Chapter 13

Influence of Human Leukocyte Antigen on Susceptibility of Tropical Pulmonary Infectious Diseases and Clinical Implications

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Additional information is available at the end of the chapter

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1. Introduction

Human leukocyte antigen (HLA) is the most polymorphic genetic system in humans, with numerous alleles, and subsequently, various possible combinations [1]. These genes, the products of histocompatibility complex (MHC) [2] are located in the short arm of chromosome 6 at band p 21.3 [2] and are divided into three classes, I, II and III [1]. HLA class I is responsible for coding the molecules HLA-A, -B and -C, present in almost all somatic cells with killing of viral infected targets by class I antigens restrict cytotoxic T-cell (CD8+) function [2] while HLA class II genes code the molecules HLA-DR, -DQ and -DP [1] by presentation of exogenous antigens to T-helper cells (CD4+) or antigen presenting cells (APC) [2]. This polymorphism contributes to the differences in susceptibility to diseases among genetically distinct groups [1]. The molecules coded for by the HLA system are responsible for the antigen presentation [1]. The T lymphocytes that are linked to HLA molecules only recognize antigens by the antigen-specific cell surface receptor-antigens interaction [2], thus the HLA antigens [1] and MCH molecules [2] apparently participate in controlling susceptibility and resistance to various diseases. Some infectious diseases were considered as familial before the finding of the causative microorganism and early twin studies indicated that there was a substantial host genetic influence on susceptibility to diseases such as polio and tuberculosis (TB) [3]. At present, it has been confirmed that human genetic variation demonstrates a major influence on the course of diseases caused by several infectious microorganisms [3].

2. Severe Acute Respiratory Syndrome and HLA

Recently, Itoyama *et al* reported that the deletion of the 287 bp *Alu* repeat (D allele) in intron 16 of the angiotensin converting enzyme 2 (*ACE 2*) gene is associated with hypoxemia and diffuse alveolar damage in patients with severe acute respiratory syndrome (SARS) [4] and may protect acute lung injury and respiratory failure [5]. Nevertheless, there may be potential confounders to a genetic association study as the following: 1) the dead patients were excluded from this study, 2) hypoxemia was defined as requiring oxygen supplementation, and 3) only 44 patients were studied [6]. Some HLA subtypes, particularly *HLA-B*0703* and *HLA-DRB1*0301* alleles have been demonstrated to be more prevalent in patients with SARS [7] and those with poorer outcomes [8]. On the other hand, the polymorphism in *ACE II* gene, coding for a functional receptor of the SARS-coronavirus, was not associated with the susceptibility or outcome of SARS [9]. A previous study revealed that *CXCL10(-938AA)* gene is always protective from SARS infection whenever it appears only jointly with either *Fg12(+158T/*)* or *HO-1 (-497A/*)*, whereas *Fg12(+158T/*)* is associated with higher SARS-infection susceptibility unless combined with *CXCL10/IP-10(-938AA)* which is associated with lower susceptibility [10]. Chan *et al* concluded that the *ACE I/D* polymorphism was not directly associated with increasing susceptibility to SARS-coronavirus infection and was not associated with poor outcome after SARS-coronavirus infection [6]. A recent study in Taiwan demonstrated that *HLA-Cw*1502* [11], *-DR*0301* [11], and *-A*2402* [12] alleles conferred resistance against SARS infection. CD209L homozygote individuals [13] and low-mannose-binding-lectin-producing genotypes [14] have been demonstrated to have a significantly lower risk and increased risk of SARS infection, respectively. A previous study among Vietnamese population with SARS revealed that polymorphisms of two interferon-inducible genes, *2′, 5′-oligoadenylate synthetase 1* (*OAS-1* (G-allele in exon 3 and the one in exon 6)) and *myxovirus resistance-A* (*MxA*) were associated with SARS infection [15]. The single nucleotide polymorphisms (SNPs) in *MxA* was associated with the progression of SARS [15]. The SNPs in *OAS-1* were associated with SARS-coronavirus infection or SARS development [15]. The GG genotype and G-allele of G/T-SNP at position -88 in the *MxA* gene promoter were demonstrated more frequent in hypoxemic group of patients with SARS than non-hypoxemic group [15]. They may be related to the response of SARS patients to interferons (IFNs), particularly those with AA genotype of the A/G-SNP in exon 3 of *OAS-1* may respond to IFN treatment more effectively than those with AG or GG genotype [15]. If SARS re-emerges, IFN could be a promising candidate to treat patients with SARS [16-23]. These findings may contribute to the perception of IFN-induced antiviral response to SARS infection. SARS-coronavirus infection elicited both CD^{4+} and CD^{8+} T-cell responses to the M protein in recovered SARS patients that persisted for a long period of time [24]. This may have significant implications in developing SARS vaccines [24]. A previous study indicated that a *HLA-A*0201*-restricted decameric epitope P15 (S411-420, KLPDDFMGCV) derived from the S protein that was found to localized within the angiotensin-converting enzyme 2 receptor-binding region of the S1 domain could significantly enhance the expression of *HLA-A*0201* molecules on the T2 cell surface [25]. P15 then stimulated IFN-γ-producing cytotoxic-T lym-

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phocytes (CTLs) from the peripheral blood mononuclear cells of former SARS patients and induced specific CTLs from P15-immunized *HLA-A*2.1*-transgenic mice *in vivo* [25]. Significant P15-specific CTLs then were induced by *HLA-A*2.1*-trangenic mice that was immunized by a deoxyribonucleic-acid (DNA) vaccine encoding the S protein [25]. This suggested that P15 was a naturally processed epitope [25]. Thus, P15 could be a novel SARS-associated coronavirus-specific epitope and a potential target for evaluation of candidate SARS vaccines and characterization of virus control mechanisms [25].

3. Tuberculosis and HLA

HLA studies conducted in India revealed that there was association of *HLA-DQ 1* and *-DR 2* antigens with susceptibility of pulmonary TB [26]. A study in North Indian patients demonstrated that the allele *DRB 1*1501* of *HLA-DR 2* was higher compared with *DRB 1*1502* [26] whereas *HLA-DQB 1*0601* (a subtype of *HLA-DQ 1*), *-DRB 1*1501* and *DPB 1*02* were demonstrated to be positively associated with pulmonary susceptibility among South Indian patients [26]. Antigen processing gene 2 and mannose-binding protein (MBP) genes along with *HLA-DR2* have been associated with pulmonary TB [26]. Mannose-binding lectin-54 heterozygotes may be associated with protection against TB meningitis [26]. *HLA-DQB 1*0601* and *HLA-DRB 1*0803* were associated with TB disease progression in Korean populations [27]. The frequencies of *HLA-DQB 1*0402* and antigens DR4 and DR8 were significantly decreased in patients with pulmonary TB but the frequencies of *HLA-DQA1*0101*, *-DQB1*0501*, and *-DRB1*1501* were significantly increased in immunocompetent patients with pulmonary TB [28]. An increased frequency of *HLA-B*27* in the Greeks, *HLA-A*2* and *-B*5* in the Egyptians, *HLA-B*5*, *-B*15* and *-DR*5* in the North American blacks, *HLA-B*8* in the Canadians was observed [26] whereas *HLA-DQB1*0502* and *-DQB1*0503* alleles were demonstrated among the Thai and Vietnamese TB patients, respectively [26, 29]. *HLA-B*17-tumor-necrosis-factor-α-238/A*, *-tumor-necrosis-factor-α-308/2* and *-tumor-necrosis-factor-β-2* have been shown to be associated with TB bacteriological relapse among Indian population [30]. Recently, a novel *HLA-DR*-restricted peptide E7 from the ESAT-6 protein of *Mycobacterium tuberculosis* before and during TB treatment was used to prepare modified *HLA-DR*08032/E7* and *HLA-DR*0818/E7* tetramers to monitor tetramer-positive CD4+ T-cells in direct staining of single specimen and flow cytometric analyses and resulted in 0.1 to 8.8% in the initial pulmonary TB patients' blood, 0.1 to 10.7% in pleural fluid of the initial tuberculous pleuritis patients, 0.02 to 2.2% in non-TB patients' blood, 0.02 to 0.48% in healthy donors' blood and mostly resulted in 0 to 0.2% in umbilical cord blood [31]. After 90-120 days of initial TB symptoms, levels of tetramer-positive $CD4^+$-T cells in tetramer-positive $CD4^+$-T cells reached and kept at low even normal at 0.03 to 0.3% [31]. Tetramer-positive, interferon-γ-producing and/or tumor-necrosis-factor-α-producing $CD4^+$-T cells in pulmonary granuloma, lymph node and cavernous tissues of TB patients could be detected by *in situ* staining [31]. Sensitivity and specificity of tetramer molecules should be confirmed in the future in order to develop possible diagnostic reagents and research [31].

4. Human Immunodeficiency Virus Infection (HIV)/Acquired Immunodeficiency Syndrome (AIDS) — Related tropical pulmonary infectious diseases and HLA

The World Health Organization (WHO) estimates that 8-10 million new cases of TB globally occur each year [32]. Although AIDS is the same disease as HIV disease in all part of the world, this microorganism is mostly in many tropical countries [32]. In tropical countries, TB and bacterial pneumonia represent the major pulmonary infections among the patients with HIV-infection/AIDS [32]. Although the spectrum of HIV disease/AIDS is quite broad, the majority of the pulmonary infections in HIV-1 infected patients are similar to those observed in non-HIV infected persons [32]. The geographical differences are primarily due to varying frequencies rather than the kinds of infections [32]. Of all the pulmonary infections encountered in the tropics obviously *Mycobacterium tuberculosis* is one of the most significant pathogenic microorganisms [32]. A recent study on HLA and AIDS in children with AIDS revealed that the presence of homozygous *HLA-B* or *-C* alleles was associated with more rapid disease progression, in contrast, the presence of *HLA-B*27* or *-B*57* alleles was associated with slower disease progression which remained significant after adjustment for age, gender, race, and baseline HIV-1 log ribonucleic acid (RNA), $CD4^+$-T cell count and percent and weight for age Z score or other genetic variants including *CCR5-wt/Δ32* (CCR5 = chemokine (C-C motif) receptor 5), *-59029-G/A*, *CCR2-wt/64I* (CCR2 = chemokine (C-C motif) receptor 2), *CX_3CR1-249-V/I* (CX_3CR1 = chemokine (C-C motif) ligand 3-like 1), *-280-T/M*, *SDF-1-180-G/A* (SDF-1 = stromal cell-derived factor-1), *MCP-1-G/A* (MCP-1 = monocyte chemotactic protein-1), *MBL2-A/O* (MBL = mannose-binding lectin), *MBL2-X/Y* (MBL = mannose-binding lectin), *MBL2-P/Q* (MBL = mannose-binding lectin), and *MBL2-H/L* (MBL = mannose-binding lectin) [33]. Additionally, the *HLA-A*24* allele was associated with more rapid central nervous system (CNS) impairment and the *HLA-Cw2* allele protected against disease progression [33]. For HLA class II, the presence of the *HLA-DQB1*2* allele protected against both HIV-1 disease progression and CNS impairment [33]. HLA concordance between a mother and her infant is associated with increased risk of HIV transmission whereas HLA discordance decreases the risk of mother-to-child HIV transmission [34, 35]. HLA class I homozygosity [36, 37] and children who have the same HLA class I alleles at both sites with their mothers at one of more HLA locus [38] are at increased risk for more rapid disease progression.

4.1. HIV-infection/AIDS-TB Co-infection and HLA

Studies from Haiti and sub-Saharan Africa have demonstrated that 17% to 66% of TB cases are HIV-1 seropositive while 50% of HIV-seropositive patients with pulmonary symptoms are sick with TB [32]. A previous study in Brazilians by Figueiredo *et al* revealed that *HLA-A*31*, *HLA-B*41*, *HLA-DQB1*5*, and *HLA-DRB1*10* alleles, were over- represented in acquired-immunodeficiency-syndrome (AIDS) patients with TB, indicated that these HLA molecules are associated with susceptibility to TB in Brazilian patients with AIDS [39].

4.2. HIV-infection/AIDS-related community acquired pneumonia

A previous study in Kenya in 1976 demonstrated that 20% of patients presenting with pneumonia to Kenyatta National Hospital had pneumococcal bacteremia which was very common among HIV-infected patients (26% of the HIV-1 seropositive group versus 6% of the seronegative group) [40] whereas *Streptococcus pneumoniae* pneumonia has been the most common cause of bacterial pneumonia same as in the pre-AIDS era [32]. Approximately, 17% of medically hospital admissions to the one of East Africa's largest hospital are community acquired pneumonia (CAP) [32]. Gilks *et al* reported that invasive pneumococcal disease among the female prostitutes in Nairobi, Kenya was the most frequently encountered serious HIV-associated infection and was more common than TB [40]. Pneumococcal pneumonia occurred at a significantly higher rate among HIV- seropositive patients, particularly HIV-1 serotype [40]. The clinical presentation of pyogenic pneumonia in HIV-1 seropositive patients was similar to that observed in HIV-seronegative ones [40]. The acute onset of fever and cough was the most common presentation [40]. Although, approximately, 10% of patients with lobar pneumonia in the tropics fail to improve with penicillin treatment, there is no significant difference in penicillin treatment response in both HIV-seropositive and HIV-seronegative patients [40]. In tropical and developing countries, penicillin, because of it antimicrobial tolerance and cheapness, is still the drug of choice for CAP regardless of HIV status [40]. The mortality rate was higher among HIV-1 seropositive patients with CAP than HIV-1 seronegative persons with CAP (17% versus 8%) [40]. Recurrence of pneumococcal disease occurred 22% among the prostitutes in Nairobi, Kenya which rate of recurrence increased both in Kenya and the United States of America [40].

4.3. HIV-infection/AIDS-related pulmonary *Nocardia asteroides* infectionasteroides infection

Nocardiaasteroides is a branching filamentous, beaded Gram-positive-rod microorganism which is usually found worldwide in soil and decaying organic matter and usually produces disease in immunocompromised persons, particularly HIV-1 infected individuals although few cases have been reported from the tropical regions [32]. The earliest report of AIDS patients from Rwanda demonstrated one of 26 cases diagnosing *Nocardia asteroides* pleuropneumonia whereas one of 50 AIDS patients with pulmonary interstitial infiltrates in Zimbabwe was diagnosed pneumonia [32]. In previous studies in Uganda, Cote d' Ivoire, and Zaire, three of the 57, one of 52, and occasional AIDS patients who underwent post-mortem examination revealed histopathologically pulmonary military nocardiosis, respectively [32]. Clinical manifestations of pulmonary nocardiosis in HIV-1 infected patients are usually non-specific [32]. The majority of cases present with fever, cough, night sweats, malaise, and body weight loss [32]. Although nocardiosis is frequently disseminated at the presentation, the lungs are the most common site of involvement, particularly upper lobes [32]. Thus, pulmonary nocardiosis is roentgenographically indistinguishable from pulmonary TB [32]. Because of rarely positive-blood culture, culture of the respiratory specimens is the definitely diagnostic method [32]. Due to 47% of patients was indicated of nocardiosis so the diagnosis should be suspected if the characteristic morphology is detected on Gram staining [41]. This microor-

ganism is also weakly stains the acid fast [32]. According to ability to stain the acid fast coupled with the roentgenographic presentation of this microbial pulmonary infection, it may contribute to be misdiagnosed as pulmonary TB [32]. It is likely that sulphonamides (trimethoprim-sulphamethoxazole) will be effective in HIV-1 infected patients with nocardiosis whereas sulphonamides have been the treatment of choice for nocardiosis in non-HIV-1 infected patients [32]. Other antimicrobial agents with *in vitro* bactericidal activity to *Nocardia ÿsteroids* include amoxicillin-clavulanic acid, minocycline, amikacin, and third-generation cephalosporin [32]. Treatment duration is at least 6 to 12 months and, perhaps, indefinitely since recurrences have been reported [32].

4.4. HIV-infection/AIDS-related pulmonary melioidosis

Melioidosis is caused by the Gram-negative motile bacillus, *Burkholderia (Pseudomonas) pseudomallei* [32]. A previous study in Bangkok, Thailand, 49 cases were observed between 1975 and 1987 [32]. Of these patients, 20 had localized disease while 29 had disseminated disease [32]. Almost all of these patients had an underlying immunocompromised condition like hematological malignancy, collagen vascular disease, and diabetes mellitus [32]. One case had AIDS and presented with left lung infiltrates and recurrent bacteremic melioidosis [32]. More than 750 cases of melioidosis have occurred during the last two decades, and over 75% of the patients were farmers [32]. The disease is endemic in southeast Asia, west Africa, and northern Australia [32]. The clinical manifestations of melioidosis are non- specific but in immunocompromised patients, they usually present with fever and pulmonary infiltrates [32]. The roentgenographic presentation is also non-specific and may demonstrate diffuse infiltrates, hilar adenopathy, lung abscess, or extensive pneumonia, thus the diagnosis requires isolation of this microorganism, particularly by culture of blood and/or respiratory samples in cases with disseminated disease [32]. A previous study by Cheepsattayakorn *et al* at the 10th Zonal Tuberculosis and Chest Disease Center, Chiang Mai, Thailand in 2001 among a number of patients with clinical and roentgenographic presentations mimicked *Burkholderia (Pseudomonas) pseudomallei* pneumonia revealed no detection of the laboratory-confirmed cases but having dramatic response to 6-12 months of tetracycline treatment [42]. A previous study in Thailand reported that 14 immunocompromised melioidosis patients with disease dissemination had a treatment delay or were appropriately treated, all but one were dead [32]. Thus, rapid and early diagnosis and treatment with combined antimicrobials is crucial [32]. It should be emphasized that most HIV- infected/AIDS patients in Thailand are urban dwellers and that most melioidosis cases occur in farmers [32]. Thus, the incidence of melioidosis is expected to increase as the HIV epidemic spread into rural area [32]. *Burkholderia (Pseudomonas) pseudomallei* is usually susceptible to tetracycline, chloramphenicol, trimethoprim-sulphamethoxazole, and third-generation cephalosporin [32]. If the patient is seriously clinical toxic, two antimicrobials are usually recommended during the initial 30 days and followed by 60-150 days of trimethoprim-sulphamethoxazole alone [32]. In septicemic melioidosis, trimethoprim-sulphamethoxazole plus a third-generation cephalosporin are recommended [32]. For patients who are intolerant to trimethoprim-sulphamethoxazole, another antimicrobial listed above should be replaced [32].

4.5. HIV-infection/AIDS-related fungal pneumonia

4.5.1. Pulmonary histoplasmosis

Histoplasma capsulatum is a dimorphic soil dwelling fungus which is rare in Africa before the AIDS epidemic [43]. This microorganism is endemic in the Americas [43]. Histoplasmosis was reported in 1984 in a Zairean AIDS patients and subsequently was identified in a few post-mortem-examined lungs in Zaire [43]. African histoplasmosis is also caused by *Histoplasma duboisii*, a fungal disease which is not increased in Congo but occurs mainly in Central and West Africa [44]. Carme *et al* reported a 26-year-old Congolese male with disseminated *Histoplasma duboisii* infection [45]. In 1987, a white heterosexual European patient was reported with African histoplasmosis [46, 47]. Three Belgian AIDS patients who had lived in Africa disseminated *Histoplasma duboisii* infection whereas one of these patients developed pulmonary disease [48]. An African HIV-2 infected child from Guinea Bissau was reported with disseminated disease [46]. Amphotericin B remains the drug of choice for the treatment of histoplasmosis with AIDS [49]. Ketoconazole, with or without a prior course of amphotericin B, has been used, but sometimes with unacceptable results [50]. After induction therapy, patients should be maintained on lifelong maintenance therapy with either weekly intravenous amphotericin B, oral itraconazole, or oral fluconazole [50].

4.5.2. Pulmonary cryptococcosis

Cryptococcus neoformans, a budding encapsulated yeast is distributed worldwide [50]. In Haiti, the prevalence of cryptococcosis among AIDS patients was approximately 13% whereas as many as 30% of AIDS patients in some areas of subsahara Africa had cryptococcosis [51]. Most of the patients present with disseminated disease or meningitis although the lungs is the usual portal of entry, thus, isolated pulmonary involvement is unusual [32]. A previous study in Bujumbura, Burundi demonstrated that only one patients of 222 cases was diagnosed cryptococcal pneumonia [52] while two of 40 Ugandan patients in a previous study were diagnosed cryptococcal pneumonia [53] but no cases with pulmonary cryptococcosis in Cote d' Ivoire was reported in a post-mortem study [54]. Previous data from Rwanda indicated that cryptococcal pneumonia was common in this country [55, 56]. Between January 1990 and March 1992, 28 Rwandese HIV-1 infected patients were diagnosed cryptococcal pneumonia by isolation from sputum, pleural fluid, and bronchoalveolar lavage (BAL) [55]. The serum cryptococcal antigen testing was negative in all patients without extrapulmonary site of infection [55]. Generally, there are two varieties of *Cryptococcus neoformans*, and gattii [57]. Most HIV-1 infected cases were reported of neoformans variety [57]. Variety gattii is mainly restricted to tropical and subtropical areas [57]. Since 1987, six cases of variety gattii have been reported from Rwanda, Brazil, and Zaire [57]. One Rwandese patient with negative serum and cerebrospinal fluid cryptococcal antigen demonstrated right hilar adenopathy accompanying a right lower lung infiltrate [57]. *Cryptococcus neoformans* variety gattii was isolated from the BAL fluid when the patient did not respond to penicillin and trimethoprim-sulphamethoxazole [57]. Taelman *et al* demonstrated that itraconazole(200 mg/

day) was effective in preventing future disease dissemination for Rwandese patients with isolated pulmonary cryptococcosis [56]. Fluconazole (400-800 mg/day) has been shown to be effective as primary treatment as well as long-term therapy (200- 400 mg/day) [50]. In the USA, the drug of choice for treatment of cryptococcosis is amphotericin B, with or without flucytosine [50]. Nevertheless, these antimicrobials are frequently not available in tropical countries [50].

4.5.3. Pulmonary paracoccidioidomycosis

Paracoccidioidomycosis is caused by the dimorphic fungus *Paracoccidioides brasiliensis* [58]. The patients with paracoccidioidomycosis may present with cutaneous form, isolated pulmonary involvement, or disseminated form [58]. Most patients present with disseminated involvement [58]. Only few cases involving HIV-1 infection have been reported despite its endemicity [58]. The chest roentgenographic findings demonstrate notable diffuse reticulonodular infiltrates, and sometimes with hilar adenopathy [59]. Patients have been successfully treated with various regimens including amphotericin B, imidazole compounds, and sulphadiazine [60]. Itraconazole (100 mg/day) appears to be more effective than ketoconazole (200-400 mg/day) which has been successfully used to treat paracoccidioidomycosis in immunocompetent patients with unknown treatment duration [60]. Nevertheless, the recommended treatment duration is 6 to 18 months [60]. At least two patients have been placed on suppressive therapy with sulphadiazine (1-6 g/day) for lifelong prophylaxis with good early results [60].

4.5.4. Pulmonary penicillosis

This disease caused by the usual dimorphic fungus, *Penicillium marneffei*, both in normal and immunocompromised hosts [61]. This fungus is endemic to southeast Asia and southern China [61]. Most cases have been reported as a systemic mycoses [61]. A previous study from Thailand demonstrated that 11 of the 21 patients had a cough as their presentation [61]. Of the 6 cases with abnormal chest roentgenographic findings, 3 showed diffuse reticulonodular infiltrates, 2 had localized interstitial infiltrates, and 1 had a focal alveolar infiltrate [61]. Definite diagnosis is usually made from cultures of blood, bone marrow, or skin biopsy [61]. The current treatment of choice is 6-8 weeks of Amphotericin B (40 mg/kg) [32]. In in above study in Thailand by Supparapinyo *et al*, 6 of 8 patients who were treated with Amphotericn B responded well [61]. Nevertheless, 6 of 9 patients who were treated with 400 mg itraconazole for eight weeks also well responded [61]. Unfortunately, 4 patients died before treatment started [61]. *Penicillium marneffei* infection may become more common as HIV-infection/AIDS move into rural areas as with melioidosis [32].

4.5.5. Pneumocystis jeroveci (carinii) pneumonia (Pulmonary pneumocystosis)

Currently, the taxonomy of *Pneumocystis jeroveci (carinii)* is in question, but recent data demonstrated it is closely related to fungus [62]. Generally, *Pneumocystis jeroveci (carinii)* is a ubiquitous microorganism found every region of the world [63]. During the course of HIV

disease/AIDS, 75% of the patients may develop *Pneumocystis jeroveci (carinii)* pneumonia (PCP) [64]. A previous study by Cheepsattayakorn *et al* at the 10th Zonal Tuberculosis and Chest Disease center, Chiang Mai, Thailand between 1999 and 2000 among 49 HIV-infected/AIDS patients who had clinical manifestations and chest roentgenographic findings compatible with PCP revealed that only one patient demonstrated induced sputum-reverse transcriptase polymerase chain reaction (RT-PCR)- confirmed PCP whereas two patients were confirmed by blood RT-PCR [65]. Nevertheless, the frequency of PCP is quite different in tropical countries [66]. Blaser *et al* reported that 20% of PCP occurred among HIV-infected/AIDS individuals native to the tropics (35%) was significantly lower than for HIV-infected/AIDS individuals in more developed countries (73%) [66]. PCP has been detected in 37% of AIDS patients of African origin in the USA and in 14-24% of African patients with AIDS treated in Europe [67]. The question is whether the exposure to *Pneumocystis jeroveci (carinii)* occurred in Africa or after leaving is not known. A previous study from Zimbabwe reported that of 50 HIV-infected/AIDS patients with acute interstitial pneumonia, 17 and 16 were diagnosed PCP and TB, respectively [68]. By using sputum induction with hypertonic saline, researchers in Tanzania reported that 3 of 83 specimens (3-6%) were positive for *Pneumocystis jeroveci (carinii)* [69]. A number of previous studies in 229 AIDS cases from Haiti indicated that PCP was detected in only 7% of 131 cases compared with 71% of the first 80 AIDS patients noted at the New York Hospital in New York City, USA [70]. Chequer *et al* reported their study in Brazil of 2,135 adult AIDS patients and demonstrated that 425 cases (20%) were diagnosed PCP whereas PCP plus another infection was detected in 265 cases (12%) [71] whereas 45% of homosexual urban AIDS patients in southern Brazil were diagnosed PCP [72]. The clinical and roentgenographic presentations of PCP are likely to be similar among the different regions [68]. Nevertheless, the frequent occurrence of TB in developing countries makes differentiation of the two diseases difficult [68], but in one study, the clinical picture most consistent with PCP was a respiratory rate of over 40/minute [68]. In contrast, the coarse reticulonodular infiltrates on the chest roentgenogram is most likely to be TB [68]. Currently, the treatment of choice for PCP is trimethoprim-sulphamethoxazole [32]. Other alternative antipneumocystis drugs are often not available in the tropical countries [32]. It has been postulated that HIV-infected/AIDS patients in the tropics die before they become immunocompromised enough to develop PCP [54, 73, 74].

4.6. HIV-infection/AIDS-related parasitic pneumonia

4.6.1. Pulmonary strongyloidiasis

Very few parasitic diseases have been reported to cause pneumonia in HIV- infected/AIDS patients [32]. A helminth, *Strongyloides stercoralis* which is commonly found in many tropical and subtropical areas, has occasionally been reported as the cause of pulmonary disease [32]. The prevalence of this helminth in stool specimen varies from region to region as the following : 26-48% in subsahara Africa, 15-82% in Brazil, 1-16% in Ecuador, and 4-40% in the USA [75]. Although the prevalence of strongyloides infection in southeast Asia is high, but no cases have been reported in the English language literature [32]. There have been rela-

tively few cases reported of helminth infection in AIDS patients in the tropics despite its high prevalence [32]. In a previous study in Brazil, 10% of 100 AIDS patients were infected with *Strongyloides stercoralis* [76] whereas in a study in Zambia, 6% of 63 HIV-infected patients with chronic diarrhea were infected with *Strongyloides stercoralis* [77]. The parasitic females live in the mucous membrane (wall) of small intestine of humans, particularly in the lamina propria of the duodenum and proximal jejunum whereas the parasitic males remain in the lumen of the bowel and they have no capability to penetrate the mucous membrane [78]. The rhabditiform larvae that emanating from the eggs pierce the mucous membrane and reach the lumen of the bowel [78]. These larvae are then passed with feces and can penetrate the intestinal epithelium or perianal skin without leaving the host by metamorphosing into filariform larvae in the lumen of small intestine [78]. This contributes to autoinfection and persistence of infection for 20 to 30 years in individuals who have left the endemic regions [79]. Most patients with hyperinfection present with cough, fever, and breath shortness and usually diffuse pulmonary infiltrates [80]. The definite diagnosis is identifying the helminth in the respiratory specimens or stool [80]. Previous reports demonstrated that at least two cases with strongyloides hyperinfection had concomitant PCP [81, 82]. In a previous review of the literature revealed that only surviving patients were treated with thiabendazole, 25 mg/kg twice a day for five days with three courses 10 days apart followed by monthly course of thiabendazole whereas the duration of treatment in HIV-1 infected individual is unknown [82]. Generally, most patients have died directly or indirectly from their strongyloides hyperinfection [82]. It seem cautious to treat any patient who is infected with *Strongyloides stercoralis* detected in the stool despite the rarity of clinically significant strongyloides infection in HIV-infected/AIDS patients [82].

4.6.2. Pulmonary ascariasis

Ascaris lumbricoides is the most common intestinal helminthic infection [83]. Both fertilized and unfertilized eggs are passed in the feces and released in the soil [84]. Infection occurs through soil contamination of hand or food with eggs and then swallowed [84]. The eggs hatch into larvae in the small bowel, call " first stage ", then moult into second-stage larvae in the lumen of the small bowel. The second-stage larvae penetrate the wall of the intestine and migrate via lymphatics and capillaries to the hepatic circulation and to the right side of the heart and then reach the lungs [84]. The second-stage larvae larvae moult twice more in the alveoli to produce third- and fourth-stage larvae. The fourth-stage larvae which are formed 14 days after ingestion migrate upward to the trachea and then are swallowed to reach back the small bowel [84]. The fourth-stage larvae take approximately 10 days for migration from the lungs to the small intestine [84]. It takes 10-25 days to produce eggs after initial ingestion [84]. The migrating larvae can induce tissue- and lung- granuloma formation with macrophages, neutrophils, and eosinophils [85]. This may produce a hypersensitivity in the lungs and result in peribronchial inflammation, increased bronchial mucus production and finally, bronchospasm [85]. *Ascaris lumbricoides* can produces both specific and polyclonal IgE [85]. Elevation of IgG4 levels in patients with ascariasis have also been reported [86]. Symptomatic pulmonary involvement may range from mild cough to a Lof-

fler's syndrome which is a self-limiting lung inflammation and is associated with blood and pulmonary eosinophilia, particularly childhood ascariasis [87, 88]. This syndrome can occur as a result of exposure to various drugs. Clinical Presentation may vary from malaise, fever, loss of appetite, myalgia, and headache [87, 88] to respiratory symptoms which include sputum-productive cough, chest pain, hemoptysis, shortness of breath, and wheezing [89]. Chest roentgenographic findings usually demonstrate peripherally basal opacities, but occasionally show unilateral, bilateral, transient, migratory, non-segmental opacities of various sizes [90].

4.6.3. Pulmonary ancylostomiasis

4.6.3.1. Ancylostoma duodenale

Ancylostoma duodenale can live only one year [91, 92]. Female *Ancylostoma duodenale* produces 10,000 to 30,000 eggs per day [91, 92]. Man is the only definite host [91, 92]. *Ancylostoma duodenale* larvae can enter the human host via the oral route in addition to the entry through the skin and reach pulmonary circulation through the lymphatics and venules [91]. *Ancylostoma duodenale* larvae can developmentally get arrested in the intestine or muscle and restart development when environmental conditions become favorable [93]. Bronchitis and bronchopneumonia can occur when the larvae break through the pulmonary capillaries to enter the alveolar spaces [32, 91, 92]. Pulmonary larval migration can develop peripheral blood eosinophilia [32, 91, 92]. Hookworm larvae can release a family of protein called " ancylostoma-secreted proteins (ASP) " [32, 91, 92] and can secrete low-molecular weight polypeptides which inhibit clotting factor Xa and tissue factor VIIa [94]. During pulmonary larval migration, the patients may present with cough, fever, wheezing, and transient pulmonary infiltrates that is associated with blood and pulmonary eosinophilia [32]. Both albendazole (single dose of 400 mg) and mebendazole (100 mg twice daily for three days) are drug of choice for treatment of hookworm [32]. Pyrantel pamoate (single dose of 11 mg/kg with maximum dose of 1 g, orally) is an alternative drug of choice [32]. A previous study revealed that ivermectin can effectively treat hookworm infections [32].

4.6.3.2. Necator americanus

Necator americanus larvae can infect human only through the skin [91]. The larvae reach the lungs same mechanisms as the *Ancylostoma duodenale* [32]. The interval between the time of skin penetration and laying of eggs by adult worms is about six weeks [32]. Bronchitis and bronchopneumonia can occur when the larvae break through the pulmonary capillaries to enter the alveoli [32]. Drugs of choice for treatment of *Necator americanus* are the same as the drugs of choice for treatment of *Ancylostoma duodenale* [32].

4.6.4. Pulmonary paragonimiasis

In Asia, nearly 20 million people are infected with *Paragonimus* species such as *Paragonimus westernmani* which is the main species in humans, *Paragonimus mexicanus*, *Paragonimus africa-*

nus, *Paragonimus miyazakii*, *Paragonimus phillipinensis*, *Paragonimus kellicotti*, *Paragonimus skrjabini*, *Paragonimus heterotremus*, and *Paragonimus uterobilateralis* [95-97]. Paragonimiasis is a food-borne zoonoses [32]. Humans get *Paragonimus* species when ingest raw crayfishes or crabs infected with infective metacercariae [95]. The parasite from the human gut passes through several organs and tissues to reach the lungs [95]. Adult worm live in the lungs and the eggs are voided in the sputum or feces [95]. Pulmonary paragonimiasis manifests as chronic cough, hemoptysis, chest pain, and fever [98]. Pneumothorax or pleural effusion is an important manifestation in paragonimiasis [99]. Chest roentgenographs may demonstrate infiltrates, nodules, and cavities [100]. The parasitic eggs can be shown in sputum specimens, bronchoalveolar lavage fluid or lung biopsy specimens [32].Peripheral blood eosinophilia and elevated serum IgE levels are demonstrated in more than 80% of cases with paragonimiasis [95, 99]. *Paragonimus westernmani* adult excretory-secretory products are composed of cysteine proteases which are involved in immunological reactions during parasitic infection [101, 102]. Immunoglobulin G4 antibodies to an excretory-secretory product of *Paragonimus heterotremus* had accuracy, sensitivity, specificity, and positive and negative predictive values of 97.6%, 100%, 96.9%, 90%, and 100%, respectively [103]. Paragonimiasis can be treated with praziquantel 75 mg/kg/day for three days), triclabendazole (20 mg/kg in two equal doses), niclofolan (2 mg/kg as a single dose), or bithionol (30 to 40 mg/kg in 10 days on alternative days) [95, 104, 105].

4.6.5. Pulmonary schistosomiasis

Schistosoma species that cause human disease are *Schistosoma hematobium*, *Schistosoma japonicum*, and *Schistosoma mansoni* [106]. The schistosome eggs are passed in feces (*Schistosoma japonicum* and *Schistosoma mansoni*) or in urine (*Schistosoma hematobium*) [32]. The infective cercariae in water are ingested to penetrate the human gut or penetrate human skin and finally reside at the mesenteric beds (*Schistosoma japonicum* and *Schistosoma mansoni*) and the urinary bladder vesicle beds (*Schistosoma hematobium*) [32]. Pulmonary schistosomiasis can clinically present as acute or chronic form [32]. Acute manifestations, called " Katayama syndrome " can develop three to eight weeks after skin penetration [107, 108]. The acute form presents with dry cough, wheezing, shortness of breath, chill, fever, weight loss, abdominal pain, diarrhea, urticarial, myalgia [108, 109], and small pulmonary nodules in chest roentgenographs or computed tomography in immunocompromised patients [110]. Patients with chronic form present with pulmonary hypertension and cor-pulmonale [111, 112] whereas massive hemoptysis and lobar consolidation and collapse have been reported [113]. Hepatosplenomegaly due to portal hypertension has been reported in patients infected with *Schistosoma japonicum* and *Schistosoma mansoni* [106]. In chronic form, peripheral blood eosinophilia with mild leukocytosis, IgE levels, and abnormal liver function test are reported [106]. Acute and chronic schistosomiasis can be treated with corticosteroids alone followed by praziquantel (20-30 mg/kg orally in two doses within 12 hours) and then praziquantel is repeated several weeks later to eradicate the adult flukes [106]. Acute form can be treated with artemether, an artemisinin derivative [106].

4.6.6. Pulmonary hydatid disease

Human hydatid disease is caused by *Echinococcus multilocularis* and *Echinococcus granulosus* [32]. Hydatid cysts are mainly formed in the lungs and liver [32]. Pulmonary alveolar echinococcosis (AE) is caused by hematogenous spreading from hepatic lesions [114]. The adult *Echinococcus granulosus* resides mainly in the small gut of the dogs [32]. Humans are infected by ingestion of parasitic eggs excreted in the feces of the dogs [32]. Clinical pulmonary manifestations include cough, dyspnea, chest pain, and fever [32]. Rupture of hydatid cysts into a bronchus may result in expectoration of cystic fluid containing parasite membrane, hemoptysis, asthma-liked symptoms, respiratory distress, persistent pneumonia, anaphylactic shock, and sepsis [115, 116] and elevation of IgG and eosinophilia [117]. Immunodiagnostic tests using purified *Echinococcus granulosus* antigens have preferable sensitivity and specificity for the diagnosis of AE [118]. Chest roentgenographs demonstrate solitary or multiple round opacificaties mimicking lung tumors [119]. It has been experimentally revealed that magnetic resonance imaging can detect early pulmonary AE [120]. Many year-treatment with mebendazole, praziquantel or albendazole is useful, particularly in inoperably recurrent and multiple cysts, but treatment of hydatid cyst is primary surgical [121]. The treatment of AE is radical surgical resection of entire parasitic lesion [121] but should avoid segmentectomy, lobectomy, and pneumonectomy [122-124].

4.6.7. Pulmonary trichinellosis

The most important species that infect humans is *Trichinella spiralis* [125]. Humans get parasitic infection from ingestion of raw and infected pig's muscle containing larval trichinellae [126]. The larvae develop into adults in the duodenum and jejunum [126]. The larvae undergo encystment in the muscle and a host capsule develops around the larvae and later on may get calcified [126]. Clinical pulmonary features include cough, dyspnea, and pulmonary infiltrates on the chest roentgenographs [127]. The important laboratory findings are elevation of serum aminotransferase, serum adolase, serum lactate dehydrogenase, and serum creatine phosphokinase, leukocytosis, and eosinophilia [127]. An enzyme-linked immunosorbent assay (ELISA) for identification of anti-*Trichinella* antibodies using excretory-secretory antigens may be useful in the diagnosis of *Trichinella spiralis* infection [128], a definite diagnosis can be performed by muscle biopsy (preferably deltoid muscle) [127]. Treatment of choice is with mebendazole, 200 to 400 mg, three times a day for three days followed by 400 to 500 mg, three times a day for 10 days [32]. The alternative drug of choice is albendazole, 400 mg per day for three days followed by 800 mg per day for 15 days [32]. Symptomatic treatment of trichinosis is analgesics and corticosteroids [32].

5. Filarial parasites — Related tropical pulmonary eosinophilia and HLA

This syndrome results from immunological hyperresponsiveness to human filarial parasites, *Wuchereria bancrofti* and *Brugia malayi* [129]. Tropical pulmonary eosinophilia (TPE) is one of the main causes of pulmonary eosinophilia in the tropical countries and is prevalent in filarial

endemic regions of the world particularly Southeast Asia [129, 130]. Clinical findings are cough, fever, chest pain, and body weight loss in association with massive blood eosinophilia [131]. Chest roentgenographs demonstrate military infiltrates of both lungs mimic military TB [132]. Additionally, there may be prominent hila with heavy vascular markings [133-136], but 20% of cases present with normal chest roentgenographs [137]. Some previous studies of computed tomographic scan of the chest demonstrated air trapping, mediastinal lymphadenopathy, calcification, and bronchiectasis [138]. At least 120 million people are globally infected with mosquito-borne lymphatic filariasis [137], but only less than 1% of filarial infection causes TPE [139] whereas various studies have demonstrated that filarial infection is the cause of TPE [129, 140]. A positive immediate reaction to intradermal skin tests with *Dirofilaria immitis* antigens have been demonstrated in patients with TPE [141]. Microfilariae, anatomical features of *Wuchereria bancrofti* had demonstrated in the lungs, liver, and lymph nodes of the patients with TPE [142-144], but are rarely identified in the blood [142]. A recent study revealed that the $CD45RA^+$ and $CD45RA^-$ effector cells in patients with chronic lymphatic filarial infection demonstrated a reduced activation state based on their lower expression of *HLA-DR*, contrasting with findings identified in patients with HIV-1 infection [145]. An inverse correlation between the percentage of $CD8^+$ $HLA\text{-}DR^+$ lymphocytes pokeweed mitogen-induced proliferation was observed [146]. These findings indicated that activated $CD8^+$- T lymphocytes may be involved in the pathogenesis of chronically obstructive lymphatic form of filariasis [146]. A previous study conducted by Sasisekhar *et al* demonstrated that monocytes from microfilaremic (MF) patients revealed an inability to respond to lipopolysaccharide compared to monocytes from endemic normal individuals of from patients with lymphedema [147]. Serum from MF patients demonstrated reduction of adherence and spreading of normal monocytes which was a finding not observed with serum from other clinical individuals [147]. Surprisingly, there was a significant correlation between the adherence of normal lymphocytes and the production of interleukin (IL)-1β with spontaneous secretion of IL-10 [147]. The effects noted were not a result of diminished viability or alteration in the expression of the cell surface markers *HLA-DR* and CD14 [147]. This study indicates that monocyte function is dampened in MF patients [147]. A previous study in Sri Lanka and India demonstrated that 30% of Sri Lankan patients with elephantiasis and 28% of Southern Indian patients with elephantiasis were significantly associated with *HLA-B*15* compared to 4% of Sri Lankan controls and 10% of Southern Indian controls [148]. Filarial specific IgG and IgE concentration elevation have been observed in TPE [149]. Peripheral basophils from patients with TPE was released more greater amounts of histamine when they were challenged with *Wuchereria* or *Brugia* antigens than with *Dirofilaria* antigen [149]. This indicated that TPE resulted from immunological hyperresponsiveness to human filarial parasites [149]. Leukocyte adhesion phenomenon in sera from patients with TPE using *Wuchereria bancrofti* revealed maximal positive results compared with *Dirofilaria immitis* and *Dirofilaria repens* [150]. Demonstration of living adult *Wuchereria bancrofti* in the lymphatic vessels of the spermatic cord of the patients with TPE is evidenced by ultrasound examination [151] and biopsy of a lump in the spermatic cord shows degenerating adult female filarial worm with uteri full of microfilariae [152]. There is a marked reduction of filarial-specific IgG and IgE levels in the lung epithelial lining fluid [153] and roentgenological improvement [154, 155] after 6-14 days of therapy with dethylcarbamazine citrate (DEC). The

standard treatment recommended by the World Health Organization is oral DEC (6 mg/kg/day) for three weeks [156]. The usefulness of DEC in the treatment of TPE further focuses attention on its filarial etiology [157, 158].

6. Pulmonary malaria and HLA

Four types of malarial parasites (*Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium vivax*, and *Plasmodium ovale*), the protozoa of the genus *Plasmodium* causes malaria and is primarily transmitted by the bite of an infected female *Anopheles* mosquito to infect humans [159]. A previous study in a Thai population demonstrated that the allele frequencies of *HLA-B*46*, *-B*56*, and *-DRB1*1001* were statistically different between non- cerebral severe malaria and cerebral malaria, between mild malaria and non-cerebral malaria, and mild malaria and cerebral malaria, respectively [160]. A recent study revealed that the NK cell repertoire shaped by the *KIR2DL3-HLA-C1* interaction demonstrates certain functional responses that facilitates the development of cerebral malaria [161]. The frequency of the *KIR2DL3-HLA-C1* combination was found to be significantly lower in malaria high-endemic populations [161]. This indicates that natural selection has reduced the frequency of the *KIR2DL3-HLA-C1* combination in in malaria high-endemic populations because of the propensity of interaction between *KIR2DL3* and *C1* to favor development of cerebral malaria [161]. Young *et al* conducted a study in Mali and Gambia and reported that either malaria parasite types cp26 or cp29 were found to be less, not more common in Mali population with *HLA-B*35* (37%) compared to non-*HLA-B*35*-bearing hosts (55%) whereas 51% of *HLA-B*35*-bearing Gambian population were infected with either cp26 or cp29 compared to 42% of non-*HLA-B*35*-bearing hosts [162]. A previous study in West African children demonstrates that *HLA-Bw*53*, *-DRB1*1302*, and *-DQB1*0501* which are common in West Africans are independently associated with protection from severe malaria [163]. *HLA-DR*04* alleles were observed more frequently among patients with severe malaria [164]. Additionally, carriers of the amino acid methionine at position 11 of the *DPA1* allele were more often infected with merozoite surface antigen (MSA)-1 K1 malaria parasites and less frequently with MSA-1 RO33 malaria parasite infection [164]. The main finding of patients with falciparum malaria which is the most deadly type of malaria infection is sequestration of erythrocytes containing mature forms of *Plasmodium falciparum* in the microvasculature of the organs and is quantified by measurement of *Plasmodium falciparum* specific histidine-rich protein 2 (PfHRP2) using a quantitative antigen-capture enzyme-linked immunosorbent assay [159]. Gas exchange is significantly impaired in patients with severe malaria [165]. The gold standards for the diagnosis of malaria are light microscopic examination of thin and thick stained blood smears [78, 166]. Human urine and saliva PCR detection of *Plasmodium falciparum* has been introduced [166]. In severe falciparum malaria, the roentgenographic presentations include diffuse interstitial edema, pulmonary edema, pleural effusion, and lobar consolidation [166]. Intravenous chloroquine is the drug of choice for chloroqiune-susceptible *Plasmodium falciparum* infections and those rare cases of life-threatening malaria caused by *Plasmodium*

vivax, *Plasmodium malariae*, and *Plasmodium ovale* [78, 166]. A point mutation in the *Plasmodium falciparum* chloroqiune-resistance transporter (PfCRT) gene is responsible for chloroqiune-resistant falciparum malaria [167] whereas diaappearance of the K76T mutation in PfCRT is associated with chloroquine susceptibility [168]. Oral artemisinin -based combination therapies (artesunate + mefloquine, artesunate + sulfadoxine-pyrimethamine, artesunate + amodioquine, or artemether + lumefantrine) are the best antimalarial drugs [169, 170]. Additionally, the World Health Organization (WHO) recommends oral treatment of dihydroartemisinin plus piperaquine as soon as the patients is able to take oral medication but not before a minimum of 24 hours of parenteral treatment [171]. The WHO recommended that intravenous artesunate can be used preferentially over quinine for the treatment of severe malaria caused by any *Plasmodium* species in both children and adults [172]. Oral artemisinin-based combination therapies have also demonstrated equivalent (if not better) efficacy in the treatment of uncomplicated malaria caused by all *Plasmodium* species and chloroquine-resistant *Plasmodium vivax* in both children and adults [172]. Hence, conventional therapeutic regimens continue to be efficacious [172]. Insecticide-treated bed-nets in which insecticide is incorporated into the net fibers is evidenced to be the best way to prevent malaria [173]. It is demonstrated that RTS, S/ASO2, a vaccine has demonstrated promising results in endemic areas [173].

7. Pulmonary amoebiasis and HLA

Pulmonary amoebiasis that caused by the protozoan parasite, *Entamoeba histolytica* occurs mainly by the extension from the amoebic liver abscess [174, 175]. In a nine-year prospective study in a cohort of preschool children in Dhaka, Bangladesh demonstrated that a single amino acid polymorphism (Q223R) in the leptin receptor was associated with increased susceptibility to *Entamoeba histolytica* infection [176]. Children with two arginine alleles (223R) were nearly four times more likely to infect with *Entamoeba histolytica* as compared to those homozygous for glutamine (223Q) [176]. An *in vitro* study demonstrated that leptin signaling protected human epithelial cells from amoebic killing via a STAT3- dependent pathway [177]. It was identified that children who were heterozygous for the HLA class II *DQB1*0601/DRB1*1501* haplotype were more likely to *Entamoeba histolytica* negative [178]. The immune mechanism that explains why only a subset of *Entamoeba histolytica*-exposed persons develops clinical disease is not fully understood [179]. The effect of microbiota on immune response to *Entamoeba histolytica* and its virulence is not yet known [179]. The presence of cysts or trophozoites of amoeba in the stool does not imply that the disease is caused by *Entamoeba histolytica* as other two non-pathogenic species found in humans (*Entamoeba dispar* and *Entamoeba moshkovskii*) are morphologically indistinguishable, but can be rapidly, accurately, and effectively diagnosed by a single-round PCR [78, 180, 181]. Other diagnostic methods include culture of *Entamoeba histolytica*, ELISA, indirect fluorescent antibody test (IFAT), and indirect hemagglutination test (IHA) [78, 180, 181]. A combination of serological tests with identification of the parasite by PCR or antigen detection is the best diagnostic approach [182]. Active trophozoites of *Entamoeba histolytica* can be identified in sputum or pleural specimen [78]. Physical examina-

tion reveals fever, chest pain, tender hepatomegaly, and cough are indicated pleuropulmonary amoebiasis [78]. Some patients may present with hemoptysis, expectoration of anchovy source-liked pus, respiratory distress, and shock [78]. Chest roentgenographic findings include pleural effusion, basal pulmonary involvement, and elevation of hemidiaphragm [78]. Metronidazole is the treatment of choice [183]. Diloxanide furoate, a luminal amoebiacidal drug can eliminate intestinal *Entamoeba* cysts [184]. Lactoferrin and lactoferricins, amoebicidal drugs, can be co-administered with a low dose of metronidazole to reduce metronidazole toxicity [184]. Identification of possible vaccine candidates against amoebiasis are in progressive studies [185].

8. Pulmonary leishmaniasis and HLA

Pulmonary or visceral leishmaniasis, also called " Kala azar " is caused by *Leishmania donovani* and and *Leishmania chagasi* or *infantum* [186] is transmitted by various species of *Phebotomus*, a type of sand fly [187]. *Leishmania amastigotes* can be identified in pulmonary septa, alveoli, and the BAL fluid [188, 189]. Pleural effusion, mediastinal lymphadenopathy, and pneumonitis have been reported in HIV-infected patients with visceral leishmaniasis and lung transplant patients [188, 189]. The expansion of the HIV- infection/AIDS epidemic over leishmaniasis, particularly visceral leishmaniasis endemic regions has increased the number of co-infected patients [190] indicating that visceral leishmaniasis is an opportunistic disease in HIV-infected/AIDS patients although not yet considered an AIDS-defining disease [191]. According to sharing of immune-compromising mechanisms of both infections with *Leishmania infantum* and HIV-1 that may affect the parasite control in visceral leishmaniasis co-infected patients [191]. In comparison to patients with visceral leishmaniasis alone, co-infected patients present a more severe disease with increased parasite burden, frequent relapses, and anti-leishmanial drug resistance [190, 192]. On the other hand, Leishmania infection can impair both the chronic immune activation and the lymphocyte depletion and can accelerate progression to AIDS, particularly in HIV-1-infected individuals [193, 194]. Hence, serological testings for latent infection due to *Leishmania* species are indicated in the pre-transplantation screening from endemic areas [195]. A recent study in two populations from Brazil (cases) and India (controls) demonstrated that the *HLA-DRB1-HLA-DQA1 HLA* class II region strongly contributed to visceral leishmaniasis susceptibility, indicating shared risk factors for visceral leishmaniasis that cross the epidemiological divides of geography and parasite species [196]. Several previous studies of *Leishmania donovani* in mice model demonstrated dramatic differences in visceral disease in spleens and livers in congenic mice with different H-2 haplotypes [197]. There was evidenced that noncuring and curing responses mapped to the HLA-class II molecules by using recombinant congenic mice [198] and functional analysis blocking IA or IE (corresponding to DQ and DR, respectively) molecules *in vivo* with monoclonal antibodies [199]. A significant role for $CD8^+$ T-cells has also been shown in *Leishmania donovani* [200, 201]. A previous case-control study in Tunisia demonstrated that visceral leishmaniasis was associated with *DR*/*DQ* class II genes but not with *TNF*/*LTA* or *HSP70* class III loci [202]. Associations between delayed-type hypersensitivity-positive asymptomatic

persons and *TNF* alleles were identified [203]. Positive associations between polymorphisms and various clinical phenotypes for cutaneous leishmaniasis have been demonstrated in a number of small case-control studies [204]. A recent study demonstrated a trend towards susceptibility to cutaneous leishmaniasis for alleles *HLA-DRB1*13*, *HLA- B*35*, and *HLA-B*44* [205]. *HLA-B*49* allele tended towards susceptibility to recurrent American cutaneous leishmaniasis (ACL), and *HLA-B*52* to re-infection whereas presence of *HLA-B*45* tended towards protection of against the cutaneous form of ACL [205]. *A*02B*44 DRB1*07* and *A*24B*35 DRB1*01* alleles, the most frequent haplotypes may be associated with susceptibility to ACL [205]. Immune activation can profoundly impact the visceral lieshmaniasis clinical course and prognosis, leading to increase the risk of death even under treatment of leishmaniasis [206]. Pentavalent antimonials, pentamidine, and amphotericin B, particularly the liposome formulations, and miltefosine are the drugs for the treatment of lieshmaniasis [207]. A previous study demonstrated that Poly/hsp/pcDNA vaccine can significantly decrease parasite load in spleen and liver indicating a feasible, effective, and practical approach for visceral leishmaniasis [208].

9. Pulmonary trypanosomiasis and HLA

Human African trypanosomiasis (HAT) or sleeping sickness is caused by an extracellularly protozoan parasite, called " *Trypanosoma brucei gambiense* " [209], "*Trypanosoma brucei rhodesiense* " [210] and " *Trypanosoma cruzi* " which was discovered by Carlos Chagas in 1909 [211] and endemic to West Africa and Central Africa, mostly in Democratic Republic of Congo, Angola, Chad, Central African Republic, Uganda, and Sudan [209]. HAT continues to threat more than 60 million people in 36 sub-Saharan countries [209, 212]. In mice model, hypercellularity and edema of alveolar walls, approximately 10 times thicker than normal alveolar wall are identified and results in wall thickening although parasites are not demonstrated in alveoli [211]. Thickening and edema of bronchial walls of small and medium size bronchi due to parasite infiltration and significant inflammatory reaction (except large bronchi) in mice model were observed [211]. These bronchial inflammatory changes result in bronchial lumen reduction [211]. Most infected mice demonstrated infiltration of the walls of large blood vessels with extensive clusters of parasites in the myocytes of the muscular stratum and accompanying by an inflammatory reaction, interstitial edema, and rupture of muscle fibers [211]. These pathologically lung changes can contribute to pulmonary alveolar hemorrhage, bronchiolitis, and pneumonitis [211]. Pulmonary emphysema was also observed in the lungs of infected rats [213]. By the statistical analysis, the difference between experimental groups in lung-parasitic distribution and the degree of inflammatory reaction demonstrated no statistical difference [211]. Most Mexican strains demonstrated cardiomyotropism [211] and could cause pulmonary hypertension that could result in a dilatation of the right ventricle which is a typical characteristic of Chagas' disease caused by *Trypanosoma cruzi* without affecting the left ventricle [211]. However, many cases of Chagas' disease with pulmonary hypertension associated with right ventricular dilatation could attribute to left ventricular failure [214]. Several HLA alleles and haplotype associated with Chagas' disease have studied [215]. The

highly polymorphic HLA class I (A, B, and C) and II (DR, DQ, and DP) molecules determine the efficiency of presentation of *Trypanosoma cruzi* epitopes to $CD8^+$ and $CD4^+$ T-cells, respectively [215]. A previous study in Mexican population demonstrated that *HLA –B*39* and *HLA-DR4* alleles were associated with *Trypanosoma cruzi* infection while *HLA-A*68* and *HLA-DR16* allele were markers of protection of development of chronic Chagas' cardiomyopathy (CCC) and heart damage susceptibility, respectively [216]. Another study in Mexico revealed that *HLA-B*39* and *HLA-DR*4* alleles were also more frequently identified in patients with Chagas' disease [1]. A previous study in south-eastern Brazil demonstrated that *HLA-A*30* and *HLA-DQB1*06* alleles were associated with susceptibility to Chagas' disease and protection of Chagas' disease, respectively in regardless of the clinical form of the disease, respectively [217] while *HLA-DR2* allele was associated with susceptibility to chronic Chagas' disease [218]. Nevertheless, in another previous study revealed that polymorphism of *HLA-DR* and *HLA-DQ* alleles did not influence on the susceptibility to different clinical forms of Chagas' disease or the progression to severe Chagas' cardiomyopathy [219]. A study in Chile, it was found that *HLA-B*40* antigen in the presence of Cw3 was significantly lower in patients with CCC [220] and was higher expressed in subjects without cardiac disease in the city of Santiago [221]. A previous study in Venezuela in comparison of HLA class II allele frequencies between patients with Chagas' disease and controls demonstrated a higher frequency of *DQB1*0501*, *DRB1*01*, and *DRB1*08* alleles, and a decreased frequency of *DQB1*0303* and *DRB1*14* alleles whereas patients with congestive heart failure and arrhythmia revealed decreased frequency of *DRB1*1501* allele [222]. A higher frequency of the *HLA-DPB1*0401* allele and *DPB1*0401-HLA-DPB1*2301* or *DPB1*0401-DPB1*3901* haplotype was identified in patients with cardiac manifestations in an endemic area of central Venezuela [223] whereas susceptibility between *HLA-C*03* allele and CCC was confirmed [224]. In several Latin American mestizos from different countries and patients with CCC, there was an increase frequency of *HLA-A*31*, *-B*39*, and *-DR8* alleles and a decrease of frequency of *HLA-DQ1*, *-DQ3*, *-DR4*, and *-DR5* alleles [225]. A study in Bolivia revealed that *HLA-DRB1*0102*, *- DRB*1402*, and *MICA*011* alleles were in strong linkage disequilibrium and there was association between the *HLA-DRB1*01-B*14-MICA*011* haplotype and the resistance against chronic Chagas' disease whereas the frequencies of *HLA-DRB1*01* and *HLA- B*1402* alleles were significant lower in patients with electrocardiogram alteration and/or megacolon compared with a group of patients with indeterminate clinical form [226]. In a study in Argentine population, the class II alleles *HLA-DRB1*0409* and *HLA-DRB1*1503* were significantly more prevalent in Chagas' disease and *HLA-DRB1*1103* allele was associated with Chagas' disease resistance whereas increased frequency of *DRB1*1503* allele was identified in patients with CCC [227, 228]. A previous study on treatment of relapsing trypanosomiasis in Gambian population demonstrated that a 7-day course of intravenous eflornithine was satisfactory and would result in substantial savings compared with the standard 14-day regimen although the prior regimen was inferior to the standard regimen and could be used by the national control programmes in endemic areas, provided that its efficacy was closely monitored whereas melarsoprol remains the only effectively therapeutic option for new cases [229]. In animal experimental studies, eflornithine and melasoprol synergistically act against trypanosomes since the former drug decreases the trypanothione production, the target of the latter drug [230, 231]. A recent study demonstrated

that oxidative stress could contribute to parasite persistence in host tissue and the development of anti-*Trypanosoma cruzi* drugs [232].

10. Pulmonary larval migrans

Toxocara larval migrans caused by *Toxocara canis*, a parasite in dogs' intestine and *Toxocara catis*, a parasite in cats' intestine infected intermediate host, humans by ingestion these embryonated *Toxocara* eggs which hatch into infective larvae in the human intestine [78]. The infective larvae then penetrate the intestinal wall and are carried by blood circulation to many organs including lungs, liver, central nervous system, eyes, and muscles [78]. Granulomata then occur in these organs and later develop fibrosis and calcification [78]. A previous study indicated that *Toxocara* species infections were associated with a polarized CD4 Th2-dominat immunity and eosinophilia, mediated mainly be HLA class II molecules, and Foxp3$^+$ CD4$^+$CD25$^+$-expressing T regulatory (Treg) cells play a role in regulation of the immunopathology of *Toxocara* granulomas in experimental animals and in enhancing the expression of TGF-β1, which is an important function of Treg demonstrated during *Toxocara canis* invasion in the mouse' s brain [233]. The potential susceptibility loci HLA class II molecules are considered to be involved in regulation of a Th2-dominant immunity which is highly controlled by stimulation through TGF-β1 [233]. Exploration of TGF-β1 polymorphism, Fox3$^+$ CD4$^+$CD25$^+$ Treg cells permit insight into the contribution produced by environmental and genetic factors in influencing disease syndrome type and severity in human toxocariasis [233]. Pulmonary manifestations are found in 80% and present with severe asthma [78]. Clinical manifestations may demonstrate scattered rales and rhonchi on auscultation including fever, cough, hepatosplenomegaly, generalized lymph node enlargement, eye pain, strabismus, white pupil, unilaterally visual loss, abdominal pain, and neurological manifestations [78]. Some cases may present with severe eosinophilic pneumonia and may contribute to respiratory distress syndrome [234-236]. Chest roentgenogram may demonstrate localized patchy infiltrates [78]. This syndrome is usually associated with eosinophilia, elevated antibody titers to *Toxocara canis*, and increased total serum IgE level [237, 238]. About 25% of childhood patients have no eosinophilia [239]. Identification of serum IgE antibodies by ELISA [240] and *Toxocara* excretory-secretory antigens by Western-blotting method have been reported for diagnosis [241]. Nevertheless, serodiagnostic methods cannot distinguish between past and current infections [240, 241]. *Toxocara* eggs or larvae cannot be identified in the feces since human is not the definitive host [78]. Histopathological examination of lung or liver biopsy specimens may reveal granulomas with multinucleated giant cells, eosinophils, and fibrosis [78]. *Toxocara* larval migrans may be spontaneous resolution, therefore, mild to moderate symptomatic patients need not any treatment [78]. However, patients with severe *Toxocara* larval migrans can be treated with diethylcarbamazine 6 mg/kg/day, 21 days) [242], mebendazole (20-25 mg/kg/day, 21 days) [243] or albendazole (10 mg/kg/day, 5 days) [244]. Exacerbation of the inflammatory reactions in the tissues due to killing of the larvae may occur, therefore, antihelminthics plus corticosteroids is recommended [78].

11. Pulmonary toxoplasmosis and HLA

A celled protozoan parasite, called " *Toxoplasma gondii* " which are primarily carried by cats is causal microorganism [245]. Humans are infected by ingestion of parasitic cyst- contaminated uncooked milk product, vegetables or meat [78]. The clinical manifestations are influenza-liked illness, myalgia or enlarged lymph nodes [78] which is the most common recognized clinical manifestation [246]. Pulmonary involvement has been increasingly reported in HIV-infected/AIDS patients [78]. Pulmonary manifestations may be interstitial pneumonia, diffuse alveolar damage or necrotizing pneumonia [247]. Nevertheless, obstructive or lobar pneumonia has been reported in a 49-year-old Spanish heterosexual man [246]. Early pregnancy with toxoplasmosis can cause fetal death, and chorioretinitis and neurological symptoms in the newborn whereas chronic disease can cause chorioretinitis, jaundice, convulsion, and encephalitis [78]. Association between the *HLA-DQ*3* allele and the susceptibility to toxoplasmic encephalitis in HIV-infected/AIDS patients has been reported [248]. A previous study among Caucasians demonstrated that the *DQ3* gene frequency was significantly higher in infected infants with hydrocephalus than subjects without hydrocephalus [249]. In infected- mice model, human major histocompatibility MHC-class II transgenes reduced parasite burden and brain necrosis that was consistent with the observed association between *HLA-DQ*3* allele and hydrocephalus in human infants [249]. In the murine model, the *DQ3* (*DQ8*, *DQB1*0302*) gene protected less than *DQ1* (*DQ6*, *DQB1*0601*) [249]. These significant findings can provide characterization of the human immune responses that are pathogenic or protective in *Toxoplasma gondii* infections. Diagnosis of toxoplasmosis is based on detection of the protozoan parasites in the body tissues [78]. Sputum examination was used in diagnosis of pulmonary or disseminated toxoplasmosis in a 14-year-old allogeneic bone marrow recipient with graft- versus-host disease by identification of *Toxoplasma gondii* tachyzoites in sputum smears [250]. Serodiagnosis is unable to discriminate between active and chronic *Toxoplasma gondii* infection due to ability to increase the antibody levels without active disease [78]. A real-time-PCR-based assay in BAL fluid has been performed in HIV-infected/AIDS patients [251]. Toxoplasmosis can be treated with a combination regimen of pyrimethamine and sulfadiazine [78].

12. Pulmonary dengue viral infection and HLA

This disease is caused by dengue virus (DENV) that belong to the family *Flaviviridae*, genus *Flavivirus*, and is transmitted to humans by *Aedes* mosquitoes, mainly *Aedes aegypti* [252]. Four serotypes of virus have been identified ; DENV-1, DENV-2, DENV-3, and DENV-4 [252]. An estimated 50 million-infected people occur each year and more than 2.5 billion people are being at risk of infection [253]. Epidemic with high incidences of dengue hemorrhagic fever have been linked to primary infection with DENV-1 followed by infection with DENV-2 or DENV-3 whereas it indicated that the longer the interval between primary and secondary infections, the higher the risk of developing severe disease [254-256]. In adults, primary infections with each of four DENV serotypes, especially with DENV-1 and DENV-3, frequently results in dengue fever whereas some outbreak of primary infections with DENV-2 have been predominantly subclinical [257]. However, adult- dengue infec-

tions are frequently accompanied by a tendency for severe hemorrhage [258] and can be life-threatening when infections occur in patients with chronic diseases such as asthma and diabetes [259-261]. Several HLA class I alleles, female sex, AB blood group, a single-nucleotide polymorphism in the tumor necrosis factor gene, and a promoter variant of the DC-SIGN receptor gene are the host factors that increase the risk of severe dengue disease [262-267]. Notably, the first outbreak in the Americas occurred in 1981, which coincided with the introduction of the possibly more virulent DENV-2 Southeast Asian genotype whereas the less virulent indigenous DENV-2 genotype was already circulating in the region [259, 268-270]. Age has been demonstrated to influence the disease outcome following a secondary infection with heterologous DENV [271]. In Asia, the risk of severe disease is greater in children than in adults, in contrast to the Americas [272, 273]. Nevertheless, the finding that dengue hemorrhagic fever or dengue shock syndrome is noted primarily in a relative small percentage of secondary DENV infections and to a much lesser extent in primary infections although with virulent strains indicates that host factors must be critical determinants of severe DENV disease development [252]. There is evidence that DENV antigen is present in the pulmonary vascular endothelium [274] whereas liver is the organ commonly involved in human DENV infections including mouse model [275, 276]. Glucose-6-phosphate dehydrogenase deficiency which is highly prevalence identified among African population [277] can cause abnormal cellular redox, therefore affecting production of hydrogen peroxide, superoxide, and nitric oxide indicating oxidative stress [278]. Viral proliferation and virulence by increasing viral receptors on target cells or increasing of viral particles is known to be affected by oxidative stress [278], therefore, glucose-6-phosphate dehydrogenase deficiency may contribute to increased replication of DENV in monocytes [277]. Several human HLA class I alleles *(-A*01*, *-A*0207*, *-A*24*, *- B*07*, *-B*46*, *-B*51*) [262, 264, 279] and HLA class II alleles *(-DQ*1*, *-DR*1*, *-DR*4*) [263, 280] are associated with development of dengue hemorrhagic fever. Additionally, a recent study demonstrated that significantly higher frequency of *HLA-A*33* allele in dengue fever patients, *HLA-A*0211* allele in dengue hemorrhagic fever cases compared to controls and dengue fever cases, respectively [281]. The frequency of *HLA-B*18* and *HLA-Cw*07* alleles were significantly higher in DENV-infected cases compared to controls [281]. The combined frequency of *HLA-Cw*07* with *HLA-DRB1*07/*15* genotype was significantly higher in dengue hemorrhagic fever cases as compared to dengue fever cases and controls but the frequency of combination of *HLA-Cw*07* allele without *HLA-DRB1*07* allele was significantly higher in dengue fever cases compared to controls [281]. This study results indicate that *HLA-A*33* allele may be associated with development of dengue fever whereas *HLA-B*18* and *HLA-Cw*07* alleles may be associated with symptomatic dengue infection requiring hospitalization [281]. A previous study demonstrated that *HLA-A*0207* and *HLA-B*51* alleles was associated with dengue hemorrhagic fever in patients having secondary DENV-1 or DENV-2 infection only and children with *HLA-A*24* allele were more likely to develop dengue hemorrhagic fever [282]. After secondary dengue infections, *HLA-B*44*, *-B*62*, *-B*76*, and *-B*77* alleles revealed to protect against development of clinical disease [282]. Clinical findings in early febrile stage include fever, headache, malaise, rash, body pain, and later develops pleural effusion [258, 283], both lower lobes infiltration [283], bilateral perihilar edema [284], ascites, bleeding, thrombocytopenia (platelet < 100,000 per mm^3), hematocrit > 20%, and clinical warning signs such as restlessness, severe and continuous abdominal pain, persistent vomiting and a sud-

den reduction in body temperature associated with profuse perspiration, adynamia (vigor or loss of strength) and sometimes fainting which can be indicative of shock due to plasma extravasation [258]. Dengue disease must be excluded from two syndromes related to hantavirus, hemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus pulmonary syndrome (HPS) in Americas [285-287]. HPS is typically characterized by acute noncardiogenic pulmonary edema and circulatory shock whereas fever, hemorrhagia, and acute renal failure are hallmark findings in HFRS [288]. Laboratory diagnosis of DENV infection include virus isolation, serodiagnostic tests (MAC-ELISA, IgG ELISA, IgG : IgM ratio, neutralization assay), nucleic acid-amplification tests (real-time PCR, reverse-transcriptase PCR, nucleic acid- sequence based amplification assay (NASBA)), and antigen detection (NS1 antigen and antibody detection) [258]. DENV complications include massive hemorrhage, disseminated intravascular coagulation, non-cardiogenic pulmonary edema, respiratory failure, and finally develops multiple organ failure [258]. In uncomplicated dengue cases, treatment is only supportive, but in cases with prolonged or recurrent dengue shock, intravenous fluids should be administered carefully according to dosage and age to prevent pulmonary edema [258]. DENV control and prevention strategies include vector control and vaccine development [258]. Current approaches to vaccine development involve using deoxyribonucleic acid vaccine, chimeric viruses using yellow fever vaccine, subunit vaccine, inactivated viruses, attenuated viruses, and attenuated dengue viruses as backbones [289-294]. An Acambis/Sanofi Pasteur yellow fever-dengue chimeric vaccine is in advanced Phase II testing in children in Thailand [258]. A possible licensed vaccine will be available in less than 10 years [258].

13. Pulmonary leptospirosis and HLA

Leptospirosis is a zoonotic disease caused by genus *Leptospira* which belongs to the phylum of spirochaetes [295]. The 8 pathogenic species of this genus are *Leptospira interrogans*, *Leptospira borgpetersenii*, *Leptospira noguchii*, *Leptospira santarosai*, *Leptospira kirschneri*, *Leptospira alstonii*, *Leptospira alexanderi*, and *Leptospira weilii* [295]. Transmission of leptospirosis requires continuous enzoonotic circulation of the pathogen among animal reservoir or as commonly referred-maintenance host [295]. *Leptospira* serovars reveal specific host preferences with regard to their ability to produce high-grade carriage [295]. Rats (genus *Rattus*) serve as reservoirs for the Icterohaemorrhagiae serogroup while house mice (*Mus musculus*) are the reservoir for the Ballum serogroup [295]. Additionally, serovars often do not cause significant disease in highly adapted-reservoir hosts [295]. A previous study demonstrated that *HLA-DQ*6* allele increased risk of laboratory-confirmed leptospirosis [296]. Pathogenic species produce a systemic infection after an environmental exposure, establish persistent renal and urinary shedding in reservoir animals and cause tissue damage in multiple organs of susceptible hosts [295]. Humans are incidental hosts in which leptospirosis produces acute disease manifestations and does not induce a disease carrier state [295]. The incubation period varies from 2 to 30 days [295]. Clinical presentation in human leptospirosis includes acute febrile illness that often cannot be differentiate from other causes of acute fever illness [295]. The clinical manifestations include fever, headache, myalgia (especially calf muscle), and prostration associated with any of the following symptoms or signs: cough, hemoptysis,

breathlessness, conjunctival suffusion, jaundice, oliguria or anuria, internal organ hemorrhages, skin rash, cardiac arrhythmia or failure, and meningeal irritation [297]. Leptospirosis-associated pulmonary hemorrhage syndrome was first described in China and Korea and then was brought to global attention by a large outbreak of severe-from disease in Nicaragua in 1995 [295]. The risks of developing severe leptospirosis include a critical threshold of qPCR- determined leptospiremia, identification of the infective strain, and early laboratory results [298]. The illness usually resolves after the first week of symptoms [295]. The presumptive diagnosis was made from a positive result of a rapid screening test such as latex agglutination test, IgM ELISA, dipstick, lateral flow, etc [297]. The confirmatory diagnosis includes isolation of the organism from blood or other clinical specimens, a positive PCR result, and fourfold or greater rise in titer or seroconversion in microscopic agglutination test (MAT) on paired samples obtained at least 2 weeks apart [297]. Severe case usually treated with intravenous benzylpenicillin (30 mg/kg up to 1.2 g intravenously and 6-hourly for 5-7 days) [297]. Oral administration of doxycycline (2 mg/kg up to 100 mg, 12-hourly for 5-7 days), amoxicillin, ampicillin, or tetracycline is the treatment of choice in less severe cases [297]. The third-generation cephalosporins, such as ceftriazone and cefotaxime, quinolone antimicrobials may also be effective, but Jarrisch-Herxheimer reactions can occur after the start of antimicrobial treatment [297]. The patients should be appropriate monitored and care supported, such as mechanical ventilation, dialysis, etc [297]. A recent study in Thailand demonstrated that only the latex test could be considered cost-effective when compared to the no-antimicrobial option, and that latex test, microcapsule agglutination test, and lateral flow were still inferior to empirical treatment (7-day course of doxycycline, 100 mg bid treatment) [299]. A recent study on vaccine candidates for protection of leptospirosis successfully demonstrated LBJ_2271 as a protein candidate for further study of antigenic immune stimulation for vaccine development [300] whereas another recent study revealed that czcA and its four subunit vaccine peptides could be ideal T-cell driven efficacious vaccine against this disease [301]. Until epidemiologically-validated immune correlates are determined and discovery of vaccine candidates will likely continue to rely on the search for new virulence factors and outer membrane proteins of the organism.

14. Conclusions

Most of several studies have inconclusively demonstrated statistical association between HLA class I and II molecules and susceptibility to a range of complex tropical pulmonary infectious diseases, particularly parasitic pulmonary diseases. The globalization of neglected tropical pulmonary infectious diseases can alert the healthcare providers in diagnosis in recent immigrants or travelers from endemic areas who present with respiratory manifestations and peripheral blood or tissue eosinophilia. A complete re-evaluation of the true impact of HLA/MHC genes on susceptibility to tropical pulmonary infectious diseases. Summary of association between known HLA alleles and susceptibility of some tropical pulmonary infectious diseases are shown in Table 1.

Disease	Known HLA	Influence	Reference
SARS	*HLA-B*0703, HLADRB1*0301*	More prevalent and more poorer outcome	7, 8
	CXCL10(-938AA)/Fg12(+158T/)* or *CXCL10(-938AA)/HO-1(-497A/*)*	Protective	10
	Fg12(+158T/)*	Susceptible	10
Tuberculosis	*HLA-DQB1*0601, HLA-DRB1*1501HLA-DPB1*02, HLA-DRB1*0803, HLA-DQA1*0101, HLA-DQB1*0501HLA-DRB1*1501, HLA-DQB1*0502, HLA-DQB1*0503*	Susceptible	26, 27, 28, 29
	*HLA-DQB1*0402*	Decreased frequency	28
	*HLA-B*17-tumor-necrosis-factor-α-238/A, HLA-tumor-necrosis-factor-α-308/2, HLA-tumor-necrosis-factor-β-2*	Relapse	30
HIV-Infection/AIDS	*HLA-B*27, HLA-B*57*	Slow progression	33
	*HLA-A*24*	More rapid central nervous system impairment	33
	*HLA-Cw*2*	Protective against disease progression	33
	*HLA-DQB1*2*	Protective against both disease progression and central nervous system impairment	33
	*HLA-A*31, HLA-B*41, HLA-DQB1*5, HLA-DRB1*10*	Susceptible to TB disease	39
Filariasis	*$CD8^+$ $HLA\text{-}DR^+$*	Susceptible to chronically obstructive lymphatic form	146
	*HLA-B*15*	Susceptible	148
Malaria	*HLA-B*46, HLA-B*56, HLA-DRB1*1001, HLA-B**	Susceptible	160, 162
	*KIR2DL3-HLA-C1, HLA-Bw*53, HLA-DRB1*1302, HLA-DQB1*0501*	Protective	161, 163
Amoebiasis	*HLA-DQB1*0601/DRB1*1501*	Protective	178
Leishmaniasis	*HLA-DRB1, HLA-DQA1*	Susceptible to visceral or pulmonary leishmaniasis	196
	*HLA-DRB1*13, HLA-B*35, HLA-B*44, HLA-A*02, HLA-B*44, HLA-DRB1*07, HLA-A*24, HLA-DRB1*01*	Susceptible to cutaneous leishmaniasis	205

Disease	Known HLA	Influence	Reference
	*HLA-B*49*	Susceptible to recurrent cutaneous leishmaniasis (American type)	205
	*HLA-B*52*	Susceptible to re-infected cutaneous leishmaniasis American type)	205
	*HLA-B*45*	Protecive against cutaneous leishmaniasis (American type)	205
Trypanosomiasis	*HLA-B*39, HLA-DR4, HLA-A*30, HLA-DQB1*0501, HLA-DRB1*01, HLA-DRB1*08, HLA-DPB1*0401, HLA—DPB1*2301, HLA-DPB1*3901, HLA-C*03, HLA-A*31, HLA-B*39, HLA-DR8, HLA-DRB1*0409, HLA-DRB1*1503*	Susceptible to infection and development of Chagas' disease	1, 216, 217, 222, 223, 224, 225, 227, 228
	*HLA-A*68, HLA-DR*16, HLA-DQB1*06, HLA-B*40, HLA-DQB1*0303, HLA-DRB1*14, HLA-DRB1*1501, HLA-DQ1, HLA-DQ3, HLA-DR4, HLA-DR5, HLA-DRB1*0102, HLA-DRB*1402, HLA-MICA*011, HLA-DRB1*1103*	Protective against development of chronic Chagas' cardiomyopathy and cardiac damage	216, 217, 220, 225, 226, 227, 228
Toxoplasmosis	*HLA-DQ*3*	Human hydrocephalus	249
	*HLA-DQ*6, HLA-DQB1*0601*	Protective in murine model	249
Dengue	*HLA-A*01, HLA-A*0207, HLA-A*24, HLA-B*07, HLA-B*46, HLA-B*51, HLA-DQ*1, HLA-DR*1, HLA-DR*4, HLA-A*0211, HLA-Cw*07* (in combination with *HLA-DRB1*07/*15* genotype)	Susceptible to development of dengue hemorrhagic fever	263, 280, 281
	*HLA-A*33, HLA-HLA-Cw*07*	Susceptible to development of dengue fever	281
	*HLA-B*18, HLA-Cw*07*	Susceptible to symptomatic dengue infection	281
Leptospirosis	*HLA-DQ*6*	Increased risk of laboratory confirmation	296

Table 1. Association between some Tropical Pulmonary Infectious Diseases and known Human Leukocyte Antigens

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