the introduction of anti-retroviral therapy (ART) in the 1990s, there has been a significant decrease in mucocutaneus candidiasis[61]. Mucocutaneous candidiasis can mainly occur in three forms: oropharyngeal, oesophageal, and vulvovaginal diseases.

Oropharyngeal candidiasis (OPC) is the predominant form, present in up to 93% of untreated advanced HIV - with 60% having at least one episode per year with frequent recurrences [62]. ART significantly reduces the risk of oral candidiasis in HIV-1 infection; however, smoking appears to increase the risk [63].

Esophagitis due to Candida species can occur in up to 20% of those who are ART naïve[64]. Risk factors for Candida esophagitis in this population include prior oropharyngeal candidiasis, low CD4 count and use of antibiotics. [65] The severity of esophagitis negatively correlates with CD4+ cells count[66].

Systemic invasion is considered rare in HIV patients, with an estimated incidence below <1%[67,68], and usually occurs as a late event, when CD4 are under 50 cells/mm3[38]. Haematogenous dissemination rarely occurs, probably because the polymorphonuclear function in HIV patients is sufficient to prevent it. Still, Candidiasis is the second most frequently reported IFI in PLWH, behind Cryptococcosis[38,69]. Most cases of invasive candidiasis in HIV patients are candidemia, and its mortality is around 31%. [67]

The most common *Candida* species involved in infection is *Candida albicans*, accounting for at least 80% of mucocutaneous candidiasis and around 50% of IC - although the proportion of non-C. *albicans* species has been increasing since the advent of ART[70,71]. ART is the most effective therapy for OIs, including candidiasis. Since its use, studies have suggested that azole-resistant Candida species have been reduced to <10% [72,73], at least in part to the significant decrease in the use of azoles, and subsequent decrease in the selection pressure of antifungals.

The prior forms of mucocutaneous candidiasis can be found in other immunocompromised patients, particularly impaired cell mediated immunity.

Besides systemic immunity deficiencies, impaired local oral defence due to prolonged use of inhaled steroids, due to salivary dysfunction (eg.: Sjögren's disease) or radiation therapy.

Esophagitis is commonly found in patients with hematologic malignancies, after SOT and recipients of chemotherapy, radiation, and corticosteroids. Besides these acquired deficiencies, it is also common in patients with primary immunodeficiecies associated with fungal infections, including chronic mucocutaneous candidiasis, caspase recruitment domain-containing protein 9 (CARD9) deficiencies, chronic granulomatous disease, congenital neutropenia, and leukocyte adhesion deficiency type I.

Immunocompromised patients at special risk for candidemia and invasive candidiasis include those with hematologic malignancies, recipients of solid

organ or hematopoietic cell transplants and those given chemotherapeutic agents. Neutropenia is common in these settings, and most transplant recipients are additionally receiving glucocorticoids. Extensive gastrointestinal mucosal damage, broad-spectrum antibiotics, and central venous catheters act as complementary common risk factors in this population. IC is the most common IFI in all SOT types except for lung transplant recipients – where aspergillosis comes out as the most reported[74].

Hepatosplenic candidiasis (also known as chronic disseminated candidiasis) is a particularly difficult infectious complication seen almost entirely in patients with hematologic malignancies who have just recovered from an episode of neutropenia, such as those who have undergone chemotherapy. In adults with acute leukaemia, the incidence has been reported to be as high as 7%[75]. It presents as persistent fever (usually high and spiking), which often accompanied by right upper quadrant discomfort or pain, nausea, vomiting, and anorexia.

The incidence of each species in invasive disease is superimposable to the one seen in HIV – around 50% for C. *albicans*, and the other half C. non-*albicans*. Different causes of immunosuppression may predispose to Candida species. C. *glabrata* appears to be more common in malignancy and transplant (both HSCT and SOT), while C. *krusei* is most often seen among patients with underlying hematologic malignancies who are receiving fluconazole prophylaxis[76].

Cryptococcosis

Cryptococcosis is the most prevalent fatal fungal disease worldwide[58]. Cryptococcal infection preferentially affect patients with defects in cell-mediated immunity, but it may also occur in immunocompetent hosts – although later many have been found to have subclinical immune defects or other underlying predisposing conditions[77].

Cryptococcus are ubiquitous and infection typically starts by inhalation of environmental basidiospores or small yeast cells (<5 mm) that deposit into pulmonary alveoli[78]. Cryptococcus can then disseminate from the lungs, causing infection in a wide variety of tissues – mainly CNS, but also skin, eye, prostate, bone and gastrointestinal tract. Alternatively, infection can occur via direct inoculation of tissue from traumatic injury.

C. *neoformans* is the most common cause of cryptococcosis, has a worldwide distribution and tends to affect primarily immunocompromised patients causing meningoencephalitis, while C. *gattii* has a restricted geographic distribution and more frequently affects immunocompetent patients, predominantly causing pulmonary infection[78].

Before the introduction of ART, 5% of all HIV-infected persons developed cryptococcosis. Since then, the incidence has decreased by approximately one-half[21].

Failure to control latent infection in alveolar macrophages because of HIV infection leads to systemic dissemination, with cryptococcal meningitis (CM) being the most frequent manifestation. CM is a devastating infection associated with a high case fatality rate, primarily associated with advanced HIV disease (typically a CD4 T cell count < 100 cells/mm3) [55].

Symptoms of CM are nonspecific, including headache, fever, altered mentation, lethargy, memory loss. In contrast to bacterial meningitis, meningism is rare - occurring in about 20% of patients [79]. Cranial neuropathies and seizures may be present, either due to raised intracranial pressure (present in up to 70% of patients[80]) or mass lesions. Cryptococcomas, a parenchymal granuloma caused by cryptococcal organisms, are more common in immunocompetent host than in patients with HIV, and C. *gattii* is usually the causative pathogen[81]. Disease onset is variable, but the burden of fungal organisms is usually high in severely immunocompromised and consequently patients may have a shorter onset of signs and symptoms and higher intracranial pressures, compared to immunocompetent hosts[82].

The presentation of pulmonary cryptococcosis in patients with HIV is more acute and severe than in other hosts. Manifestations are non-specific, with fever being the most common symptom, followed by cough, dyspnoea, and headache. Dissemination from the lungs to the CNS occurs in 65 to 94 percent of cases of HIV-associated pulmonary cryptococcosis. [83,84]

Cryptococcal immune reconstitution inflammatory syndrome (IRIS), provoked by restoration of host immunity after initiation of ART, has emerged as a major cause of morbidity and mortality with HIV-associated CM [85]. IRIS mimics a worsening cryptococcal infection and may present as lymphadenitis, cellulitis, aseptic meningitis, cerebral mass lesions, hydrocephalus, or pulmonary nodules[86]. There are no reliable specific diagnostic tests for IRIS, turning its diagnosis and posterior management into a clinical challenge.

Cryptococcal infection is responsible for up to 7% of the IFIs in SOT recipients, – lagging behind Aspergillus and Candida[74] – showing a higher incidence in heart and kidney transplant recipients[87]

. Infection occurs mostly >18 months after transplantation[74,88], although it can arise within the first 30 days if it occurs as donor-derived infection through the transplanted organ[89]. CNS is the most common site of infection, but the proportion of patients with pulmonary involvement is higher than in HIV patients [74,88]. Acute respiratory distress syndrome is more common in this group of immunocompromised as well[89]. Calcineurin inhibitors appear to be associated with a decreased likelihood of central CNS involvement but are associated with an increased likelihood of skin, soft tissue and bone involvement[90]. Skin involvement is also common in SOT recipients (seen between 10-18% of patients [91,92]). Cellulitis is an increased recognized presentation among these patients and may also be a manifestation of IRIS[93]. IRIS develops in about 5–11% of the SOT recipients about 4–6 weeks after antifungal therapy is started [94]. IRIS is associated with increased risk of allograft failure[95].

In contrast, cryptococcal disease appears to be distinctly unusual in HSCT recipients, more so in allogeneic transplants. The reason for this discrepancy is not precisely understood, by thymic regeneration (rendering T cells more effective against *Cryptococcus* spp.) and early posttransplant use of fluconazole are plausible explanations[96].

The incidence of cryptococcosis in cancer appears to be similar to most recent data in SOT recipients - with a 1-year incidence of 0.2%[97] Most cases occur in patients with hematological malignancies, particularly lymphoma[21] – this may be explained due to a combination of cancer-related immune alteration and specific T-cell depleting agents used to treat these cancers. Incidence is much lower among patients with solid malignancies. CNS involvement was more common in hematologic malignancy, while patients with solid malignancies were more likely to have any pulmonary involvement[97].

Notably, mortality from cryptococcal infection is higher among non-HIV, non-SOT immunocompromised hosts, probably due to the delayed diagnosis in this population.

Disseminated cryptococcosis, although rare, is also seen are among hosts with mild immune impairment, such as those under corticosteroid therapy and in those with diabetes mellitus[21]. A few cases have been described with patients with autoimmune diseases, such as systemic erythematosus lupus[98]. Patients receiving monoclonal TNF-a inhibitor therapy are also at risk for cryptococcosis, especially pulmonary cryptococcosis.[99]

4. Protozoaria

Protozoa are among the most important pathogens that can cause infections in immunocompromised hosts. These microorganisms particularly infect individuals with impaired cellular immunity, such as those with hematological neoplasia, renal or heart transplant patients, patients using high doses of corticosteroids, and patients with acquired immunodeficiency syndrome[100].

Immune compromise can modify the severity and manifestation of some parasitic infections. More widespread use of newer immunosuppressive therapies, the growing population of individuals with immunocompromised states as well as the prolonged survival of these patients have altered the pattern of parasitic infection.

Various serological, parasitological, histological, and molecular methods for the diagnosis of these infections are currently available and early institution of specific therapy for each of these organisms is a basic measure to reduce the morbidity and mortality associated with these infections.

The protozoa that most frequently cause disease in immunocompromised patients are *Toxoplasma gondii*, *Trypanosoma cruzi*, different Leishmania species, *Cryptosporidium parvum* and Isospora; the first two species cause severe acute meningoencephalitis and acute myocarditis, Leishmania sp. causes mucocutaneous or visceral disease, and Cryptosporidium and Isospora can lead to chronic diarrhea with hepatobiliary involvement[101].

In immunocompetent individuals, infections with Toxoplasma, Cryptosporidium, and Isospora usually have a subclinical presentation and are self-limited[100–102]. In immunocompromised individuals, opportunistic protozoans result in more severe disease[101,103]. Most studies describing the impact of opportunistic protozoans in immunocompromised hosts have been limited to patients with HIV[100,103].

However, the demographics of immunocompromised individuals are changing with new indications for immunosuppressive treatments, broader organ transplant criteria, and increasing life expectancy for people with chronic diseases[100].Some studies show that solid organ transplantation and hematologic malignancies have become the most common underlying conditions for patients with toxoplasmosis and cryptosporidiosis.

The data available upon protozoan infections in non-HIV immunocompromised patients is scarce, not only due to the geographic distribution of the agents but also the rare use of severe immunosuppression in endemic areas. The literature determines the same course of treatment for both immunocompetent and

immunosuppressed patients, suggesting different lengths of treatment in cases of immunosuppression, being the severity of affection of humoral and cellular immunity the determining factor[104].
Also, there is no unequivocal data upon the outcome of these patients, which is a limiting factor for the analysis of the subgroups of immunosuppressed patients (HIV vs non-HIV).

Cryptosporidium

In humans *Cryptosporidium parvum* and *Cryptosporidium hominis* are the most common species described. Infective oocysts are transmitted by fecal–oral contamination of food or water and occasionally by inhalation.
Epidemics have been associated with contaminated public water reserves, as well as fruits and vegetables washed with contaminated water. These organisms cause a self-limited moderate gastroenteritis in the immunocompetent host. In patients with HIV this organism can be responsible for severe enteritis. The range of gastrointestinal symptoms can manifest as a similar syndrome in patients with a wide spectrum of immune dysfunction. Susceptible patients include neutropenic hosts, hematopoietic and solid organ transplant recipients, and individuals with primary immunoglobulin deficiencies[105]. In these patients, infection with Cryptosporidium spp. is associated with prolonged severe gastrointestinal involvement. The relative absence of effective therapy for this pathogen increases its impact[106].

Toxoplasmosis

Toxoplasma gondii is a ubiquitous, obligate intracellular coccidian protozoan parasite of humans and other warm-blooded animals. Infections are transmitted by the ingestion of tissue cysts in meat, oocysts contaminating food or water, transplantation of infected organs, or accidental inoculation. This parasite has a particular tropism for the brain, heart, lungs, pericardium, and lymphoid tissues.
The persistence of Toxoplasma cysts in host tissues may contribute to maintenance of immunity against reinfection; however, their presence comprises a risk for reactivation of infection in immunocompromised patients. In these patients the main issue is the failure to generate a specific antibody response to acute infection, or this response will be delayed[107].
In HIV negative patients, most reported cases occur in those with hematopoietic malignancies during chemotherapy (especially those under corticosteroids), typically resulting from the reactivation of latent infection in the absence of a limiting immune response, also in organ and hematopoietic transplant recipients generally due to dissemination from the transplanted organ.
There is also a case report that describes the reactivation of cerebral toxoplasmosis in a patient with rheumatoid arthritis when humanized monoclonal anti-TNF-α (tumor necrosis factor-alpha) antibody (infliximab) was added to an existing immunosuppressive regimen[108].

Strongyloidiasis

Strongyloides stercoralis is an intestinal nematode found worldwide in moist soil contaminated by human feces[100,103]. Occupational exposure to contaminated feces can result in transmission of this disease.
Uniquely, *S. stercoralis* has an autoinfective cycle that allows infection to persist in the host indefinitely without the need for an external environment. In the immunocompetent host, this nematode can cause a chronic, and occasionally, life-long parasitosis[102].During chronic uncomplicated infections and disseminated hyperinfections, *S. stercoralis* filariform larvae may migrate to the skin, causing most commonly a migratory, pruritic, raised, linear rash called 'creeping eruption' or 'larva currens' and crops of urticarial eruptions.
In the development cycle of *S. stercoralis* within the human body the transformation of rhabditiform larvae into invasive filariform larvae in the gut is referred to as an autoinfectious cycle.
Corticosteroids may reduce local inflammation, thus impairing the ability of the gut to contain the parasites. With increased numbers of larvae completing the autoinfection cycle, large numbers of worms can enter the systemic circulation producing a hyperinfection syndrome associated with sepsis or meningitis with enteric organisms causing significant morbidity and mortality in immunocompromised patients. Glucocorticoid treatment and human T-lymphotropic virus type 1 (HTLV-1) infection are the two conditions most specifically associated with triggering hyperinfection.
Disseminated infection is characterized by massive multiplication of larvae and has been reported in people with a broad spectrum of immune defects, specially
individuals with hematopoietic malignancies or connective tissue disease being treated with immunosuppressive therapies and hosts with congenital or acquired hypogammaglobulinaemia.

Patients on corticosteroid therapy, hepatic and renal transplant recipients, patients with renal failure, systemic lupus erythematosus, asthma, chronic dermatosis, chronic infections (lepromatous leprosy, tuberculoid leprosy, and tuberculosis) as well as those with neoplastic conditions (lymphoma, leukaemia, and solid tumors), protein-calorie malnutrition, chronic alcoholism, AIDS and achlorhydria, are at higher risk for strongyloidiasis. Eosinophilia is frequently absent in disseminated infections and in patients receiving corticosteroids

Control strategies to prevent transmission and complications of this parasitic disease need to be reinforced in immunosuppressed patients; therefore, screening tests for strongyloidiasis are recommended in endemic regions before immunosuppression begins.

Leishmania

Leishmania includes a broad genus of flagellate protozoa with a worldwide distribution. In highly endemic areas, more than 30% of the inhabitants may have asymptomatic infections[102,107].

Autoimmune diseases are relatively more prevalent in developed countries than in developing countries, and immunosuppressors, especially immunobiologics, are expensive and consequently may not be widely available in developing countries accounting for the low number of case reports of leishmania in immunosuppressed patients.

Leishmaniasis has been recognized in a broad spectrum of both normal and immunocompromised individuals. Cutaneous leishmaniasis is characterized by the development of cutaneous papules that evolve into nodules that ulcerate. Healing leads to the production of depressed scars. Local inflammation is lymphocytic and granulomatous, with necrosis of the skin occurring early. In the mucocutaneous form of the disease, organisms spread via the bloodstream or lymphatics to the mucosal surfaces of the nose, mouth, pharynx, and larynx. In visceral leishmaniasis, a chronic, and if untreated, highly lethal disease, infected macrophages from the skin serve as a reservoir for organisms that infect spleen, lymph nodes, liver, bone marrow, and intestinal mucosa[102,107].This infection causes hyperplasia of focal lymphoid tissue with granulomata. Ulceration of mucosal surfaces may occur. Parasitization of macrophages and Kupffer cells results in enlargement of the liver and spleen. Recovery from leishmaniasis appears to be followed by a long-lasting immunity, and in immunocompetent persons, second infection is rare. There is nearly uniform detection of antibodies against a broad range of Leishmania antigens in immunocompetent individuals and in non-AIDS immunocompromised patients with visceral disease. In addition to AIDS, underlying disorders that predispose to visceral leishmaniasis include lymphoreticular neoplasia, renal transplantation, protein-calorie malnutrition, systemic lupus erythematosus, and corticosteroid therapy. In endemic areas malnutrition is probably the most important immunosuppressive mechanism predisposing to severe visceral leishmaniasis. In solid organ transplant recipients, pulse-dose steroids, antilymphocyte antibodies, and intensified immune suppression may accelerate disease.[115]

The impact of immunosuppression on the natural progression of leishmaniasis is uncertain, studies suggest that following infection, Leishmania amastigotes remain viable, virulent, and can induce progressive disease under conditions of immunosuppression.

However reinstituting immunosuppression after curing leishmaniasis does not seem to increase the risk of reactivation. There is no specific consensus regarding the management of leishmaniasis in immunosuppressed patients, although vector control is essential[107].

Cystoisospora

Cystoisospora belli (formerly known as *Isospora belli*) is a coccidian, unicellular protozoan parasite that primarily infects the intestinal epithelium. *Cystoisospora belli* is found worldwide, but infections are more common in tropical and subtropical areas[102,103].

Gastrointestinal infections secondary to *Cystoisospora* are uncommon in developed countries but can be acquired by travelers to endemic countries. *Cystoisospora* can also be a copathogen with other enteric organisms, such as *Enterocytozoon bieneusi*, in geographic regions with high levels of fecal contamination of surface water.

In contrast, a history of treatment or prophylaxis with trimethoprim-sulfamethoxazole for Pneumocystis infection in an HIV-infected patient is associated with a decreased risk of developing cystoisosporiasis.

Cystoisospora has also been reported in patients with other cellular immunodeficiencies, such as human T-lymphotropic type 1 infection lymphoblastic leukemia, adult T-cell leukemia, hypogammaglobulinemia, Hodgkin's disease, and non-Hodgkin lymphoma[102]. It has also been reported in patients taking immunomodulators such as TNF-inhibitors[102]. Infections are acquired by the ingestion of sporulated oocysts from food or water

contaminated with human feces. After ingestion, the parasite invades enterocytes within the small intestine.
Sexual transmission via oral-anal contact and person-to-person transmission may be possible but do not appear to be common.
The major manifestation of *Cystoisospora* infection is a watery, non-bloody diarrheal illness of sudden onset. Commonly seen associated symptoms include malaise, anorexia, abdominal pain, headache, vomiting, and dehydration. Fever may also be present. *Cystoisospora* infection has also been associated with acalculous cholecystitis in immunocompetent and immunodeficient patients and with reactive arthritis in the HIV-infected host[101,103].
The clinical course of infection varies with the immune status of the host. While symptoms are usually self-limited in the immunocompetent host and diarrhea usually resolves after 7 to 10 days, cystoisosporiasis is often a chronic, debilitating diarrheal infection in immunocompromised hosts, who may relapse without long-term antibiotic suppression. In patients with AIDS, untreated infection is associated with protracted clinical course with severe diarrhea and weight loss, clinically indistinguishable from cryptosporidiosis. The secretory stool output can also lead to severe volume loss, renal insufficiency, and electrolyte disturbances.
Other immunocompromised patients can also present with severe disease

5. Others

Cytomegalovirus

Cytomegalovirus (CMV) is a relative ubiquitous human herpesvirus[109] , usually contracted at an early age[1], causing a mononucleosis-like syndrome[21]. Following primary infection, CMV can remain latent in the immunocompetent[1,109,110]. In the immunocompromised it can cause disease by reactivation, reinfection or by primary infection, with significant morbidity and mortality[1,109]. It can cause disease in several organs: retinitis, pneumonitis, colitis, or disseminated disease[1,21], with gastrointestinal being the most common in immunocompromised patients[110]. Disease presentation varies according to different types of immunodeficiency[1,21]. Retinitis is the most common presentation in patients with HIV, while in cancer and transplantation pneumonitis and fever is more common, and other causes disseminated disease[1,21,109].
Although disease presentation varies, clinical course is often similar, with insidious presentation when compared to immunocompetent[1,110] and later diagnosis, which requires identification of CMV DNA in a sample[1]. Treatment is with ganciclovir, prophylaxis following an infection (secondary) can be with ganciclovir or valganciclovir and primary prophylaxis with valancyclovir[1]. However, primary prophylaxis is not indicated in HIV patients, and slowly being replaced by early routine detection of CMV DNA in blood[21].
Outcomes are better for HIV patients, although relapse is common[21]. In transplanted patients mortality remains high, and graft rejection a major issue[21]. Both in HIV patients and in immunocompromised patients by other causes "indirect effects" of CMV serostatus have been reported, correlating to higher mortality[109].

Kaposi syndrome

Kaposi's sarcoma (KS) is caused by infection by the human herpesvirus-8 (HHV-8) which is an oncogenic virus. When alone, the HHV-8 infection is not sufficient for the development and progression of the KS, requiring an immune deficiency state[111,112].
HIV infection dramatically changes the prevalence of KS, which was a rare disease before its epidemic[113].
KS is classified as: classic – typically in elderly men of the Mediterranean area or Jewish ancestry; endemic or African KS – common in the sub-Saharan Africa, affecting young adults and children; epidemic or AIDS-associated KS; iatrogenic KS and, KS that has been reported in men who have sex with men (MSM) without HIV infection[112–115].
The HHV-8 can be transmitted through the saliva, sexual contact, perinatal infection, hematogenous routes (like blood transfusion) or by reactivation of a latent infection in an organ donor, which can happen in iatrogenic KS[112,113,116]. It happens to be more frequent in men than in women (2.5:1 ratio), in MSM (with or without HIV) and in HIV patients[112,113,116]. The risk factors for HHV-8 transmission are increased age, sexual activity with men, increased number of sexual contacts, medical history of sexually transmitted diseases, coinfection with other virus (like hepatitis B and herpes simplex virus) and immunodeficiency[116,117].
The clinical manifestations may be different depending on the distribution and severity according to the variants of KS, with the most severe manifestations appearing in the epidemic and iatrogenic variants. Lesions could be located at the skin, mucosa, lymph nodes and viscera (for example:

lung, liver or gastrointestinal involvement). However, the cutaneous lesions are transversal to all, presenting as multiple pigmented (purple, red, dark brown) and painless macules, papules or nodules, that do not lose color with pressure. They can ulcerate and bleed and be associated with pain and edema and more frequently found in the lower limbs[114,115,118]. Lymphedema occurs in 20% of KS patients and can cause lots of pain and have a major impact on the quality of life[114]. When there is lung involvement, patients usually present with cough, dyspnea and hemoptysis, and pulmonary lesions appear like pleural effusion or an infiltrate[115,119]. Gastrointestinal lesions are often asymptomatic but can also ulcerate, bleed and cause obstruction[115]. Visceral lesions are more severe and possibly life-threatening in the epidemic and iatrogenic KS forms, typical of a later manifestation of KS and unusual as an isolated site for initial presentation.

Until now, there is not a valid staging classification for the KS, the only one that exists just applies to the epidemic or AIDS-associated KS. So, management and treatment should be based on the extension and severity of the disease: local, locally aggressive and disseminated disease[115]. Localized skin lesions can be treated with topical or intralesional agents (topical 9-cis-retinoid acid or intralesional bleomycin) and with radiotherapy or surgical excision. Systemic treatment lies on chemotherapy reserved for the patients who are still symptomatic after other treatments and for the ones who have disseminated disease with or without visceral involvement[114].

The emergence of ART led to a substantial decline in its incidence, however, KS is still more frequent in PLWH[112,113].

Cases of KS are more frequent in HIV-1 infection compared to HIV-2 infection[115] and MSM typically diagnosed at an early age – 40 years old for PLWH versus 60 years old for the general population[112]. In HIV-patients viral load and the CD4 count appear to be important and independent factors for the development of KS[112]. Other risk factors are male gender, age and not receiving ART[114].

Clinical course in HIV-patients is variable and can range from asymptomatic disease to life-threatening assuming rapidly progressive and disseminated forms.

The first line treatment is the initiation of ART as soon as possible. This therapeutic approach reduced the risk of developing KS and also prolonged survival in KS patients treated with chemotherapy[112,118].

Prognosis of epidemic KS depends on: increased age (≥50 years old), low CD4 cells counts, the time of appearance, detectable HHV-8 viraemia, systemic symptoms and having other HIV-related illnesses[118]. Mortality in these patients has decreased with the advent of ART and survival ranges from 71-94%[118].

KS that appears in other immunosuppressed states is named iatrogenic KS. It was first described in kidney transplant recipients, but also occurs in other organ-transplanted recipients (OTR) and in patients with chronic immunosuppression for autoimmune disorders[120] and those on immunosuppressive therapy[112,114–116,119]. The drugs most frequently associated with the development of iatrogenic KS are corticosteroids, cyclosporine, azathioprine and rituximab[111,116,119]. However, only corticosteroids are associated with an increased risk of KS[117,121].

The incidence of KS is much higher in these patients than in the general population mainly because humoral and cellular responses are affected by immunosuppressive agents that weaken the immunological surveillance system, allowing reactivation of a latent HHV-8 infection[111]. Infection in OTR can also be caused by an infected donor, although it is less frequent[111]. Iatrogenic KS is the most common HHV-8 related disease and neoplasm after solid organ transplantation[122].

The timing for the development of KS in OTR goes from 13 months to 3 years, with risk achieving peak at 1-2 years after transplantation and decreasing afterwards, probably due optimized doses of immunosuppresion[112,117–119]. The risk factors are male sex, higher age at transplant, number of HLA-B locus mismatch and more aggressive immunosuppressive regiment[112,118]. Related to the transplant itself, lung recipients are the ones at a higher risk[112], probably related with the immunosuppressive agents used.

Another crucial factor is that more HIV-positive recipients are being transplanted and more HIV-positive donor organs are being recovered, which can modify the epidemiology of KS[122].

Clinical manifestations are typically cutaneous, mucosal lesions are presented with more severe signs and symptoms but also with more frequent visceral involvement – 10% of OTR[122]. Gastrointestinal and lymph node locations are the most common visceral involvements and are much more common in heart, lung, or liver recipients – than in kidney recipients[114,119,122].

In these patients, treatment consists in reducing immunosuppression, modifying immunosuppressive agents and – in the most severe cases where this strategy fails – chemotherapy[114,123]. Reducing immunosuppression can result in complete remission of KS in 30 to 50% of the cases, however must be performed cautiously to avoid graft rejection[122,123].

Regarding mortality, it is lower than previously described[118], reaching about 60% in OTR[122]. However, there are case series that describe renal graft survival in KS kidney OTR of 85% and 75% at 5 and 10 years, like overall survival in kidney OTR[114,118].

HPV

Human Papillomavirus (HPV) is the most common sexually transmitted disease worldwide and 50 to 80% of sexually active men and women will be infected at least once in a lifetime, without necessary developing any disease[124–126].

HPV is transmitted by skin-to-skin or mucosa-to-mucosa contact and enters the body by mucosal or cutaneous trauma which promotes entrance of HPV in the epithelial cells[127]. Based on this way of transmission, HPV is classified into cutaneous and mucosal types. HPV infects undifferentiated deeper layers basal epithelial cells with mitotic capacity by which HPV maintains cell division and guarantee its multiplication and persistence[125] and epithelial transition zones susceptible to carcinogenesis[128].

There are a lot of risk factors already known for HPV infection such as: early sex debut, multiple sexual partners, long-term inflammation caused by recurrent genital infections, long-term use of hormonal contraceptives, hormonal changes during pregnancy, cervical trauma during labor, failure to undergo HPV vaccination, HIV infection and not being circumcised[124,129].

HPV could be classified by its oncogenic potential in high-risk (HRHPV), probably high-risk and low-risk (LRHPV)[124,125,127,130]. HPV 16 and 18 are the most common oncogenic types and associated with the high risk of progression to cancer - causing about 70% of all invasive cervical cancer worldwide[124,127,131].

The most common manifestation of HPV infections are genital warts, with LRHPV 6 and 11 counting for 90% of the cases, with 11 to 12 months of median time in men and 5 to 6 months in women, between infection and development of these lesions[125,131]. The incidence and prevalence are similar in women and men with peaks between 20 and 29 years old[125]. Genital warts are considered as one of the major risk factors for the development of anal and oral cancers[125]. Warts are usually asymptomatic flat, papular or pedunculated growths on the mucosa or epithelium but can cause pain, itching or dyspareunia[132].

There are many risk factors to progression to high-grade lesions and cancer: persistence of HPV infection, infection with oncogenic types, age over 30 years, infection with multiple HPV types, human immunodeficiency virus (HIV) infection, long-term exposure to hormonal contraceptives, immunosuppression, and tobacco use[127,129]. Treatment is directed for the HPV-lesion or HPV-related cancer[132]. Global annual mortality related to HPV is 8.2%[129] and morbidity is still high related to many regions of the world having scarce resources, vaccination coverage being unavailable or incomplete and nonexistence or unfollowed screening programs[125].

HIV was shown to influence the natural history of HPV types[133] and has been associated as a major cofactor with HPV to induce cervical cancer, as HIV-patients are at a higher risk of persistent HPV infection[126], through the direct effect of HIV and immunosuppression caused by active HIV infection[128]. Lower CD4 cell counts have a direct relationship with HPV infection, pre-cancerous lesions, and risk of anogenital cancers[132]. HIV-positive patients also present a higher prevalence - 44.8% to 91.2% - and persistence of HRHPV[134,135]. Even with emergence of ART incidence of HPV-related cancers remained elevated in PLWH[132].

Clinical manifestations are the same as in the general population. However, anogenital warts, AIN and CIN occur more frequently in PLWH, with prevalence of CIN estimated at about 20-40%[134]. Cervical cancer in PLWH is more aggressive and less responsive to standard therapies, resulting in a poor prognosis[126] and has a high risk of relapse and higher mortality[132]. Survival after treatment of anal and oropharyngeal cancer is similar in PLWH and in the general population[132]. Vaccination in HIV-patients has been shown to be safe and provide immunogenic benefits[126,134].

Immunosuppression causes a reactivation of latent HPV infection with a decrease in viral clearance and consequently persistence of HPV[135]. The incidence of HPV infections is higher among immunosuppressed patients such as OTR and autoimmune diseases[134,135]. Immunosuppression is also an independent risk factor for the development of HPV-related neoplasms because it decreases the capacity to eradicate HPV and enables HPV replication in infected cells[136]. This risk reaches 20% after 10 years of immunosuppression – three to five times higher than the general population[134] and is linked to the dose and duration of immunosuppressive therapies[134].

Clinical manifestations are the same as in the general population, although with more severe forms. In OTR prevalence of warts corresponds to the duration of immunosuppressive therapy, increasing to 50-92% in 4-5 years after transplantation[136]. This population is

also at an increased risk of developing AIN and anal cancer with reports of approximately 122-fold risk[134] and head and neck cancers, with prevalence 3-times higher[136].

Treatment options are the same as in the general population, but immunosuppressed patients are more refractory to treatment and in solid OTR the therapeutic treatment options are influenced by the need to preserve the graft.[134]. Reduction in immunosuppression therapy can be considered, in the presence of recurrent or refractory disease treatment or the switch from calcineurin inhibitors to mTOR[136].

Conclusion

In this paper, we attempted to summarize the most frequent opportunistic infections differences between patients immunosuppressed by HIV and other causes. Indeed, patients immunocompromised from cancer, chemotherapy and immunotherapy, autoimmune diseases and their treatment, organ transplant recipients and other immunodeficiencies, have very different clinical courses of OI than HIV, as we have explored. Often the immune dysfunction differences, atypical clinical course, may result in worser outcomes.

Over the last decade we have observed improvements in management of both HIV and its OI, through early detection and treatment but also prevention through early introduction of ART and prophylaxis. However, we have not witnessed that in other forms of immunocompromise and still a lot remains to be known regarding these patients, which are now overgrowing due to novel immunotherapies and evolution in transplantation.

Disclosures

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