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TITLE
"FUNGAL INFECTION IN IMMUNOCOMPROMISED PATIENTS-A META ANALYSIS"

SUBMITTED

BY

SURAJ KUMAR YADAV

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"FUNGAL INFECTION IN IMMUNOCOMPROMISED PATIENTS-A META ANALYSIS"

DISSERTATION

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In partial fulfilment of the need for the award of degree of

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In

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BY: -SURAJ KUMAR YADAV

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This is to certify that research work entitled "Fungal infection in immunocompromised patients - A meta analysis" submitted by **Suraj Kumar Yadav, Dr.Tasneem Siddiqui, Dr.Ausaf Ahmad** for ethical approval before the Institutional Ethics Committee IIMS&R.

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DEDICATED TO

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INTRODUCTION

INTRODUCTION

In the ultimate decades, the frequency of hospitalacquired fungal infections has risen. New technology and therapies, together with bone marrow or solid-organ transplants and chemotherapeutic marketers have come to be not unusualplace at many clinical centers, ensuing in lots of immunocompromised individuals. Invasive tracking equipment, parenteral nourishment, broad-spectrum antibacterial medicines, and assisted ventilation, in addition to remedy in professional units, have helped to deal with sufferers with formerly deadly or lethal situations and feature given existence to preterm toddlers formerly taken into consideration to be nonviable. However, those achievements have ended in an growth withinside the quantity of extraordinarily sick, immunocompromised, hospitalized sufferers. In addition, the AIDS pandemic has brought to the growing quantity of immunocompromised people. These immunocompromised sufferers are exceptionally liable to nosocomial infections because of organisms together with fungi that had been formerly taken into consideration to be of low virulence or “nonpathogenic”. Fungal infections in those sufferers are regularly intense, unexpectedly progressive, and hard to diagnose or deal with. Fungi are eukaryotic cells; they may be greater complicated than bacteria. A thorough appreciation and expertise of fungal infections, healing modalities, are wanted amongst clinicians and microbiologists to offer higher affected person care [1]. Systemic fungal contamination is the main purpose of dying in sufferers with intense neutropenia. Prophylaxis of systemic fungal infections at some point of neutropenia after anticancer chemotherapy has been studied for plenty years. A preceding meta-evaluation confirmed that antifungal prophylaxis ended in considerable discounts in fungal contamination–associated mortality and invasive fungal contamination as compared with the manipulate group. In sufferers present process hematopoietic stem mobileular transplantation or with extended neutropenia, ordinary mortality became advanced with the aid of using antifungal prophylaxis. Fluconazole is extensively used to save you systemic fungal

contamination at some point of the remedy of hematologic malignancies. Fluconazole isn't always completely powerful in opposition to Candida aside from C albicans and isn't always powerful in opposition to Aspergillus, while itraconazole reportedly reveals hobby in opposition to Correspondence and reprint requests. These fungi. Another meta-evaluation confirmed a considerable discount in invasive fungal contamination with the aid of using the prophylactic use of itraconazole. A latest meta-evaluation of more than one randomized trials of fluconazole and itraconazole did not show any considerable distinction in mortality or the frequency of invasive fungal contamination. An extra randomized observe evaluating itraconazole and fluconazole can be wanted. In Japan, no randomized multicenter observe evaluating itraconazole and fluconazole has been published. It is likewise essential to decide whether or not there's any distinction among Japan and Western nations withinside the consequences of antifungal drugs, due to the fact the colonizing fungi can be different. Although the oral-answer shape of itraconazole has been advocated for prophylactic use to save you systemic fungal contamination, best the tablet shape is to be had in Japan; however, the tablet shape of itraconazole has an inherent hassle with aberrant absorption via the intestine. The prophylactic impact of the tablet shape ought to additionally be studied. We attempted to carry out a randomized, managed observe to analyze the noninferiority of itraconazole drugs as opposed to fluconazole drugs for systemic fungal contamination prophylaxis in sufferers receiving in depth chemotherapy for acute myeloid leukemia (AML) or high-danger myelodysplastic syndromes (MDS) [2]. Host-directed therapies (HDTs) intention to empower the host to correctly combat an contamination in place of without delay focused on the pathogen and had been proposed as an adjunctive remedy for infections because of antibiotic-resistant microbes, consisting of fungi. A promising goal for HDT improvement in opposition to IA is the autophagy-lysosomal degradative axis, collectively with its related pathways. In immunocompromised sufferers, circulating monocytes and tissueresident immune cells, as alveolar macrophages withinside the lungs, are the first – and every now and then best – line of protection in opposition to fungal invasionn. These expert phagocytes stumble on unique conserved pathogen related

molecular patterns (PAMPs) withinside the fungal mobileular wall via their sample popularity receptors (PRRs), upon which they internalize the conidia and coordinate the host antifungal response. Once internalized, conidia-containing vesicles can be centered with the aid of using autophagy-associated mechanisms to be degraded with the aid of using in the long run fusing them with lysosomes. Autophagy-associated mechanisms consist of selective autophagy and LC3-related phagocytosis (LAP), each recognized as effective protection mechanisms activated downstream of spore popularity in innate immune phagocytes at some point of fungal invasions. However, DHN-melanin, a essential issue of the A. fumigatus conidial mobileular-wall, impairs autophagy in macrophages and the following oxidative burst supposed to kill the germinating spores, possibly through intracellular calcium sequestration. Thus, loss of activation of the host autophagy equipment can be a restricting thing at some point of A. fumigatus infections, and consequently growing autophagic hobby is a capability healing method for treating IA [3].

The past two decades have witnessed an increase in the number of patients who are immunocompromised as a consequence of a primary or secondary immunodeficiency disorder or from the use of agents that depress one or more components of the immune system. Broadly defined, an immunocompromised host has an alteration in phagocytic, cellular, or humoral immunity that increases the risk of an infectious complication or an opportunistic process such as a lymphoproliferative disorder or cancer.1 Patients may also be immunocompromised if they have an alteration or breach of their skin or mucosal defense barriers that permits microorganisms to cause either a local or a systemic infection (e.g., from burns or indwelling catheters). Table 1 reviews several conditions with acquired immunosuppression and the alterations in host defense that increase the risk of infection.[4]

Invasive fungal infections (IFI) have significantly increased over the past years due to advances in medical care to the at-risk immunocompromised population . The number and heterogeneity of patients at risk have

increased, especially due to the wider use of intensive myelosuppressive and/or immunosuppressive agents in the treatment of haematological cancers (in particular in those with acute myeloid leukaemia and myelodysplastic syndromes), the growing number of patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) and the increasing aged population. In Europe, the number of stem cell transplantations almost doubled between 2000 and 2016 and at the same time, new at-risk populations were identified, as patients with severe influenza or chronic obstructive pulmonary disease . The IFI incidence is approximately 6 cases per 100,000 persons per year. Rates of IFI-related mortality in Europe depend on the pathogen, geographical location and underlying characteristics of the patients, with rates ranging from 38 to 80% for invasive aspergillosis. The most frequent filamentous fungi (moulds) isolated from IFI are Aspergillus spp., but Fusarium spp., Scedosporium spp. and fungi belonging to Mucorales order are increasingly seen. Invasive fungal infections caused by these fungi are a major cause of morbidity and mortality in patients with haematological malignancies [5].Invasive fungal infections (IFIs) are foremost causes of morbidity and mortality among the critically ill and immunosuppressed pediatric patients in intensive care units (ICU). IFIs are most commonly caused by Candida spp., Aspergillus spp., Cryptococcus spp., Histoplasma capsulatum, Coccidioide simmitis, Paracoccidioides spp., and Fusarium spp. A study among children with acute lymphoblastic leukemia (ALL) found that the prevalence of IFI was 9.7%. IFIs result from the defects in immune mechanisms among the immunosuppressed individuals and invasive procedures. The pathogen enters through the puncture sites of the skin, gastrointestinal tract lesion, indwelling catheters and is spread by the hematogenous route in different parts of the body. Immunodeficient children with malignancy, malnutrition, and prematurity were reported to be susceptible to develop IFIs. Prolonged use of antibiotics, corticosteroids, chemotherapy, invasive procedure, and longer duration of hospital stay were identified as the critical risk factors for IFIs. It was documented that IFIs were associated with higher mortality among children ranging from 23% to 48.2%. Candidemia is the leading IFI; with an incidence rate between 4.3 to 8.1 cases/10,000 admissions. Among IFIs, Candida species were

found to be responsible for 59.1% of infections among pediatric acute myeloid leukemia patients in Taiwan. In the gastrointestinal tract, commensal candida translocate, spread hematogenously, and colonize, resulting in deep-seated candidiasis. Globally the incidence of nosocomial candidiasis has increased in infants and children in tertiary care centers. A Turkish study found that the incidence of nosocomial candidemia ranged from 3.2 to 6.9 per 1000 admissions over nine years. In ICU settings, it was responsible for 10% to 42% of all bloodstream infections (BSIs) and the fourth most common BSI pathogen in children [6].

The amino acid sequence of human PCT was described in 1982 confirmed the significance of elevation of calcitonin precursors in patients with burn respiratory tract. The significance of PCT and the first publication about it`s role in identification of bacterial sepsis was in 1993. High concentrations of PCT have been found in the blood of the most of 79 children suspected with infections. In this group 19 patients with severe bacterial infections had high serum PCT concentrations. In many other publications the value of PCT was confirmed in patients with sepsis, SIRS and neoplastic diseases. There is only a few publications about the role of PCT in sepsis diagnose in HIV infected patients or among other diseases in patients with immunodeficiency [7].

Mucormycosis (also called zygomycosis) is a group of rare but infectious opportunistic fungal infection caused by fungus of the Mucorales order of the class Zygomycetes. Generally Mucor, Rhizopus, Absidia, and Cunninghamella genera are most often included in this order. Although “Mucormycosis" and "zygomycosis" are sometimes used interchangeably, however fungus under zygomycosis genera are not much pathogenic. Around 38 species out of 261 of order Mucorales are generally human infectious and related to vasotropic, mainly causing tissue infarctions. The mucormycosis spectrum ranges from cutaneous, rhinocerebral, and sinopulmonary to disseminate and frequently fatal infections, prominently in immunocompromised hosts. The Mucorales being ubiquitous in nature is predominant in the soil and in

decaying organic matter, such as leaves, compost piles or rotten wood. Mucormycosis is considered as the third most angioinvasive fungal infection following Candidiasis and Aspergillosis. It is a sudden and severely developed invasive fungal infection having diverse unexpecting factors that includes renal failure, lymphomas, leukemia, uncontrolled diabetes, malnutrition, immunosuppressive therapy, organ transplantation and AIDS malignancies. Further, because of the increasing cases of diabetes mellitus and cancer, the prevalence of occurrence of infection cause by mucormycosis is on peak. Diseases caused by the group of fungi have been classified by several authors into six forms namely rhino-orbital cerebral mucormycosis (ROCM), pulmonary, cutaneous, gastrointestinal, disseminated and uncommon sites based on the location of their occurrence. Among all, ROCM being the most commonly occurring one is caused also reported the involvement of Cunninghamella in the pulmonary or disseminated form, while Apophysomyces and Saksenaea were seen in the cutaneous type [8].

The introduction of polymerase chain reaction (PCR) technology in 1985 as a means to amplify nucleic acids has revolutionized clinical medicine. It has become an essential element in diagnosis of infections and malignant conditions and is an important tool in both forensic medicine and prenatal diagnosis. It is also essential for molecular biology research. From a difficult and time-consuming technology that relied on the visual interpretation of stained gels to detect the presence of amplification products, it has evolved into a simple and rapid, easy-to-use approach. It also provides the means to perform quantitative PCR, which uses precision optics and DNA-binding fluorescent dyes or fluorescent labels to monitor amplification in real-time. The PCR, which was developed by scientists at Cetus, involves the in vitro enzymatic synthesis of millions of copies of a specific DNA segment. The reaction is based on the annealing and extension of two oligonucleotide primers that flank the target region in duplex DNA; after denaturation of the DNA, each primer hybridizes to one of the two separated strands such that extension from each 3′ hydroxyl end is directed toward the other. The annealed primers are then extended on the template strand with a DNA

polymerase. These three steps (denaturation, primer binding, and DNA synthesis) represent a single PCR cycle. If the newly synthesized strand extends to or beyond the region complementary to the other primer, it can serve as a primer binding site and template for a subsequent primer extension reactions. Consequently, repeated cycles of denaturation, primer annealing, and primer extension result in the exponential accumulation of a discrete fragment whose termini are defined by the 5′ ends of the primers. The length of the products generated during the PCR is equal to the sum of the lengths of the two primers plus the distance in the target DNA between the primers. PCR can amplify double or single-stranded DNA, and with the reverse transcription of RNA into a cDNA copy, RNA can also serve as a target [9].

With the advent of highly active antiretroviral therapy (HAART) in 1996, patients infected with HIV are living longer and dying from illnesses other than AIDS. Liver disease due to chronic hepatitis C is now a leading cause of mortality among patients coinfected with HIV and hepatitis C virus (HCV) in the developed world. The prevalence of end-stage renal disease (ESRD) is also increasing among HIV-infected patients, for whom solid organ transplant (SOT) is the only therapeutic option and HIV infection is not a contraindication. Recent experience in North America and Europe indicates that 3- to 5-year survival in HCV/HIV-coinfected liver recipients is lower than that of HCV-monoinfected recipients. Conversely, 3- to 5-year survival of non-HCV-coinfected liver recipients and kidney recipients is similar to that of non-HIV-infected patients. Experience with heart, pancreas and lung transplantation in HIV-infected patients is very limited. The post-transplant period is complicated by the risk of infection and becomes even more problematic as a result of factors such as pharmacokinetic and pharmacodynamic interactions between drugs (antiretrovirals, immunosuppressors and antimicrobial agents), the increased rate of acute rejection, and HCV re-infection in HIV-infected liver recipients, which is the main cause of mortality. In this context, team learning curves could improve the prognosis of these patients[10]

Infectious complications remain a major obstacle in the successful treatment of patients with malignant

diseases. This part of the ESCMID guidelines focuses on the special need of this patient population with malignancies that had received chemotherapy or radiotherapy. Candida diseases played a pivotal role in the past in patients with malignancies. In an Italian study, patients with AML and ALL developed candidaemia at incidence rates of 2–3% and 4–5%, respectively. In one German hospital, candidaemia remains a disease with a high fatality rate. Studies report an overall mortality risk as high as 38% with an attributable mortality of 19%. Risk factors such as previous triazole exposure, age, high APACHEII scores, renal failure and neutropenia contribute to these high mortality rates. A change in the Candida species epidemiology also needs special attention since fluconazole sensitive C. albicans is not the sole cause of disease. Therefore, Candida diseases deserve special attention in this high-risk population. We included recommendations for haematopoietic stem cell transplant recipients, which is an integral part of the guideline.

This guideline is divided into four parts: prophylaxis, pre-emptive/empirical therapy strategies, targeted treatment and specific situations in patients with malignancies [11].

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

In Study By Alba Luz Rodriguez et al, A total of 867 articles were identified, of which 65 studies were included in the SR, and the data of 18 were summarized in the metaanalysis. The flowchart for the selection and exclusion ostudies is presented in Figure 1. Characteristics of the included studies. An overview of the studies is provided in Supplementary Table S1, showing a summary of the selected studies, including authors, year of publication, country, RFs for infection, design, and methodologic quality according to the NOS and AMSTAR tools, and the JBI evidence levels. The distribution showed a recent downward trend: 38 (58.5%) of the studies were published between 2009 and 2012, whereas 27 (41.5%) were published between 2013 and 2016. Most of the studies had an observational design: there were 40 (61.5%) prospectiveretrospective cohort studies, 14 (21.6%) were case-control studies, 5 (7.7%) were cross-sectional studies, 5 (7.7%) were SRs, and 1 (1.5%) was an RCT.

In Study By Stephani R. Earnshaw at al, Out of 1,000 at-risk patients, 41 IFIs were estimated to occur; 109 IFIs would have occurred without prophylaxis. Use of a DD strategy was estimated to identify and treat 33 of those cases, whereas ET would have likely identified 10 cases. However, 57 patients would have been treated via ET. Although increased costs occurred due to diagnostic testing for the DD strategy, per-patient costs related to antifungal agent use were higher in patients receiving ET and average patient total costs were reduced (£20,230 for DD versus £21,351 for ET). Days in the intensive care unit (ICU) and general ward accounted for . 40% of the total costs and . 58% of the cost reduction came from reduced antifungal costs. Given that survival among patients was similar (90.32% for DD and 89.50% for ET), a DD strategy was a cost-saving (less costly and more effective at -£136,787 per death avoided) strategy. Base-case results are presented in Table 1. Sensitivity analysis. One-way sensitivity analysis (Fig. 1) found the difference in total costs were most sensitive to changes in the relative increase in the number of patients treated

empirically versus the DD strategy, such that ET became less costly when fewer patients were treated unnecessarily. The cost of treating via ET approached the cost of treating via a DD strategy when ET causes treatment of less than 1.5 times more patients. Results were also sensitive to changes in the day at which switching occurs due to nonresponse to liposomal amphotericin B when treating empirically. In this situation, the sooner patients treated with ET could switch to caspofungin, the lower an ET patient's costs became because patients were switched to a cheaper drug. This led us to perform a scenario analysis in which we compared the DD strategy with an ET strategy in which all patients were treated with caspofungin as a first-line antifungal agent. Although the cost of first-line caspofungin treatment was lower, ET with caspofungin.

In Study By Found K. ABBED at al, The current study focused on the ability of clinical yeast isolates from hospital-acquired fungal infections to produce hydrolytic enzymes, biofilm, and determine drug susceptibility patterns so that all of these factors contribute to the establishment and enhancement of yeast pathogenicity, as well as increased resistance to antifungal treatment by various mechanisms, including preventing drugs from reaching fungal cells through biofilm formation. Acknowledgement The authors gratefully acknowledge the faculty and technical staffs of the clinical and physiological laboratory, Department of biology, College of Science, University of Basrah, Basrah, Iraq for support.

In Study By Yoshikaju Ito at al, In patients with hematologic malignancies, neutropenia is commonly observed after chemotherapy. The most common cause of fever during neutropenia is considered to be infection, although the rate of positive bacterial cultures is low. Klastersky proposed the concept of febrile neutropenia, a persistent fever of unknown origin but strongly suggesting infectious disease during neutropenia [15]. The empiric use of antibiotics is recommended in cases with febrile neutropenia before the results of microbiological studies are obtained. Bacteria are a major pathogen in such cases, but fungi should also be considered when febrile neutropenia persists after the administration of antibacterial agents.

Once systemic fungal infection has occurred during neutropenia,

it is difficult to achieve success with antifungal therapy. Systemic fungal infection in hematologic malignancies is generally linked to a poor prognosis; therefore, the empiric use of antifungal agents is also necessary in neutropenic patients when fever persists despite the use of antibiotics [16]. In addition to empiric therapy for neutropenic patients with persistent fever, the prophylactic use of antifungal drugs during and after chemotherapy has been studied [1,2,5,6]. The routine use of antifungal prophylaxis for all neutropenic patients is currently controversial [1,2]. A metaanalysis by Bow et al showed that antifungal prophylaxis is effective for reducing the frequency of invasive or superficial fungal infection and fungal infection–related mortality [1]. However, the overall mortality did not improve significantly. In a subset analysis, patients with prolonged neutropenia or who had undergone allogeneic stem cell transplantationshowed a significant decrease in overall mortality after receiving antifungal drugs, compared with patients who received no prophylactic treatment with antifungals [1]. Among antifungal drugs, fluconazole has been widely used as prophylaxis and is significantly effective in improving overall mortality for patients who undergo allogeneic stem cell transplantation. Another meta-analysis was performed by Kanda et al to clarify the prophylactic effect of fluconazole [2]. They reported that it decreased the overall mortality in patients with a risk of greater than 15% for developing systemic fungal infection, whereas no significant effect was seen in low-risk patients [2]. This result suggests that antifungal prophylaxis with fluconazole should be considered for patients with a high risk for fungal infection.

In Study By G Forn-Cuni at al, Infections caused by azole-resistant Aspergillus pose a lifethreatening challenge to the immunocompromised population [50]. The ubiquitous use of azoles, not only for human therapy but also for food production and environment preservation, is driving a worldwide rise of antifungal resistance to this class of drugs, rendering current first-line clinical treatment options ineffective [6,51]. There is therefore an increasing need to diversify our antifungal treatments [17]. In addition to the discovery

and application of new and improved antifungals, HDTs offer a potential solution as adjunctive or standalone treatment to drug-resistant infections. As exemplified here, the zebrafish embryo IA model provides a useful platform to study both the host-pathogen interaction in detail using intravital microscopy and to preclinically test the effect of drugs on a population level. We observed a high degree of variability in the immune response between infections, even with similar number of phagocytes in the infection foci and comparable infection loads. We believe that this heterogeneity (both in the host and the fungal cells) creates stochastic environments that lead to a dynamic relationship between host and pathogen, which mimics the individual variation seen in human disease and is therefore complementary to in vitro studies using homogenous cell types. Despite this variability between individuals, population-level results, such as the increased susceptibility after treatment with corticosteroids as dexamethasone, are consistent with previous reports both in zebrafish and in humans, showing the robustness of the model for drug discovery [28,52]. A notable exception was the treatment with the Ppp3/calcineurin inhibitor FK506, in which we could not reproduce a higher susceptibility at concentrations that did not affect the normal embryo development [29,53]. These differences may be due to fungal or zebrafish strains used, which are known to affect infection dynamics [26,40,54,55]. We did, however, find hypersusceptibility in zebrafish using cyclosporin A, another Ppp3/calcineurin inhibitor associated with clinical IA.

In Study By Cristina Verissimo at al, During the study period (January 2013 to May 2020), 103 cases were submitted to our surveillance program and 76 were validated, the majority of them from Lisbon and the Tagus Valley region. Included cases were categorized as invasive fungal infections (IFI) (N = 53) and as subcutaneous fungal infections (SFI) (N = 23) (Table 1). Overall, these infections were more frequently reported in males (N = 51) and less frequently in females (N = 25). The median age of patients was 59.5 years (ranging 3–90 years). Table 1 shows these data discriminated by type of infection (IFI and SFI). The validated 76 reports were distributed as follows: 54 cases of proven fungal infections from which 31 were classified as IFI and 23 as SFI, totaling 71.1% (N = 54) of proven fungal infections and 28.9% (N = 22) of

probable IFI (Table 2). The obtained results show that 11 IFI cases were caused by endemic fungi. Invasive proven and probable fungal infections represented 69.7% (N = 53) of total cases. Analysis of our data revealed a predominance of localized infections (N = 66). Disseminated infections were observed only in 10 cases. From these latter, nine were classified as proven IFI, four of them were caused by endemic dimorphic fungi and one was classified as a probable IFI.

In Study By Nusrat Jahan Shaly at al, Globally, immunocompromised children are more susceptible to develop IFIs [2]. According to the best of our knowledge, this was the first study in Bangladesh that evaluated the spectrum, frequency, associated factors, and outcome of IFIs among hospitalized ill children admitted in the critical care ward. The identification of around 11% probable IFIs among our study children is the most important observation. 4.53%, 7.97%, and 0.72% of the children with IFIs had invasive candidiasis, aspergillosis, and histoplasmosis, respectively. Our objective was to identify fungal pathogen (Candida species, Pneumocystis jirovecii, Aspergillus species, Cryptococcus species, and Histoplasma Capsulatum), and the detection of specific species was beyond our scope. Candida spp. were associated with suppressed cell-mediated immune response, and it was the most prevalent fungal pathogen in malnourished children [49]. In developing countries like Bangladesh, invasive aspergillosis is not rare. A study from Bangladesh conducted with the aim of identifying the histopathology and etiology of childhood pneumonia found Pneumocystis carinii (PC) and Aspergillus in 4% and 3% autopsy patients, respectively. This opportunistic infection is primarily due to malnutrition and weakened host defenses throughout persistent serious illnesses [50]. Disseminated histoplasmosis could be found in children with no underlying disease other than malnutrition [51]. In our study, we did not find any children who were positive for Pneumocystis jirovecii and Cryptococcus spp. positive. Perhaps it might be due to the low prevalence of HIV in the general population in Bangladesh [52]. A study from the HIV unit of Dhaka hospital of icddr,b showed that 24 HIV-infected children were admitted over three years. Among them, 16.7% children had

Pneumocystis jirovecii pneumonia (PCP) [53]. Cryptococcosis and histoplasmosis are not frequent in Bangladesh. Bangladesh is still a low prevalent country for HIV. The first reported case of disseminated Histoplasmosis in Bangladesh was in 1982 [54]. A systematic review on Histoplasmosis from Bangladesh found 26 patients over 55 years from 1962 to 2017. All were male patients aged 8–75 years, and four had HIV/AIDS. Disseminated histoplasmosis was present in 22 patients, and four patients had localized oropharyngeal disease [55]. Among under-5-year-olds there was a case report of disseminated histoplasmosis in a 3-and-a-half-year-old boy from Bangladesh [56]. Our study also found a deficient proportion of invasive Histoplasmosis in under-5-year-old children. Shahrin et al., found six presumptive cryptococcal meningitis cases among HIV-infected adults over three years [57]. Based on this data, it was estimated that the rate of cryptococcal meningitis was 0.01 (15/100,000) in each year in Bangladesh among HIV infected patients [29]. From Bangladesh, we do not find patients with cryptococcal meningitis in non-HIV patients except one case report of post-renal transplant cryptococcal meningitis [26]. In our study, we did not find any children positive with cryptococcal infection.

In Study By Brygida Knysj at al, The tests included 108 people of both sexes, in whom HIV-1 infection was recorded, 80(61%) men and 51 (39%) women. The average age of the test group was 33.3 years old. 63 (58.3%) people were infected by intravenous use of intoxicants. The control group consisted of 23 people not infected with HIV-1. Characteristics of the tested group are in table 1. HIV RNA was tested in most patients' plasma, where in over 65% with T CD4 lymphocyte < 200 cell/μL count, in 75% people with CNS disorders and in 70.5% with T CD4 lymphocyte > 500 cell/ μL count. The patients who entered the study did not get yet cART and thus HIV viremia was connected with the lack of antiviral therapy. During observation 16 (12% of the observed population) patients died including 5 women and 6 men. The average age of the patients who died was 39.87 years old. JCV/BKV infections were found in 27 HIV-1 infected people, which constituted 25 % of this group: with 18 (16.7%) JCV cases and 9 (8.3%) BKV. The

infections were confirmed on the basis of genetic material presence in urine. JCV and BKV was not found in any patients' blood or cerebrospinal fluid. The average age of the patients was 35.7 years old. In the group of patients with no symptoms from CNS with T CD4 lymphocyte count < 200 cell/μL JCV DNA was detected in urine in 5 (11.4%), and BKV in 7 (15.9%) cases, whereas in the group with neurological conditions JCV in 3 (15%) and BKV also in 3 (15%) cases, (together in 6 (40%) people).

For over ten years there have been available viruses' genetic material tests. Owing to that 4 genotypes and 18 subtypes of JC virus which exist in Africa, Europe, America, Asia and Oceania have been isolated (3). However, in our study there was a significant difference between the HIV positive groups and control group concerning occurrence of JCV and BKV infections, indicating increased prevalence in HIV positive individuals regardless the immunological status. JCV presence can be found in HIV-1 infected patients who do not suffer from PML. Andreoletti showed JCV in 26 % people with T CD4 lymphocyte count < 200/μL, 18% of patients with TCD4 lymphocyte count >200/μL (12), Calderelli in 40% people in brain tissue and in kidneys (13), Ferrante in 49% patients in urine and 10 % of peripheral blood monocular cells (14), Lednicky in 30 % patients in urine (15), and Tornatore in 38 % patients in of peripheral blood monocular cells (16). In our test group the proportion of JCV/BKV infections in people who were not diagnosed with PML was 40.7% in patients with T CD4 lymphocyte count < 200/μL and similarly 40.7% in people HIV infected with T CD4 cells count > 500/μL. The achieved information is consistent with the data from Ferrante and co.'s report with regards to a low lymphocyte count and diverge from the data concerning people with a high T CD4 lymphocyte count (the tests concerned various materials) (14). Due to a different biological material being tested and little literary data the results achieved by us and other researchers are difficult to compare and it may be an approximation only.

1. JCV and BKV infection may be asymptomatic in HIV-1 infected people and concerns patients at various HIV-1 infection stages
2. In patients with extreme immunological deficit BKV infection prevailed.

3. BKV infection may be connected with development of PML in people HIV-1 positive.
4. Urine test for JCV and BKV presence constitutes an important diagnostic test facilitating PML diagnosis.

In Study By Pawet Swieki at al, Table 1 presents the CD4 count in both studied groups before implementation of treatment and at the end of observation. After 2 years of treatment the mean increase in CD4 count was similar in both groups and amounted to 310 cells/μL and 361 cells/μL respectively. Even though these values were similar, the lowest increase in CD4 count was achieved in group treated with AZT/3TC and PI, whereas the highest in group treated with d4T/3TC and PI. Table 2 presents concentration of triglycerides and total cholesterol before inclusion to the study and in week 96 of observation. Table 3 presents the percentage of subjects with increased concentration of triglycerides and total cholesterol before inclusion to the study and in week 96 of observation. In the first group elevated concentration of triglycerides was revealed in 38.5% of persons, and total cholesterol - in 13,5% of subjects. After 2 years of treatment these values increased to 59.3% and 45.6% of subjects respectively. In the second group elevated values of TG concentration were revealed in 40% of subjects, total cholesterol in 23.5%, and after 96 weeks of treatment 47.7% of subjects had elevated TG concentration, and 37.7% total cholesterol concentration. The highest increase of both TG as well as TC was observed in the group treated with d4T/3TC regimen. Performed studies have shown that both d4T/3TC and AZT/3TC regimens are effective as backbone of CART. Similar immunological values are achieved using above mentioned regimens. Elevation of TG and TC level during antiretroviral therapy is much more frequent in persons treated with d4T/3TC and is not dependent on type of the third drug used. This regimen in persons with hyperlipidaemia should be used only in exceptional situations, and systematic monitoring of concentration of both cholesterol and triglycerides is necessary during therapy. Antiretroviral treatment with use of three drugs in most drug combinations leads to changes in blood lipid concentrations, mainly in form of elevation of cholesterol and triglycerides

concentration. Changes in blood lipid concentrations in HIV infected patients were revealed even before antiretroviral treatment for many years [14-16]. This problem has definitely increased from the time of introduction of CART. However there is no perfect drug combination, careful choice of drugs, based on former analysis of patient's predispositions is key issue for effective long-term therapeutic effect. It was shown in performed studies that elevated triglycerides concentration occurs in 40% of subjects, whereas elevated total cholesterol in 13% of subjects even before starting CART. In observations of other authors elevated cholesterol and triglycerides concentration was shown in 60% of subjects [17-19].

In Study By DorotaRogowska- Sjadkowska at al, Diagnosis of HIV infection at the primary infection stage is of paramount importance both for the patient and for his sexual partners. If the patient is aware of the infection, he/she has a chance to modify his behaviour so as not to transfer HIV to sexual partners. It has been known for a long time that during the primary infection, the high plasma viral load (6) probably corresponds to semen viral load (7), it is strongly correlated with the risk of sexual transmission (8) and therefore epidemic growth, and transmission of drug resistance.

In Study By Jacek Gasiorowski at al, Generalized alopecia (alopecia universalis), a variant of alopecia areata, is a disease of unknown etiology, although is believed to be of autoimmune origins arising from a combination of genetic and environmental influences (2). Among HIV infected patients, alopecia could be a possible adverse event associated with the use of different drugs, especially protease inhibitors (8). The most commonly mentioned cause of alopecia induced by protease inhibitors is the alteration of retinoids metabolism (2,5). There have also been reports on alopecia in patients treated with indinavir, lopinavir/ritonavir, atazanavir (1,2,3,4). We report this case of hair loss in a patient treated with combination of saquinavir and boosted lopinavir. To our knowledge, there are 3 reports of lopinavir/ritonavir-related hair loss in the literature (2,3,4), our being the fourth one – if alopecia in the described patient was actually caused by lopinavir/ritonavir use. There have been no reports concerning alopecia after saquinavir use so far. We cannot establish whether generalized hair loss in our patient was

due to lopinavir or saquinavir alone or both drugs used simultaneously. We also do not know what influence treatment with two boosted PIs had on the severity of this side effect. In our patient, other reasons of hair loss, such as immune reconstitution syndrome, secondary infections, nutritional disorders, endocrine dysregulation and exposure to other drugs were excluded (2). According to literature reports, alopecia was rapidly reversible in most patients and hair re-growth was usually seen 6 – 8 weeks after stopping the regimens in question (1,2,3,5). In our patient, 4 weeks after discontinuation of PIs use, slow re-growth of new hair, however moustache only, was noticed. In comparison to other reports, in this case the duration of treatment probably responsible for alopecia was very long, as well as the duration of hair loss (1,2,3,5). We do not know if there would be any relationship between the duration of treatment and the possibility of achieving hair re-growth and to what extent (complete or partial only). Although generalized hair loss due to PIs use is rare, clinicians should be aware of this side effect, especially because of its possible negative influence on patients' quality of life (2). A switch to a PI-sparing regimen may be required in some cases. Other antiretroviral drugs could also cause dermatologic disorders, alopecia among others.

In Study By Toine Mercier at al, As the goal of the EORTC/MSGERC consensus definitions is to facilitate standardization and the selection of a more homogeneous population of patients with IA for clinical treatment trials, the proposed galactomannan cutoffs are higher than those typically used in clinical care. This results in a higher specificity and diagnostic likelihood, at the expense of a slightly lower sensitivity. In the end, the cutoffs that are being proposed are based on a consensus decision on the optimal tradeoff between diagnostic certainty and ensuring that a sufficient number of patients remain eligible for enrollment in treatment trials. It is important to note that all cutoffs mentioned in these consensus documents are based on the Platelia Aspergillus assay. We hope that the application of the new criteria in clinical, diagnostic, and epidemiologic research of IA will result in further standardization and improved comparability.

In Study By Thavrew at al, Trichosporon is a yeast found as a commensal in the gastrointestinal tract and skin in humans. 5 Disruption of the mucosal barrier with chemotherapy along with neutropaenia attribute to higher rate of infection in patients with haematological malignancies. However, other factors such as presence of invasive central lines and administration of total parenteral nutrition are also risk factors for Trichosporon infection similarly to Candida which is the commonest cause of fungaemia. 6 . Trichosporonosis was found to be the second most common fungal infection in patients with haematological malignancy. 1 However, the epidemiology of yeast infections has changed with the use of antifungal prophylaxis around the world. Prophylaxis with azoles led to significant reductions of Trichosporon infections. However, this uncommon yeast re-emerged with echinocandin prophylaxis in recent decades. 7 Echinocandins are not frequently used as antifungal prophylaxis in Sri Lanka. Skin lesions are the second most common tissue involved in trichosporonosis and are present in 30% of patients with invasive disease. The skin lesions are mainly on the extremities but also involve the trunk and face which was similar to the pattern in our patient. Lesions are typically haemorrhagic macular or macular papular which differs from the skin lesions in infections with Candida spp. which are punctate, pseudopustular with a rim of erythema. 6.

In Study By G. Mancuso at al, Understanding of how fungi disseminate from the initial infection is essential for correct diagnosis and management. The main barriers against fungal infections are physical barriers such as the skin and mucous surfaces of respiratory, gastrointestinal and urinary tracts. These barriers work in conjunction with cells of innate immune system to prevent colonization and infection. The activation of PRRs in response to PAMPs, such as β-glucan and α-mannan, is crucial for the initiation of innate immune responses. Numerous reports suggest the presence of several cellular mechanisms underlying fungal recognition that lead to the production of different host defense factors. Besides C-type lectin-like receptors (CLRs) other receptors, such as the intracellular receptors that recognize cytoplasmic nucleic acids are crucial in inducing host innate immune defenses against fungal pathogens. One of the best

characterized of these mechanisms is the detection of cellwall structures by receptors located on the host cell surface. This mechanism that leads to the production of inflammatory cytokines, such as TNF-α and IL-23 is independent from TLRs. Conversely, the second best characterized mechanism is dependent from TLR or TRL adaptors and requires the release of fungal nucleic acids that are detected by TLR7 and TLR9 triggering MyD88- and IRF1-dependent responses. Patients with certain immunocompromised or immunosuppressed conditions are unable to mount an effective innate immune response capable of preventing potentially life-threatening infections by fungal pathogens. IFIs continue to be associated with high morbidity and mortality rates due to the spread of drug-resistant strains and lack of rapid diagnostic tools. Rapid and accurate diagnosis of fungal infection is critical to begin effective treatment as soon as possible. In this context, understanding the complex host-pathogen interaction such as the cooperation between CLRs and TLRs in the development of antifungal innate immunity will be critical for the development of effective treatments in the future.

In Study By Alexandre Noel de Tilly at al, Overview of studies included in this review—Nineteen articles were extracted from PubMed and Google Scholar. Table 2 summarizes the key characteristics and conclusions from these studies. The total amount of participants in the collective studies was 3517. Of these, 3489 persons were HIV- or AIDS-positive. Of the 28 non-HIV subjects, two were immunosuppressed children. Trials were conducted in different countries of varying populations with different socioeconomic realities [19]. The countries included in this review article are Belgium, Canada, Chile, France, Mexico, Uganda, the United Kingdom, and the United States. Of the 19 examined articles, 16 trials were performed with patients who had some manifestation of oropharyngeal candidiasis. Two trials were carried out with patients who presented with talaromycosis, and one study examined systemic fungal infections. Fifteen trials were performed on HIV- or AIDS-positive adults, one trial included both immunocompromised and HIV+ patients, one trial was performed with HIV/AIDS-positive children, one trial with immunosuppressed children, and one was unspecified.

This review article demonstrated that antifungal therapies have significantly different treatment efficacy regarding clinical success, infection relapse prevention, patient prescription regimen adherence, and potential for developing resistant fungal strains. Due to the different antifungal drug families and their different mechanisms of action, it is important to explore the potential of non-first-line therapies for oropharyngeal fungal infections in HIV+ or AIDS+ persons. Some studies demonstrate that a variety of factors (adherence, drug of use, length of treatment, etc.) contribute to refractory or treatment-resistant candidiasis, and that fluconazole should be treated with caution due to increased resistance. Unfortunately, due to the volatile and multi-factored nature of evolutionary or adaptive biology, it is difficult to pinpoint the cause and effect regarding developing antifungal resistance. This emphasizes the need for novel discoveries to combat increased antifungal resistance. Here, research into other types of intravenous immunoglobulin antibodies for treatment of oral candidiasis is beneficial and warranted.

In Study By Flavia Akemi Nakayama Henschel at al, Of the 3,679 records, 38 (1.033%) presented some SFI. Four medical records were not properly filled out and were excluded. Therefore, 34 (0.924%) individuals were included. Men were much more affected (n = 31; 91.18%), and ages ranged from 28 to 69 years (average 46.9 years). Most of the individuals were Caucasian (n=18; 52.94%) and farm/rural workers (n = 16; 47.05%). 31 (91.18%) individuals were diagnosed with PCM and 3 (8.82%) with histoplasmosis. Although several cases of candidiasis were observed, all were superficial infections and were excluded from the analysis. The jugal mucosa and alveolar ridge were the most affected sites. All patients underwent incisional biopsy of the oral lesion and were referred for a chest radiograph and then to the infectologist for treatment at the University Hospital of Maringá, state of Paraná, Brazil. Table 1 lists general data.

Among the patients diagnosed with PCM (n = 31), 90.32% were men (n = 28; 28-69 years; mean 47.21 years); 18 (58.06%) were Caucasian, 12 (38.71%) melanoderma and in one case (3.23%), this information was missing. The majority of patients worked in agriculture (n = 15; 48.38%) and other occupations

included drivers (n = 4; 12.90%), bricklayers (n = 3; 9.67%). Retirees (n = 2; 6.45%) and missing information (n = 7; 22.58%) completed the sample. The lesions were often multiple, with the jugal mucosa (n = 13; 25.49%) and alveolar ridge (n = 12; 23.52%) affected in most cases (Figure 1). In two (23.52%) patients, there was a diffuse lip enlargement. The age range of patients found in our analysis was 28-69 years, with an average of 46.9 years

Of the three male patients (50-55 years; mean: 52.67 years) diagnosed with histoplasmosis, two (66.66%) were melanoderma and in one case (33.33%), the information was missing. Regarding the profession, one (33.33%) was a rural worker, one (33.33%) was a bricklayer and one (33.33%) was a mechanic. Again, multifocal involvement was frequent, and the palate, jugal mucosa and alveolar ridge were affected (Figure 2). All patients were immunocompetent.

We report the experience of 25 years in a reference service in the diagnosis and treatment of oral lesions in southern Brazil. Epidemiological studies represent an important tool for the design of risk factors for a disease in a population. It is known that habits, ethnicity, geographical position and socioeconomic situation are some of the factors that influence the incidence of various diseases. In particular, SFI are endemic, emphasizing the importance of knowing their risk groups and clinical characteristics. Moreover, the socioeconomic impact caused by these diseases can be remarkable, adding to the serious and potentially fatal course of some cases.

Opportunistic fungal infections remain an important cause of morbidity and mortality in immunocompromised patients. The most important parameter that determines the success of treatment of these infections in immunosuppressed patients is the speed at which a diagnosis is made and treatment is initiated [16]. Although HIV is the causative agent of AIDS, the main cause of morbidity and mortality in these patients is opportunistic infections due to weakened humoural and cell-mediated immunity [17]. Opportunistic infections range from viral, fungal, bacterial and parasitic infections [18]. In the present study, the most prevalent Candida species obtained from oral thrush lesions was C. albicans. An increasing

trend of non albicans Candida infections has also been reported by others [19], and this trend has been favoured by the extensive use of fluconazole [20]. In 45 of 65 isolates of Candida species, pseudohyphae were found, which have long been known as a sign of fungal infection [21]. pneumonia due to P. jirovecii is one of the common opportunistic fungal infection. The main reason for the low incidence of pneumocystis in India is inaccessibility of high quality diagnostic laboratories and low yield specimens, as bronchoalveolar lavage is not performed in most hospitals [22]. Cryptococcosis has been found to be the most common systemic fungal infection among AIDS patients (7.02%). Its incidence is on the rise with the rapid spread of the AIDS [23]. Similar occurrences have been reported by Sharma SK et al., (4%), Mulla SA et al., (3.7%) and Mbanya D et al., (2.9%) [24-26]. CNS cryptococcosis is one among the foremost important risk factors related to HIV infection contributing to a really high degree of morbidity and mortality among immunocompromised patients [9]. Hence, surveillance of mycosis in immunocompromised especially HIV infected individuals and adopting an appropriate treatment at early stages is necessary [26]. In this study, various opportunistic fungal infections showed to be correlated with the absolute CD4+ counts; the CD4+ counts for the patients suffered from oropharyngeal candidiasis, pneumocystis pneumonia, cryptococcal meningitis was ≤200 cells/μL. This finding is also supported by other published literature [17]. In this study, oropharyngeal candidiasis was the most common opportunistic fungal infection. Prevention of opportunisti

In Study By Pavneet Kaur at al, The present study was carried out in 185 immunocompromised patients. The various malignancies included were breast cancer (53 patients), leukaemias/ lymphomas (17 patients) and lung cancer (8 patients) on patients receiving chemotherapy. Opportunistic fungal infections caused by Candida spp. were found in 67 (46.8%) patients, representing the most common causing agents. Cryptococcal meningitis (C.neoformans) was positive in 13 (38.2) and pneumocystis pneumonia (P.jirovecii) was positive in 1 (12.5) patients. The distribution of various opportunistic fungal infections is presented in [Table/Fig-3]. Demographic profile of various patients with opportunistic infections is presented Opportunistic fungal infections remain an important cause of morbidity and

mortality in immunocompromised patients. The most important parameter that determines the success of treatment of these infections in immunosuppressed patients is the speed at which a diagnosis is made and treatment is initiated [16]. Although HIV is the causative agent of AIDS, the main cause of morbidity and mortality in these patients is opportunistic infections due to weakened humoural and cell-mediated immunity [17]. Opportunistic infections range from viral, fungal, bacterial and parasitic infections [18]. In the present study, the most prevalent Candida species obtained from oral thrush lesions was C. albicans. An increasing trend of non albicans Candida infections has also been reported by others [19], and this trend has been favoured by the extensive use of fluconazole [20]. In 45 of 65 isolates of Candida species, pseudohyphae were found, which have long been known as a sign of fungal infection [21]. pneumonia due to P. jirovecii is one of the common opportunistic fungal infection. The main reason for the low incidence of pneumocystis in India is inaccessibility of high quality diagnostic laboratories and low yield specimens, as bronchoalveolar lavage is not performed in most hospitals [22]. Cryptococcosis has been found to be the most common systemic fungal infection among AIDS patients (7.02%). Its incidence is on the rise with the rapid spread of the AIDS [23]. Similar occurrences have been reported by Sharma SK et al., (4%), Mulla SA et al., (3.7%) and Mbanya D et al., (2.9%) [24-26]. CNS cryptococcosis is one among the foremost important risk factors related to HIV infection contributing to a really high degree of morbidity and mortality among immunocompromised patients [9]. Hence, surveillance of mycosis in immunocompromised especially HIV infected individuals and adopting an appropriate treatment at early stages is necessary [26]. In this study, various opportunistic fungal infections showed to be correlated with the absolute CD4+ counts; the CD4+ counts for the patients suffered from oropharyngeal candidiasis, pneumocystis pneumonia, cryptococcal meningitis was ≤200 cells/μL. This finding is also supported by other published literature [17]. In this study, oropharyngeal candidiasis was the most common opportunistic fungal infection. Prevention of opportunistic infections by specific measures such as good personal hygiene, early and regular medical examination of suspected individuals with opportunistic infections, prompt diagnosis, and appropriate antifungal prophylaxis and/or treatment are necessary to decrease the morbidity and mortality associated with these infections. Hence, knowledge of spectrum of opportunistic fungal infections and its correlation with CD4+ counts may help clinicians in early diagnosis and prompt treatment of opportunistic fungal infections in immunocompromised patients more efficiently, which in turn may increase their longevity

Oropharyngeal candidiasis was found to be most common opportunistic fungal infection in this setting. This study would help to extend the awareness to clinicians to come up with the right diagnosis and earlier treatment of those infections with the right management of the patients especially in resource limited regions in India.

In Study By A. J. Ullmamm at al, Fungal diseases still play a major role in morbidity and mortality in patients with haematological malignancies, including those undergoing haematopoietic stem cell transplantation. Although Aspergillus and other filamentous fungal diseases remain a major concern, Candida infections are still a major cause of mortality. This part of the ESCMID guidelines focuses on this patient population and reviews pertaining to prophylaxis, empirical/pre-emptive and targeted therapy of Candida diseases. Anti-Candida prophylaxis is only recommended for patients receiving allogeneic stem cell transplantation. The authors recognize that the recommendations would have most likely been different if the purpose would have been prevention of all fungal infections (e.g. aspergillosis). In targeted treatment of candidaemia, recommendations for treatment are available for all echinocandins, that is anidulafungin (AI), caspofungin (AI) and micafungin (AI), although a warning for resistance is expressed. Liposomal amphotericin B received a BI recommendation due to higher number of reported adverse events in the trials. Amphotericin B deoxycholate should not be used (DII); and fluconazole was rated CI because of a change in epidemiology in some areas in Europe. Removal of central venous catheters is recommended during candidaemia but if catheter retention is a clinical necessity, treatment with an echinocandin is an option (CIIt). In chronic disseminated candidiasis therapy, recommendations are liposomal amphotericin B for 8 weeks (AIII), fluconazole for >3 months or other azoles (BIII). Granulocyte transfusions are only an option in desperate cases of patients with Candida disease and neutropenia

In Study By Priyadarshani Deka at al, Mucormycosis and Aspergillosis have a remarkably high mortality with a rise in its incidence. These diseases represent the most common fungal infections after post covid recovery in many patients. The availability of iron in the host environment likely plays a very critical role in predisposing the host to mucormycosis thereby searching for an abundant iron from the host for their proper growth. Strategies‟ have been focused on depriving the fungus from evading host iron that can be beneficial

in preventing or treating the disease. Mucormycosis angioinvasion is dependent on the interaction between Mucorales CotH and endothelium GRP78 that triggers the host cell injury and are subsequently responsible for causing the virulency in the host by gaining the fungal admittance to the host‟s vascular system for causing the disease. Bronchopulmonary aspergillosis has been very common in individuals with altered lung function such as asthma and cystic fibrosis patients. Their entry into the humans through their conidial deposition in the bronchioles spaces are primarily responsible for the phagocyotosis of these conidia and cause the proinflammatory responses. IA causes high mortality among mostly neutropenic hosts once infection is established. The principal management of both the diseases are based on many intensive attempts their laboratory diagnosis often at the early phase of the infections as well as the timely adaption of an effective antifungal therapy along with reverse immune suppression therapies. The role of immunotherapy for adjunctive management to maximize its effectiveness has been well defined and larger clinical trials are therefore needed to determine its utility. However, surgery is the last resort when disease progresses despite medical therapy, or if lifethreatening invasive manifestations occur. Finally, recovery of neutrophil numbers and functioning ultimately dictates the likelihood for successful outcomes. Moreover, for the survival to be improved a sequential intervention of diagnosis and immediate effective therapeutics is always a demanding need.

In Study By I. Steiner at al, The diagnostic advancement by PCR seen in other CNS infections has not moved into the foreground for fungal CNS infections (Table 4). This is in part because of the relative infrequency of fungal CNS infections and to the lack of a gold standard against which studies evaluating sensitivity and specificity of advanced methods can be verified. The usage of CSF PCR for the diagnosis of suspected CNS cryptococcosis and CNS aspergillosis in addition to the routine methods is likely to be of value (level C recommendations). There are class IV evidence studies reporting the feasibility of CSF PCR for evaluating CNS manifestations by Histoplasma, Coccidioides, and Candida, and of tissue for CNS mucormycosis. However, we do not identify enough evidence to recommend the use of PCR as a routine

diagnostic tool in these cases.

In Study By J. M. Miro at al, Solid organ transplantation (SOT) is an appropriate therapeutic option for HIV-infected patients with end-stage organ disease. Recent experience in North America and Europe indicates that 3- to 5-year survival in HIV/HCV-coinfected liver recipients is lower than that of HCV-monoinfected recipients. Conversely, 3- to 5-year survival of non-HCV-coinfected transplant patients (liver, kidney and heart) was similar to that of non-HIV-infected patients. Preliminary experience with lung transplantation and combined kidney and pancreas transplantation is also satisfactory. Infections in HIV-infected recipients during the post-transplant period are similar to those seen in non-HIV-infected patients, although the incidence rates of tuberculosis and fungal infections seem to be higher. HIV-infected patients who are being evaluated for SOT should follow the same recommendations as those used for non-HIV-infected patients in order to prevent infections during the pre-transplant period. After transplantation, HIV-infected SOT recipients must follow recommendations on post-SOT and anti-HIV immunization and on antimicrobial prophylaxis. The recommended antiretroviral regimen is one based on raltegravir or dolutegravir plus two nucleos(t)ide reverse transcriptase inhibitors (tenofovir + emtricitabine or abacavir + lamivudine), because it can prevent pharmacokinetic interactions between antiretroviral drugs, immunosuppressive drugs and some of the antimicrobial agents used to treat or prevent post-transplant infections. In this manuscript, we review current recommendations for preventing infections both before and after transplantation. We also analyse the incidence, aetiology and clinical characteristics of opportunistic and non-opportunistic bacterial, mycobacterial, fungal and viral infections in HIV-infected SOT recipients during the post-transplant period.

Aims and Objectives

Aim: The objective of the study is to look at the type of fungal infection in immunocompromised patients

Objective:

1. To see the prevalence and disease spectrum

2. To see the effectiveness and adverse effects of various vaccines

METHODOLOGY

AREA OF STUDY; FUNGAL INFECTION IN IMMUNOCOMPROMISED PATIENTS

RESEARCH OF DESIGN: Qualitative and Quantitative.

DATA TYPE: secondary mode of data collection.

a)Data from various journal.

b)Data from books.

c)Online data from various literature reviews.

RESEARCH TOOL: secondary data from published report of

articles.

TIME FRAME: All the studies in indexed journal from 2008 to 2022

SEARCH ENGINE: Pub med, Google scholar.

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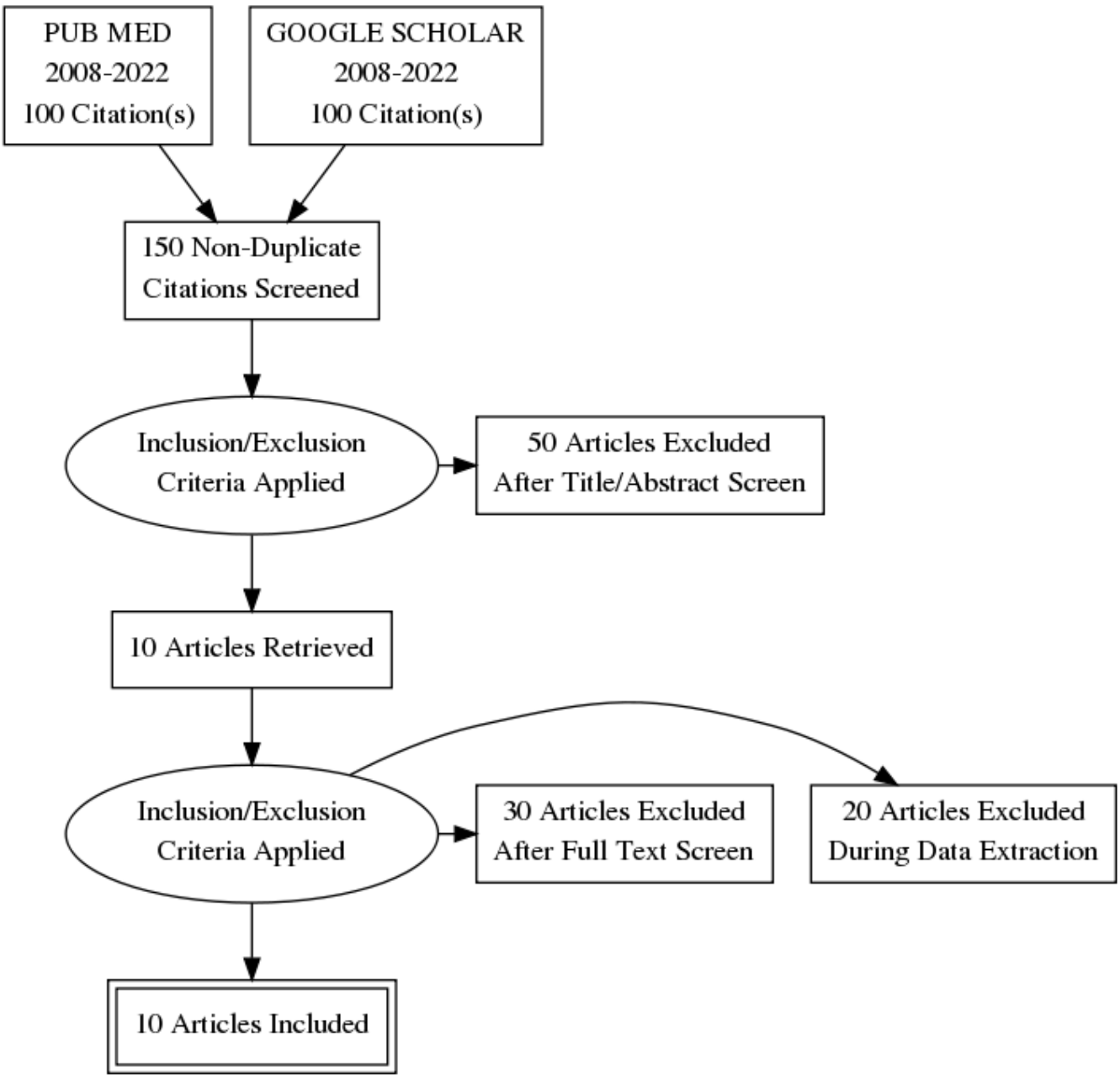
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After Title/Abstract Screen
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Inclusion/Exclusion
Criteria Applied
30 Articles Excluded
After Full Text Screen
20 Articles Excluded
During Data Extraction
10 Articles Included

RESULTS

S.NO.	AUTHOR	YEAR	COUNTARY	FINDINGS
1	Yoshikazu et al,	2006	TOKYO	In patients with neutrophil counts of >0.1 x 10(9)/L lasting for more than 4 weeks, the frequency of infection in the fluconazole group (5 of 9 patients) was significantly higher than in the itraconazole group (0 of 7 patients; P = .03). Our results suggest that both drugs were well tolerated in patients with AML or MDS who received chemotherapy and that the efficacy of itraconazole for prophylaxis against systemic fungal disease is not inferior to that of fluconazole.
2	Cristina Verissimo et al,	2022	SWITZERL-AND	It was possible to identify the etiological fungal agent in 73 cases (96%). *Aspergillus* was the most frequent genera detected, but endemic dimorphic fungi represented 14.47% (N = 11) of the total cases. Despite the small number of cases, a high diversity of species were involved in deep fungal infections. This fact has implications for clinical and laboratory diagnosis, and on the therapeutic management of these infections, since different species, even within the same genus, can present diverse patterns of susceptibility to antifungals.
3.	Fouad K.ABEED et al.	2022	Iraq	The results indicated that majority of the yeast isolates exhibited potential proteinase activity, with 24.6% exhibiting weak activity, 19.7% moderate activity, and 9.8% high activity, while 45.9% phospholipase activity, with 16.4% weak activity, 24.6% exhibiting moderate activity, and 4.9% strong activity. While hemolysin production was demonstrated in 85.2%, that 59.0% were

				strong, 21.3% moderate, and 4.9% weak. Additionally, it was possible to identify biofilm development, which occurred in 90.2% of isolates. All isolates showed sensitivity to the antifungals tested, with the exception of one *Candida glabrata* isolate that demonstrated resistance to voriconazol and two ***Candida parapsilosis*** isolates resistance to flucytosine. The results also revealed no significant changes in proteinase activity or drug susceptibility profile, but significant variations in phospholipase, hemolysin, and biofilm generation amongst yeast isolates.
4.	Alba Luz Rodriguez et al.	2017	Brazil	Of 867 studies, 65 met the criteria for review, and the data of 18 were summarized in the meta-analysis. The major RFs independently associated with HAIs were diabetes mellitus (RR, 1.76; 95% CI, 1.27-2.44), immunosuppression (RR, 1.24; 95% CI, 1.04-1.47), body temperature (MD, 0.62; 95% CI, 0.41-0.83), surgery time in minutes (MD, 34.53; 95% CI, 22.17-46.89), reoperation (RR, 7.94; 95% CI, 5.49-11.48), cephalosporin exposure (RR, 1.77; 95% CI, 1.30-2.42), days of exposure to central venous catheter (MD, 5.20; 95% CI, 4.91-5.48), intensive care unit (ICU) admission (RR, 3.76; 95% CI, 1.79-7.92), ICU stay in days (MD, 21.30; 95% CI, 19.81-22.79), and mechanical ventilation (OR, 12.95; 95% CI, 6.28-26.73).
5.	Flavia Akeminaka yama et al	2021	Brazil	Of the 3,679 records, 38 (1.033%) presented some SFI. Four medical records were not properly filled out and were excluded. Therefore, 34 (0.924%) individuals were included. Men were much more affected (n = 31; 91.18%), and ages ranged from 28 to 69 years (average 46.9 years). Most of the individuals were Caucasian (n=18; 52.94%) and farm/rural workers (n = 16; 47.05%). 31 (91.18%) individuals were diagnosed with PCM and 3 (8.82%) with histoplasmosis. Although several cases of candidiasis were

				observed, all were superficial infections and were excluded from the analysis. The jugal mucosa and alveolar ridge were the most affected sites.
6.	Stephanie R. Earnshaw et al.,	2022	USA	Increased costs occurred due to diagnostic testing for the DD strategy, per-patient costs related to antifungal agent use were higher in patients receiving ET and average patient total costs were reduced (£20,230 for DD versus £21,351 for ET). Days in the intensive care unit (ICU) and general ward accounted for > 40% of the total costs and > 58% of the cost reduction came from reduced antifungal costs. Given that survival among patients was similar (90.32% for DD and 89.50% for ET), a DD strategy was a cost-saving (less costly and more effective at -£136,787 per death avoided) strategy.
7.	Pavneet Kaur et al.,	2022	INDIA	Out of 185 patients, oropharyngeal candidasis was found to be most common (143, 77.3%) in which opportunistic fungal infections caused by Candida spp. were found in 67 (46.8%) patients representing the most common causing agents followed by Pneumocystis jiroveci (12.5%) and Cryptococcus meningitis (38.2%).
8.	G. Mancuso et al.,	2022	Europe	the existence of different cellular mechanisms that, following the recognition of fungal PAMPS, induce the production of different sets of defense factors. The development of new diagnostic methods and antifungal drugs along with a better understanding of the host immune response are key approaches to controlling invasive fungal infections.
9.	Nusrat Jahan Shaly et al.	2021	Bangladesh	In the study group, 15/138 (10.87%) children had IFIs. Among IFIs, invasive candidiasis, aspergillosis, histoplasmosis detected in 6 (4.53%), 11 (7.97%), and 1 (0.72%) children, respectively, and (3/15 [2.17%]) children had both candidiasis and aspergillosis. Children with IFIs more often encountered septic shock (26.7% vs. 4.9%; $p = 0.013$) and had a higher death rate (46.7% vs. 8.9%; $p < 0.001$) than those without

				IFIs. IFIs were independently associated with female sex (OR = 3.48; 95% CI = 1.05, 11.55; p = 0.042) after adjusting for potential confounders. Our findings thus implicate that, malnourished children with septic shock require targeted screening for the early diagnosis and prompt management of IFIs that may help to reduce IFIs related deaths.
10	Alexandre Noel de Tilly et al.,	2022	Canada	Studies demonstrated that fluconazole had different relapse durations comparative to other medications, and that posaconazole could possibly act as an alternate form of treatment. Nystatin was indicated as a first-line therapy for thrush in multiple studies but could be upstaged by miconazole nitrate in resource-poor settings. Amphotericin B was an effective treatment option and was shown to be resilient in terms of fungal resistance, however potent adverse side effects were reported. Alternative treatments, such as immunoglobulin antibodies and lemon grass, revealed promising antifungal effects for immunocompromised individuals. Taken together, this review provides a thorough summary of treatment options of oropharyngeal fungal infections in HIV/AIDS patients.

DISCUSSION

We report the experience of 25 years in a reference service in the diagnosis and treatment of oral lesions in southern Brazil. Epidemiological studies represent an important tool for the design of risk factors for a disease in a population. It is known that habits, ethnicity, geographical position and socioeconomic situation are some of the factors that influence the incidence of various diseases. In particular, SFI are endemic, emphasizing the importance of knowing their risk groups and clinical characteristics. Moreover, the socioeconomic impact caused by these diseases can be remarkable, adding to the serious and potentially fatal course of some cases.

There are two varieties of SFI: opportunistic (systemic candidiasis, aspergillosis and mucormycosis) and respiratory endemic mycoses (histoplasmosis, blastomycosis, coccidioidomycosis, PCM and cryptococcosis) (Carrasco-Zuber et al., 2016). Of these, only PCM and histoplasmosis were found in this study. All cases of candidiasis were superficial (pseudomembranous and erythematous).

PCM or South American Blastomycosis, caused by the dimorphic fungus *P. brasiliensis*, mainly affects the lungs and can involve other organs by hematogenous route, such as lymph nodes, skin and oral mucosa (Godoy & Reichart, 2003; Trindade et al., 2017; Dutra et al., 2018). Transmission occurs through inhalation of the fungus, which reaches the pulmonary alveoli (primary site of infection), where the conditions are adequate for it to begin its transition to the yeast phase (Godoy & Reichart, 2003; Marques, 2010; Dutra et al., 2018;). Frequently, the oral mucosa is affected, being the primary clinical manifestation in many patients

CONCLUSION

Trichosporonosis is an infection that should be suspected in patients undergoing chemotherapy, with neutropenic fever not responding to first line antifungals such as fluconazole. Presence of haemorrhagic macular skin lesions could be a significant feature pointing to the diagnosis of *Trichosporon* fungaemia in patients at risk of this infection. Timely treatment with voriconazole, ideally with therapeutic drug level monitoring, should be started to prevent the high mortality associated with the condition.

In short, systemic fungal infections should be included in the differential diagnosis in patients from endemic areas. In addition, the inevitable human mobility and globalization make knowledge of these mycoses necessary worldwide, especially because advanced cases in immunocompromised patients can be fatal. This requires training for clinical suspicion and application of all available tools to obtain early diagnosis, reducing morbidity, socioeconomic impact and mortality.

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