Challenges of secondary immunodeficiency and drug resistant opportunistic pathogens in developing countries

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The immune system is composed of a variety of cells and proteins viz. lymphocytes, phagocytes, and cytokines, for which one of the principal functions is microbial defense. Abnormalities of the immune system (IS), particularly the secondary immunodeficiency, are due to old age, several pathologic conditions (diabetes mellitus, lymphohematologic neoplasias, malnutrition, HIV/AIDS etc.), surgical stress or burns, and immunosuppressive therapies. Such deficits in the IS can therefore lead to unusually severe or uncommon recurrent/opportunistic infections (OIs). These infections take advantage of this weak host IS and manifest their adverse effects. The main clinical manifestation of SI, inclusive HIV/AIDS, is severe OIs with abnormally high mortality. OIs are of endogenous nature because OI-causing pathogens are also present in healthy hosts, though only in limited quantities. It is recognized that the IS normally suppresses opportunistic pathogens, and immunodeficiency causes OIs. Drug-resistant microorganisms are frequently detected in individuals with immunodeficiency, and that this drug-resistance is partially responsible for the frequent lethal outcome of OIs incurable by antibiotics. No apparent link exists between immunodeficiency and drug-resistance of the microorganisms. However, drug-resistance is a natural consequence of antibiotic abuse that results from natural selection of drug-resistant mutants under the selective pressure of antibiotics. Bacterial infections contribute to most human and animal diseases in developing countries and are those in which emerging antimicrobial resistance is most evident. Resistance to antimicrobial agents has become major health concern as a number of people with acquired/secondary immunodeficiency are also infected by drug resistant pathogens and/or opportunistic microorganisms.

Keywords antimicrobial resistance; malnutrition; opportunistic infections; antibiotics

1. Introduction

The immune system is the body's natural defense, which is composed of a complex and vital network of cells and organs that protect the body from infection. The immune system attacks and destroys anything that it recognizes as foreign and different from the body's normal healthy tissues. Therefore, the system learns and keeps memory of whatever it encounters in life [1]. A deficit in the immune system can therefore lead to unusually severe or uncommon recurrent infections. Immune deficits (immunodeficiency) may be primary or secondary. Secondary immune deficiencies or acquired deficiencies, which are the scope of this chapter, more frequent than primary immune deficiencies, are problems of the immune system that are not genetic though could be due to both internal and external factors. Treatment depends on the underlying causes and severity in the deficiency of the immune system.

2. Potential causes of secondary immunodeficiency and their effects

Secondary immunodeficiency, also known as acquired immunodeficiency, can be attributed to various immunosuppressive agents like malnutrition, aging, use of particular medications such as chemotherapy, disease-modifying anti-rheumatic drugs and immunosuppressive drugs [1, 2]. For medications, the term immunosuppression generally refers to both beneficial and potential adverse effects of decreased function of the immune system, while the term immunodeficiency generally refers solely to the adverse effect of increased risk for infection. Many specific diseases directly or indirectly cause immunosuppression. This includes many types of cancer, particularly those of the bone marrow and blood cells (leukemia, lymphoma, multiple myeloma), and certain chronic infections. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV) [1, 2]. Extreme of age such as during newborn period there are immature immune lymphoid organs, absent immunity memory, low maternal immunoglobulin G levels in premature infants, decreased neutrophil function and storage pool as well as a decreased in natural killer (NK) cell activity. These affect both the innate and specific immune systems (Fig. 1). While in elder stage (advanced ages), human beings experience decreased antigen specific cellular immunity, T cell oligoclonality and restricted B cell repertoire. Both host genetic and environmental factors shape the pattern of oligoclonality in T cells, particularly the CD8+T cell sub-set [3]. Metabolic disorders like diabetes and chronic uremia have impacts on lymphocytes proliferation, phagocytosis and chemotaxis. Reduced IL-2 receptors expression and lymphocytes responses to IL-1 in uremic individuals may be a pathogenetic factor in the progressive development of impaired immunity associated with end-stage renal disease [4]. Iatrogenic

causes like use of anti-inflammatory, immunomodulatory and immunosuppressive drug therapy have several defects of antigen-specific responses and anergy, decreased pro-inflammatory cytokines, decreased phagocytosis, weaken mucosal barriers (cytotoxic agents) and also decrease chemotaxis. Disruption of epithelial and mucosal barriers, T cell anergy caused by non-specific immune activation as consequence of surgery and trauma are evident and attribute significantly to the secondary immunodeficiencies. Viral infections such as cytomegalovirus, Epstein-Barr virus (EBV), HIV, measles virus, varicella-zoster virus are some of the important causes of secondary immunodeficiencies, which are largely due to the viruses' effects on decreasing T cell cellular response and anergy as well as defective antigen-specific antibody responses. Environmental factors such as ultraviolet light, radiation, hypoxia and space flight have been associated with noticeably increase of lymphocyte apoptosis, secretion of tolerogenic cytokines, cytopenia, decreased cell mediated immunity, stress-induced non-specific immune activation, which are attributable to acquired immunodeficiencies as well [5].

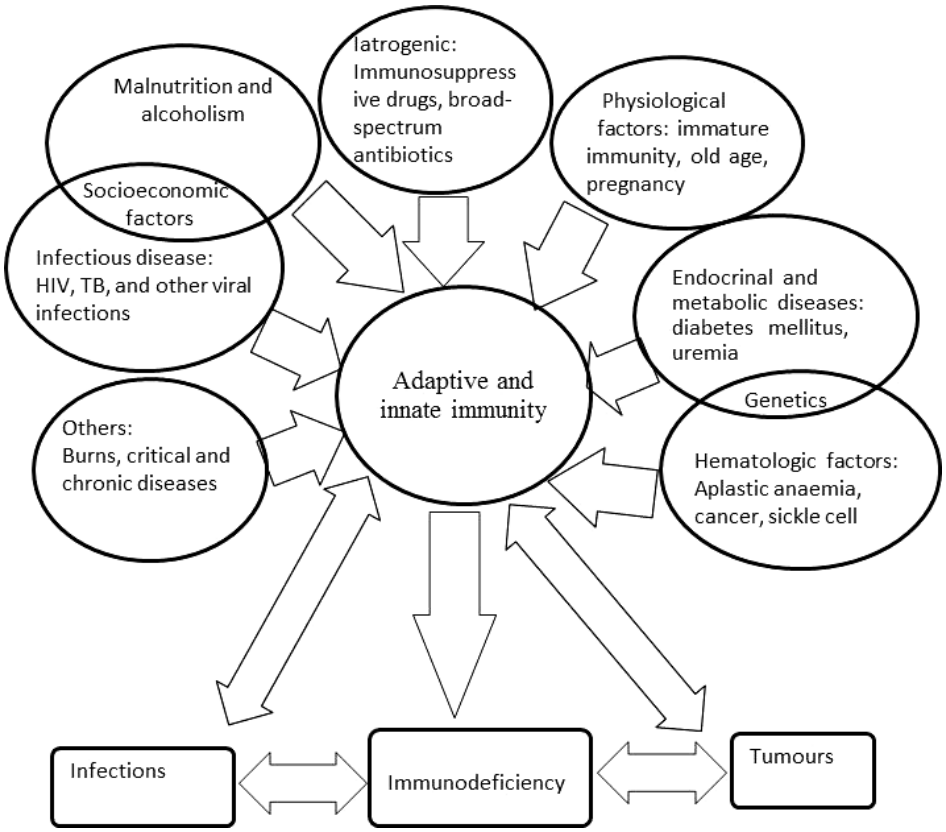

Fig. 1 Possible causes of secondary immunodeficiencies and consequences

2.1. HIV infection and secondary immunodeficiency

HIV/AIDS represents a special problem. Before its viral origin was recognized, AIDS was called "thin disease" in Africa because of its primary clinical manifestation, cachexia [6]. The HIV directly infects a number of T-helper cells and impairs other immune system responses indirectly. The technical meaning of the term "immunodeficiency" is nothing but "deviation of some parameters of the immune system from the normal state", not a lack of immunity (resistance to pathogens) itself as it may be perceived by many people. Immunodeficiency does not necessarily lead to decrease in immunity, which is not necessarily caused by immunodeficiency [1, 2]. Disease processes that lead to chronic imbalances in hormones, nutrients, and toxic metabolic waste products in body fluids may have profound effects on the function of one or more components of the immune system. Although antibacterials have greatly reduced mortality and morbidity rates for many infectious diseases, the ultimate outcome of an infectious process depends on the effectiveness of the host's immune responses. The antibacterial drugs provide a holding action, keeping the growth and reproduction of the infectious agent in check until the interaction between the organism and the defensive mechanisms of the host can subdue the invaders [7].

2.2. Immunosuppressive and immunoregulatory drugs

The use of immunosuppressive therapy has increased greatly in recent years. Patients undergoing organs transplant or on cancer therapies usually acquire immunodeficiency as result of effect of drugs or radiation on effector cells of the

immune system. The most common adverse effects include changes in cell trafficking: T cells are normally more affected than B cells, and among the T cell family, CD4 + T cells are more depleted than CD8+ T cells. Steroid drugs, for instance, can inhibit activation and maturation of lymphocytes T and B respectively, and making them unresponsive to interleukins (IL-1 and thus to IL-2). For instance, cyclophosphamide and azathioprine inhibit cytokines synthesis but not their functions by attaching to cytokine gene's promoter region and accelerate the breakdown of mRNA (IL-1 and IL–3), resulting in inhibition of T cell activation of both Th-1 and Th-2 cells as well as the inhibition of monocyte/macrophage system [1,2].

In developing countries, several chemotherapeutic agents are available as over the counter (OTC) drugs. Broad spectrum antibiotics, corticosteroids, benzodiazepines, just to mention a few are the most commonly and easily available as OTC. Benzodiazepines, particularly diazepam have been use as sleep inducer-agent indiscriminately; however, these drugs have been found to affect polymorphic mononuclear neutrophil chemotaxis, phagocytosis, general immunity and survival of mice to infections [8]. Active tuberculosis (TB) accelerates progression of HIV infection by promoting viral replication in activated lymphocytes. Glucocorticoids are used in pleural TB to reduce inflammation-induced pathology, and their use also might reduce progression of HIV by suppressing immune activation. Because of lack of resources and alternative therapies, patients and health care personnel occasionally are strained to use these agents [9].

It should be kept in mind that several OIs or diseases such as TB, pneumonia and Kaposi's sarcoma (KS) may develop during immunosuppressive treatment even in HIV-negative patients. Researches indicate that immunosuppression-associated or iatrogenic OIs may regress with the cessation, reduction, or modification of immunosuppressive therapy [10, 11].

2.3. Malnutrition (under nutrition and/or over nutrition)

Malnutrition is responsible, directly or indirectly, for 54% of the 10.8 million deaths per year in children under five and contributes to every second death (53%) associated with infectious diseases among children under five years of age in developing countries [6]. Undernourishment based on protein energy malnutrition (PEM) greatly increases susceptibility to major human infectious diseases in low-income countries, particularly in children [7, 12-17]. PEM is a common cause of secondary immunodeficiency and susceptibility to infection in humans (Table 1). Severe malnutrition during childhood affects thymic development, which compromises immunity in children by a long-term reduction of peripheral lymphocyte counts [18]. This immunodeficiency represents a key factor in susceptibility to infections and has therefore been also termed nutritionally acquired immunodeficiency syndrome [2, 19, 20]. Availability of complement components is restricted by malnutrition, thereby affecting the capacity of professional phagocytes to engulf and eliminate pathogens. In mice with experimental PEM, phagocytosis and production of reactive oxygen intermediates (ROIs) and reactive nitrogen intermediates (RNIs) by macrophages is diminished, as is antigen presentation to T cells by dendritic cells [20].

Table 1 Conditions of malnutrition and their influences on host defense functions [20].

Deficiency	Response mechanisms affected/promoted	Infection
Acute PEM	Phagocytosis, RNIs, ROIs, antigen presentation, leukocytes extravasation, inflammation, T-cell activation, T cell memory, antibody titres (IgG, IgA), cytokines secretion, leptin levels, macrophage activation.	Opportunistic, respiratory, and intestinal infections, helminths, tuberculosis, measles, influenza, *P. carinii jirovecii.*
Chronic PEM	Thymic development, T cell differentiation, T cell proliferation, T cell memory, complement and leptin levels decreased, macrophage activation	Respiratory and intestinal infections, helminths, BCG, malaria,, AIDS, measles, influenza, skin infections
Overnutrion	Permanent preactivation of leukocytes, IFN-g/TNF-a increased, suppressed NK and T cell activation, reduced phagocytosis, increased leptin concentration often paired with leptin resistance	Encapsulated bacteria, measles, opportunistic and fungal infections
Diabetes	Neutropli, macrophage functions (phsgocytosis, chemotaxis, extravasation), ROIs due to NADPH consumption by polyol pathway	TB, diseases due to opportunistic, multi-bacterial and fungal infections, osteomyelitis, diabetic foot (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumonia*).

Infection itself contributes to malnutrition. The relationship of malnutrition on immune suppression and infection is complicated by the profound effects of a number of infections on malnutrition itself. Examples of how infections can contribute to malnutrition are: (1) gastrointestinal infection can lead to diarrhea; (2) HIV/AIDS, TB, and other chronic infections can cause cachexia and anemia; and (3) intestinal parasites can cause anemia and nutrient deprivation [21-25]. Stimulation of an immune response by infection increases the demand for metabolically derived anabolic energy and associated substrates, leading to a synergistic vicious cycle of adverse nutritional status and increased susceptibility to infection. In response to infection, the immune system first executes innate and then subsequently acquired host defense functions of high diversity. Both processes involve activation and propagation of immune cells and synthesis of an array of molecules requiring DNA replication, RNA expression, protein synthesis and secretion, and therefore consuming additional anabolic energy. Mediators of inflammation further increase the catabolic response [26-30]. Maternal nutritional status may influence risk of transmission overall and during breastfeeding. Early observational studies reported that mothers with low serum retinol levels were more likely to transmit HIV to their infants [31]. This observation led to the implementation of several clinical trials in Africa on the impact of vitamin A supplementation with or without other micronutrients on mother-to-child HIV transmission, which has significantly alleviated the mother-to-child HIV transmission [32].

Under inflammatory conditions such as sepsis, mediators increase the catabolic disease state characterized by enhanced arginine use. Furthermore, arginase is induced during infection and uses up arginine as substrate. It has been suggested that depletion of this amino acid impairs T cell responses and exceeding the body's arginine production leads to a negative nitrogen balance [26]. A study in Nigeria found that the severe metabolic demands made during acute measles infection further deteriorated the condition of malnourished children, leading to further weight loss, wasting, and reduced serum levels of essential amino acids [30]. Increased energy consumption due to immune responses may also affect the efficacy of live attenuated vaccine in populations ridden with PEM. Under conditions of PEM and low leptin concentrations, glucocorticoids impair macrophage functions by decreasing nuclear factor kappa-light-chain-enhancer of activated B cells (INF-kB) translocation into the nucleus [33]. Under conditions of PEM and low leptin concentrations, glucocorticoids impair macrophage functions by decreasing NF-kB translocation into the nucleus [27].

Leptin is a central mediator connecting nutrition and immunity. It is a 16 kDa α-helix type protein similar to the cytokines IL-6 and IL-12, and is mainly secreted by adipose tissue. Levels of the pleiotropic hormone leptin, which regulates satiety, are reduced in patients with PEM. Activation and sustenance of immune responses during infection requires increased energy consumption [34]. PEM is a critical, yet underestimated factor in susceptibility to infection, including the "big three" infectious diseases: HIV/AIDS, TB, and malaria [27, 35]. The malnourished host is another condition considered as acquired immune deficiency which exhibits much immunodeficiency similar to those typically observed in AIDS. As this occurs in many regions of the third world or in developing countries it contributes to aggravate HIV infection. Some of these features include depressed cell mediated immunity (mainly as a consequence of depressed T-cell number), complement deficiencies, reduced phagocytic and microbicidal as well as tumoricidal activities of macrophages [36]. Malnutrition causes immunosuppression through a variety of mechanisms, including the involvement of leptin and the hypothalamic-pituitary-adrenal axis. PEM reduces leptin concentrations and increases serum levels of stress hormones such as glucocorticoids [13, 16, 18].

Moreover, immune defense at the epithelial barrier of the undernourished host is compromised due to altered architecture of the gut mucosa, such as flattened hypotrophic microvilli, reduced lymphocyte counts in Peyer's patches, and reduced immunoglobulin A (IgA) secretion [2, 34, 36]. Temporary PEM in mice challenged by experimental peritonitis resulted in impaired immune cell migration and extravasation, as indicated by reduced numbers of CD11b/CD18-positive cells at the site of infection. Various studies have shown that malnutrition/under nutrition has an impact on the clinical outcome of TB [15, 23, 34]. Recent researches show that HIV prevalence is highly correlated with falling calorie consumption, falling protein consumption, unequal distribution of income (inequity) and other variables conventionally associated with susceptibility to infectious disease [21]. Nevertheless, over-nutrition has negative impact on host body as well. In most if not all African and other developing countries, obese individuals demanded respect among the societies. On the other hand, skinny or slim persons were regarded as underfed/nourished, or poor and unable to feed themselves adequately. With advent of HIV/AIDS, skinny 'slim'' individuals were thought to be infected by HIV, from which the word ''slim'' came from [21]. Notwithstanding, over nutrition may result into accumulation/deposit of unused/excess of nutrients: excess of carbohydrates into fatty acids and proteins being converted to fatty acids and then stored as lipids. This kind of nutrients accumulation has detrimental effects to the body. The quantity and nature of lipids are important factors in the immune modulation. The immune parameters susceptible to modification by fatty acids supplied in the diet or free fatty acids added into cellular cultures affect lymphocyte proliferation, cytokine production, activity of NK cells, phagocytosis, and expression of markers in the surface of the cells [37, 38].

2.4. Life style: Stress and acquired immunodeficiency

Stress produces a variety of cellular changes, including the production of the "shock proteins." These proteins can make up 20% of the cell's total protein content [38]. By nature, the shock proteins are immunosuppressive. Besides activating the cells to produce massive amounts of the shock proteins, stress can also activate the so-called hormone receptors, such as estrogen receptors, even in the absence of the hormones. Stress also activates the endonucleases, which cut sections out of the DNA molecules, and activates mobile genetic elements, producing genetic instability. Like cortisol and estrogen, stress itself activates integrated retroviruses. The "endogenous retroviruses" make up nearly 10% of the human genome, and many of them locate themselves in regulatory sites in the chromosomes. Since stress lowers the discriminatory ability of the immune system, and stimulates the expression of retroviruses, the antibodies sometimes seen in association with immunodeficiency may be similar to the various autoantibodies that are also produced by stress. People who have autoimmune diseases such as lupus and Sjogrens syndrome which are promoted by estrogen [35], have antibodies which sometimes react positively in the AIDS test, and searches for the HIV virus in such people have found no evidence of it [36]. Treatments for roundworms and other parasites cause antibodies to retroviruses to appear in animals that previously tested negative**;** this might account for the high rates of positive tests for HIV in areas such as Africa in which treatment for filiariasis is common [39].

Most of the citizens of developing countries are faced with constant stress as results of illnesses and socioeconomic difficulties. The turning on of stress response for such long time, even at a low level, it can increase risks for chronic diseases. Exposure to fear and uncertainty triggers stress response. Human body can go on alert: the heart beats faster, blood pressure rises, glucose floods the bloodstream, until the source of alert or threat passes. But when threats are constant and unrelenting the physiological systems don't return to normal wears the body down over time, increasing the risks for diseases [40].

It has been widely speculated that violent conflict acts as a key contributor to the transmission of HIV. A previous study on empirical examination of the conflict-HIV relationship in 43 African countries during the period from 1997 to 2005 revealed an association between domestic and international conflict and levels of HIV/AIDS infection while controlling for a range of other influential factors. The study supports a clear positive relationship between both international and domestic conflict and climbing HIV/AIDS prevalence, as well as significant palliative effects for education and economic development on the incidence of HIV/AIDS [40].

3. Possible causes of opportunistic infections and secondary immunodeficiency

3.1. What causes opportunistic infections?

Neutrophil dysfunction underlies much of the predisposition to fungal infections predominant in patients with diabetes [41]. The decreased neutrophil function is directly related to the level of hyperglycemia. In addition, poor peripheral circulation leads to skin ulceration, and diminished delivery of neutrophils to sites of microbial entry. Some characteristic infectious complications of diabetes include disseminated candidiasis, rhinopulmonary zygomycosis (mucormycosis), and malignant otitis due to *P. aeruginosa* [3, 42]. Long-term use of broad-spectrum antibiotics or other drugs, HIV infection, or cancer; a surgical procedure such as cerebrospinal fluid shunt or cardiac or urinary tract catheterization; or immunosuppressive drugs may affect the immune system, creating opportunity for microorganisms not usually pathogenic to become pathogens. People with HIV are particularly susceptible to such infections. The main clinical manifestation of AIDS is severe OIs with abnormally high mortality. Human body is permanently exposed to a great many of species of microorganisms which are present in environment [1, 2, 34]. Of these, some are pathogenic and others are the so-called normal flora (non-pathogenic or opportunistic pathogens). There are two types of opportunistic pathogens: the ones which are normally dormant because conditions in the host are not suitable for their reproduction, independently or presence of other species (type I), and the pathogens which are capable to replicate in conditions of healthy organism, but are normally suppressed by other species of microorganism - by non-pathogenic resident flora (type II). Hence, the causes of OIs may be also subdivided into two groups: radical changes in metabolism of the host, and some factors which suppress the non- pathogenic resident microflora, antagonists of the type II opportunistic pathogens [34].

Likewise, whenever metabolism of the host deviates radically from the normal state due to disease, intoxication, and stress; such a change can make conditions suitable for some ever-present opportunistic pathogens and OI will develop. Even though such mechanisms of innate immunity protect organism from a great many of species, this protection is far from being universal. It is of paramount importance to the host that only non-pathogenic species normally dominate in its microflora and keep potentially pathogenic ones (opportunistic pathogens) at low and safe quantities. Thus, these non-pathogenic microflora protect the host from ever-present opportunistic pathogens [2, 34]. In actual fact, this interrelation is much more complex because hundreds of microbial species are involved in this process. Nevertheless, the main feature of this ecological system remains the same, that is external factors may lead to radical changes in proportions of various species in microflora [17]. Metabolic changes can also cause OI through violation of the "innate resistance" determined by peculiarities of the normal metabolism of the host (Fig. 2). Opportunistic viruses

are likely to be activated by such metabolic changes: viral reproductive cycle essentially depends on cellular metabolism [43].

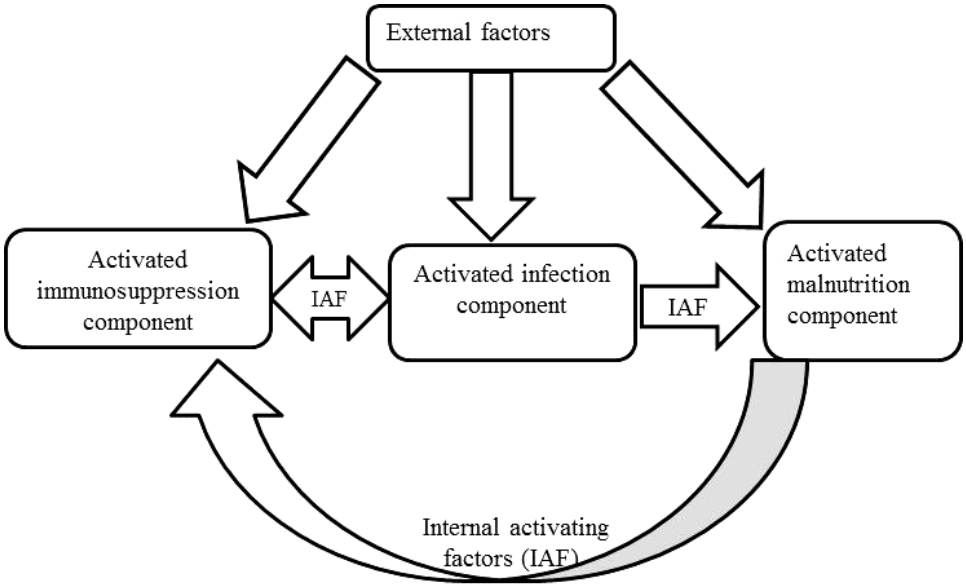

Fig. 2 External and internal factors as triggers of infections, malnutrition and immunodeficiency

3.2. Burden of secondary immunodeficiency in developing countries

Sub-Saharan Africa is considered home to more than 60% of all HIV infected cases, with an estimated adult prevalence of 8.0%. It is stated that this region has contributed more than 90% of childhood deaths related to HIV infection and about 93% of childhood AIDS-related deaths. Although no country in Africa is spared of the infection, the bulk is seen in East and South Africa, with the highest recorded rates of 20% to 50% in Zimbabwe. On the other hand, West Africa is less affected, while countries in Central Africa have relatively stable infection rates. Although infections, especially TB, have emerged as the most important HIV/AIDS-associated killers in recent times, AIDS-associated malignancies are increasingly identified in the late stages. As a result of incomplete data from African countries, it is unclear whether the epidemiology and risks of these cancers are the same as observed in the developed countries [44].

Since the advent of AIDS, epidemic Kaposi's sarcoma has become more common in both sexes in Africa, with a dramatic lowering of the male to female ratio from 19:1 to 1.7:1, especially in East Africa. Although there has been a rising trend of AIDS-associated non-Hodgkin's lymphoma worldwide, there is an apparently lower risk in Africa compared with that in the developing world. At present, there is no strong evidence linking increased incidence of invasive cervical cancer to the HIV epidemic; however, some studies have demonstrated an association between HIV and the increased prevalence of human papilloma virus (HPV) and cervical intraepithelial neoplasia [2, 44-47].

4. Correlation between opportunistic infections and T-lymphocytes immunodeficiency

It is well known that TB is the most frequent serious OIs in the developing world. Other such infections common in sub-Saharan Africa include septicemia (of which non-typhoid salmonella is the most common cause), toxoplasmosis, and bacterial pneumonia. *Pneumocystis carinii* infection, for unknown reasons, is uncommon among adults in East and West Africa but appears to be more common in South Africa. *Candida albicans* infection, common in East Africa, is an example of an OI of importance in a specific region; risk factors in these regions are largely due to acquired immunodeficiency particularly HIV/AIDS [36]. Additional challenges are posed by the different HIV subtypes in the developing world and the possibility that some may be associated with a differential risk for OIs. Therefore, OIs are a threat in the increasing populations of immunocompromised persons. In these populations, OIs pose challenges for surveillance and determination of risk factors, including those for infection with antibiotic-resistant organisms [46-52].

The human body is protected against pathogens by two mechanisms namely innate (non-specific) and specific. The later comprises of cell mediated immunity and humoral immunity. The cell mediated immunity plays major role in fighting intracellular pathogens, in which T-cell have vital function. Correlation between OI and T-immunodeficiency can be explained by the fact that severe OI, particularly which is induced by antibiotics causes stress-syndrome. Hence, T-immunodeficiency has to be expected in such cases as a consequence, not the cause of these OI. Secondly, both OI and T-immunodeficiency have common causal factors: cytostatic and cytotoxic drugs, and radiation. In individuals exposed to such factors, for example, in patients receiving anti-cancer or immunosuppressive therapy, OI can develop due to

suppression of the non-pathogenic resident flora by these factors [1, 2, 14]. Radical changes of metabolism in the catabolic reaction such as that caused by stress or by protein-calorie malnutrition, suppress both normal non-pathogenic flora (this causes OI) and the immune system (leading to T-immunodeficiency). Such mechanisms explain why people with severe and long-lasting diseases frequently suffer from OI as well as have signs of T-immunodeficiency. If T-immunodeficiency is the main cause of OI, then the immune system plays the leading role in permanent suppression of opportunistic pathogens in healthy organism. However, opportunistic pathogens are not able to induce any noticeable acquired immunity even in experiments [2, 46].

5. Challenges of infectious diseases, antimicrobial drug-resistance and acquired immunodeficiency

Drug-resistant strains of microorganisms are frequently detected in AIDS patients, and just this drug-resistance is partially responsible for the frequent lethal outcome of OI incurable by antibiotics. However, there is no any visible link between immunodeficiency and drug-resistance of the microorganisms [50]. On the other hand, drug-resistance is a natural consequence of antibiotic abuse that results from natural selection of drug-resistant mutants under the selective pressure of antibiotics [48, 50]. Selective pressure from antimicrobial agents inevitably leads to resistance development in a small subpopulation of microbes, which can subsequently spread by virtue of the rapid replication rates of microorganisms, and the efficient transfer of antimicrobial resistance genes via the process of conjugation whereby plasmids (carrying resistance genes) are exchanged among microbes. Although many social, financial and behavioural factors contribute to the emergence and dissemination of antimicrobial resistance in pathogens, inappropriate use of antibiotics constitutes one of the most important factors in this biological process [51, 52].

Methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and multi-resistant *Mycobacterium tuberculosis*, to name only a few of the many antimicrobial-resistant microbes, pose serious health challenges to biomedicine and public health. The inappropriate use of antibiotics and the underlying mechanisms of antimicrobial resistance have broad social and ethical significance that transcends individual patients or specific communities who suffer from treatment failures [51-54]. A study conducted in Nigeria indicates that a profound immunosuppression among hospitalized patients provides strong evidence against the hypothesis that patients in Africa die early in the course of HIV disease with relatively high CD4 counts, as a result of infection with pathogens of high virulence that are more prevalent in developing countries. The results are purported to be because of more rapid progression to advanced disease, perhaps as a response to chronic immune activation due to persistent exposure to pathogens, and/or because of a lack of access to prophylaxis and treatment of OIs [21, 22].

Infectious diseases are responsible for 41.9% of deaths in the developing world (WHO Global Burden of Diseases statistics), and about one in three deaths worldwide [49, 50]. Developing countries thus constitute an important market for companies selling antimicrobials drugs. Drug promotion practices that overstate the benefits and utility of medicinal drugs are thus bad for both patients and shareholders. Another consideration for developing countries is that the self-medication of antimicrobials is a common practice, since these medications can often be purchased without a prescription and their sales are poorly regulated by local governments [51, 54, 55]. In the face of these realities, drug promotion activities could lead to a greater coercive influence on consumers, whether they be healthy persons taking antibiotics for unjustified reasons or patients with infectious diseases. Therefore, all these adverse downstream consequences of aggressive drug promotion can be more deleterious in a developing world context [53]. On the other hand, in developing countries, very little is being done to control antimicrobial agents use in food animals, and there is very little data on actual antimicrobial use in agriculture, or the emergence of drug-resistant pathogens.

Most people in developing countries are taught that illnesses should be treated with medicine. Patients who have fever, inflammation of any cause, or even nonspecific illnesses commonly are prescribed an antimicrobial agent or treat themselves with drugs. Recognized epidemics of infectious diseases almost always are accompanied by an expansion in antimicrobial agents usage. The longer the duration and the larger the epidemic, the more antimicrobials are used and the higher the selective effect on resistant microorganisms. Hence, the most straightforward and potentially effective step for minimizing antimicrobial resistance problems by decreasing antimicrobial agents use is to prevent the illnesses in the first place [49, 56, 57].

In developing countries, many farms are very small (a few dozen animals) and commonly associated with household subsistence. This lifestyle has as a consequence that a large proportion of the population in developing countries (including those living in urban centers) lives in close contact with food animals, thus increasing the chances of microorganism transmission from food animals to humans through the food chain and animal handling [58]. This situation was clearly illustrated in a 2002 study of an outbreak of sepsis in pigs in China, which showed that a multi-drug-resistant strain of *Enterococcus faecium* was transferred to humans, leading to several deaths [59]. Similarly, it was also observed that resistant *Staphylococcus* species conventionally associated with animals were often present in septic wounds in Nigerian hospital patients [60].

Bacterial infections, which contribute most to human and animal diseases in developing countries, are also those in which emerging antimicrobial resistance is most evident [61, 62]. The development of resistance to antimalarial drugs is also of particular concern [63]. Moreover, there is an increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in HIV-1 infected people [61]. While in developed nations actions are being taken to address these problems, very little has been accomplished in developing countries because of the factors relating to poverty and inadequate resources [54, 63]. The transmission of antimicrobial-resistant strains between individuals is further exacerbated by the high urbanization rate in many developing countries, but also worldwide [64]. Even in developed countries, the spread of resistant microbial strains has been shown to occur not only through hospital settings but also through community-acquired infections [65]. The public health implications of human concentration on antimicrobial resistance emergence and transmission of strains affecting human populations are correlated with the poor sanitation conditions and high poverty levels in many urban areas.

6. Parasitic diseases and HIV/AIDS

Parasitic diseases have been shown to cause enhanced and prolonged immune activation [19, 21]. Chronic immune activation by parasites is associated with several significant immunologic features. A decline in CD4+ and CD8+ cells, impaired NK cell activity, increased T-cell apoptosis, and cellular anergy have all been demonstrated. These changes have been linked to the preferential activation of the Th2- type response, which in turn down-regulate the Th1- type response, hinder macrophage activity, and weaken the cytotoxic T-cell response [22]. Such responses may lead to a deleterious interaction with HIV infection [22, 32]. Gastrointestinal infections are very common in patients with HIV infection or AIDS; and diarrhoea is a common clinical presentation of these infections[66]. Reports indicate that diarrhoea occurs in 30-60% of AIDS patients in developed countries and in about 90% of AIDS patients in developing countries [67]. The aetiologic spectrum of enteric pathogens causing diarrhoea includes bacteria, parasites, fungi and viruses. Non opportunistic parasites such as *Entamoeba histolytica, Giardia lamblia, Trichuris trichiura, Ascaris lumbricoides, Strongyloides stercoralis* and *Ancylostoma duodenale* are frequently encountered in developing countries but are not currently considered opportunistic in AIDS patients [21, 68]. Findings indicate that though highly active antiretroviral therapy (HAART) plays an important role in prolonging the survival and disease-free period. However, rapidly effective HAART has often raised the inflammatory response to residual pathogens and induced OIs [69].

AIDS is overlapped by helminthic infections that are common in many regions of developing countries, which is estimated to affect more than 1,5 billion people. People highly infected with helminths in these regions have been associated with a high level of TB reactivation [27, 33]. Helminths appear as potent agents to induce Th2 response which is expressed by high IgE levels. A direct correlation of high serum IgE levels and an incidence of high skin test tuberculin have been observed in some HIV/AIDS patients [20, 33].

The prevalence of opportunistic parasitic infections has particularities in function of endemic problems of each region. *Cryptosporidium* and *Isospora belli* appear between the most frequent opportunistic parasitic infections in African patients with AIDS [26, 27]. Chagas disease appears in Latin America as an important opportunistic organism and presents frequent infection of central nervous system. Reactivation of Chagas disease in immunocompromised patients outside AIDS has been described either in cancer or in organ transplantation [26]. It has been suggested that eradication of helminthic infections may have an important impact on AIDS as well as TB in developing countries, which open a virgin arena for investigation.

The burden of morbidity and mortality associated with infectious diseases falls most heavily on people in developing countries [48, 70], and particularly on infants and children (about three million children die each year from malaria and diarrheal diseases alone [66, 67]. Moreover, hospitals in these developing countries are unable to control nosocomial infections and other infectious diseases that remain the leading cause of deaths [51]. Many sentinel hospitals have less than basic microbiology laboratory facilities; there is no end in sight to the HIV epidemic, and the prevalence rate of TB is increasing in parallel with it; hospital infections, especially surgical site infections, have become important causes of illness and death in certain hospitals in sub-Saharan Africa; and invasive medical devices and procedures are increasingly being introduced into intensive care units and operating theaters without the necessary infection control procedures.

7. Conclusions and recommendations

For about three decades now, secondary immunodeficiency particularly HIV/AIDS epidemic has devastated societies and communities in developing countries. A number of immunocompromised people have been left completely defenseless and at great risk of several infections. More than 90% of these people (over 30 million) are to be found in developing countries with about 22 million in Africa, because of the HIV/AIDS epidemic [70]. Many AIDS patients use antimicrobial drugs more frequently to protect against or treat infections, thus increasing the selection pressure for resistant organisms. Climatic and weather patterns influence the occurrence, incidence and distribution of infectious diseases such as cholera and malaria [57]. Civil wars in many developing countries have been responsible for

breakdown of health services and have resulted in refugee camps, or internally displaced people residing in camps. Such camps are often characterized by very poor hygiene and sanitation conditions, facilitating spread of infection and selection and spread of resistant microorganisms.

The current major obstacles to human health in developing regions are well understood and a large component relates to unsafe water, poor sanitation and inappropriate hygiene. In developing countries with high mortality, infectious diseases remain the main cause of death [66, 67]. About 80% of the world's population lived in developing countries, and around 25% of deaths are attributable to infectious and parasitic diseases that are rampant in these countries [67]. Resistant bacteria have emerged in these developing countries, whereby some of them regulation of the manufacture of antibiotics may not exist to any extent that would assure the quality and potency of the medications.

It must be noted that 'what happens in the developing world does not stay in the developing world'. With the globalization of travel, education, commerce and health care, antimicrobial resistance can be spread easily between developed and developing countries; antimicrobial resistance is thus a global problem and requires global and equitable solutions. Antimicrobial resistance is increasing worldwide despite efforts to minimize the problem and poses a global concern, which partly are due to high prevalence of secondary immunodificiencies and Ols that necessitate further use of antibiotics, sometimes indiscriminate use of the same, leading to spread of antimicrobial drug-resistance.

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