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REVIEW ARTICLE

Current Trends in Treatments and Targets of Neglected Tropical Disease

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ABSTRACT

Tropical diseases are one of the foremost concerns globally. Achieving health equity and ending neglected tropical diseases (NTD) is one of the goals of the Pan American Health Organization. The World Health Organization (WHO) estimates that more than 1.7 billion people require treatment for at least one NTD every year. NTDs are a diverse group of conditions caused by a variety of microbes like helminths, bacteria, prions, fungi, viruses, protozoans, etc. that affect the poor regions of the world where sanitation, hygiene, and safe water consumption are seldom. WHO is trying to eliminate 30 NTD by the end of 2030, thus achieving the Sustainable Development Goals. Leishmaniasis, Chagas disease, and Schistosomiasis are a few of the detrimental tropical infectious diseases. High levels of morbidity, economic impairment, and stigma do not necessarily translate into large numbers of deaths; overall, the NTD causes high morbidity but low mortality conditions. This manuscript briefly discusses a number of neglected infectious diseases and the currently available treatment options for them. A multidisciplinary, collaborative, and comprehensive approach can aid in the holistic management and treatment of NTD.

Keywords: Chagas disease, leishmaniasis, neglected tropical disease, novel targets, tryspsomniasis

INTRODUCTION

Diseases Caused by Protozoa

Human African trypanosomiasis (HAT)

Two parasites, *Trypanosoma brucei* gambiense and *T. brucei* rhodesiense, which are carried by tsetse flies (*Glossina* sp.), are the cause of HAT, also known as sleeping sickness. There are endemic areas in 36 African countries, endangering over 60 million people worldwide. There are differences between the clinical syndromes of gambiense and rhinosiense HAT. The zoonotic parasite *T. brucei* rhodesiense causes far more aggressive acute sickness, whereas the more human-adapted *T. brucei* gambiense causes a slowly progressive disease that usually manifests late. The initial signs of HAT are characterized by significantly enlarged posterior cervical lymph nodes, or Winterbottom's sign; other symptoms include fever, headache, and lymphadenopathy. Eventually, the term "sleeping sickness" is coined to describe nocturnal insomnia and daytime somnolence, even though total sleep duration remains constant. Changes in personality, declines in higher-order cognitive function, and Parkinsonian movement abnormalities are observed. A progressive loss in brain function leads to a coma and eventually death.[1]

Chagas disease

In the Americas, trypanosoma cruzi is thought to infect about 200 000 new cases/year, with a 15 million prevalence estimate. As a result, the most significant human parasite illness in the New World is Chagas disease. Chagas is being exported by international migration to wealthy nations as well. The vectors are night-biting triatomine (also known as "kissing") bugs that reside in wall crevices

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or on livestock. When the bugs are feeding, mature parasites are expelled in their feces and are injected directly into the conjunctival sac through damaged skin or finger transfer.[2-4]

Acute infections typically present as a moderate, self-limiting fever. Chronic Chagas disease, which most usually affects the gut (producing mega-esophagus or reactivation of latent infection, causing severe cardiac and neurological sequelae) or the heart (causing cardiomyopathy and dysrhythmias), affects about 30% of infected individuals.

Leishmaniasis

Leishmania is a genus of obligate intracellular protozoan parasites that cause over 20 different types of disease, from severe visceral sickness to self-healing cutaneous ulcers. Other than lymphatic filariasis (LF) and malaria, this group is the leading source of morbidity and mortality among human parasites. Infection can spread transplacentally, through the bite of an infected female sandfly, or through contaminated blood or organs.

The most prevalent leishmaniasis syndrome in the world and a major contributor to chronic ulcerating skin lesions is cutaneous leishmaniasis (CL). A papule appears a few weeks after infection, progressing to a nodule, an ulcer, and finally, a raised bordered depressed ulcer. This ulcer may heal by itself.[5-7]

In other cases, the lesion may diffuse to distant skin areas (i.e., New World CL) or spread to the nasal mucosa, destroying the palate and nasal septum (i.e., muco CL). The latter may impair airway integrity and result in severe face disfigurement or even death. A low-grade fever and anorexia are the first symptoms of visceral leishmaniasis (VL, also known as "kala-azar"), which can proceed to include pancytopenia, immunosuppression, large splenomegaly, hemorrhage, and death. HIV co-infection exacerbates leishmaniasis: in patients with HIV, more severe illness manifests at unique anatomical locations, and virtually all cases recur following treatment in the absence of appropriate HIV care.[8-10]

Diseases Caused by Helminths

There is proof that humans have been aware of helminths throughout recorded history, and the word comes from the Greek for worm. The STHs (Ascaris, hookworms, whipworms, and Strongyloides) are members of the phylum Nematoda, or roundworms. Additionally, filarial worms are responsible for dracunculiasis, river blindness, and LF.

The other helminth categories are Trematoda (flukes), which contains the genus Schistosoma, and Cestoda (parasitic flatworms), which includes Taenia solium and Taenia saginata. Both classes of the phylum Plasyhelminthes make up these groupings. At the moment, neither Taenia nor Strongyloides are categorized as "core" neglected tropical diseases (NTDs).[11]

Soil-transmitted helminths

A class of illnesses known as the STHs are contracted by eating or coming into touch with soil that contains worm eggs or larvae. One or more of these parasites infect over a billion humans. Kids are most impacted, as they frequently carry the most worms and are most vulnerable to their side effects, which include anemia, stunted growth, decreased physical fitness, poor academic performance, and missed school even though mortality is a rare result, this class of illnesses significantly increases the likelihood of poverty.[12-14]

The three most significant STHs are the whipworm (*Trichuris trichiura*), the common roundworm (*Ascaris lumibricoides*), and the hookworms (*Necator americanus* and *Ancylostoma duodenale*). Sub-Saharan Africa, China, and the Americas have the highest rates of disease. The lifecycles of these worms are similar in that the adults enter the gastrointestinal tract, breed sexually, and release eggs into the environment through excrement. Hookworms are not like Ascaris and Trichuris in that the larvae reach the infectious stage in the soil before penetrating unbroken skin to start the parasitic phase, as opposed to being acquired through the ingestion of eggs. The epidemiology of helminth infections differs from that of many other infections.[15-17]

Adult worms have a limited lifespan; apart from the Strongyloides, they cannot reproduce in human hosts or be spread from person to person. Additionally, the intensity of infection, which is typically determined by the number of eggs per

gram of feces, must be considered in addition to the presence or absence of infection in an individual.

Schistosomiasis

Humans are infected by five species of parasitic trematodes belonging to the Schistosomatidae family. Their life cycle is intricate and involves intermediate hosts, snails. The cercariae that infected snails release into the water are able to find and enter post-capillary venules as well as penetrate undamaged human skin.[18-20]

Before migrating to the mesenteric veins (*Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma intercalatum*, and *Schistosoma mekongi*) or the perivesical venous plexus (*Schistosoma haematobium*), further development occurs in the liver and lungs. For the rest of their lives, adult partners stay in copulo at these intravascular locations. Acute sickness, sometimes known as "Katayama fever," manifests a few weeks after the first infection and is marked by fever, lethargy, and eosinophilia. However, the majority of the schistosomiasis (bilharzias) disease burden is caused by eggs being stuck in the liver or lungs after being washed away by the portal venous system or by eggs finding their way through the walls of blood vessels, the ureters, the bladder, and the intestines. Granulomatous inflammation that results over time can cause hematuria, obstruction of the bladder, renal failure, or bladder cancer (in cases of S. hematobium infection); in cases of mesenteric schistosome infection, it can also cause periportal fibrosis, portal hypertension, ascites, and varices. Eggs that make it to the bladder lumen or bowel are released as feces or urine. Globally, there are about 200 million infected individuals, with an uneven distribution of illness severity within geographically localized endemic regions.[21-24]

LF

Filariasis, also known as LF, is a chronic infection caused by a parasite that is transmitted by mosquitoes. It can cause swelling of the limbs, the hydroceles, and the testicles. Filariasis is the second-most common cause of permanent disability worldwide after leprosy. It is currently considered one of the NTDs. Filariasis is caused by at least three species of parasitic roundworms (*Wuchereria bancrofti*, *Brugia malayi,* and *Brugia timori*) and transmitted to five species of mosquitoes**,** including Aedes, Anopheles, Culex, Mansonia, and Ochlerotatus. It influences 120 million individuals in 72 nations around the world, for the most part within the tropics and subtropical climates of Asia, Africa, the Western Pacific, South America, and the Caribbean. Four nations in America are endemic: Haiti, the Dominican Republic, Guyana, and Brazil**.** One-third of children in endemic locales are asymptomatically contaminated with W. bancrofti. Half of the patients in their 30s and 40s are infected.[25,26]

This parasitic disease primarily affects humans, and mosquitoes are its vector. Larvae are deposited into the bloodstream by the mosquito. After settling down in the lymph nodes, they develop into adult worms. The larvae preferentially deposit in lymph nodes in the femur. They reproduce sexually, with females giving birth to countless microfilariae that are released into the bloodstream at different times of the day. Adults can live up to 9 years, and females can continue to produce eggs for about 5 years. The growth of adult worms causes the lymphatics to occlude, which interferes with lymphatic drainage and makes the body more vulnerable to recurring infections, particularly those caused by fungi and streptococci. This acute-on-chronic inflammation causes lymphatic remodeling and fibrosis, which worsen contractile dysfunction. *Brugia* and *Wuchereria* species are similar in morphology and are the main cause of filariasis. They can be identified at the genus level using the size, body wall composition, thickness, and morphology of the cuticle. The presence of small filarial worms in lymph nodes is pathognomonic for either *Wuchereria* or *Brugia*. Adult worms are typically found in lymph nodes in the groin or neck, whereas microfilariae are typically found in the peripheral blood.

Microfilariae can be seen with a blood smear or other peripheral blood sample that is stained with either Giemsa or hematoxylin and eosin (H&E) stain. The blood samples should be taken after 8 p.m. The microfilariae vary in size from 200 to 300 mm in length and 2–8 mm in diameter and are identified by the terminal and subterminal nuclei in the tail region.[27-29]

S. No	Disease	Novel Targets	Recent Treatments	References
1	Leishmaniasis	1. Sterol biosynthesis 2. Purine salvage 3. Glycosyl phosphatidyl inositol (GPI) production 4. Folate biosynthesis 5. Hypusine	Regimens for Cutaneous Leishmaniasis include topical paromomycin, pentavalent antimonials and intravenous liposomal amphotericin B. For visceral disease, parenteral paromomycin, antimonials and with the recent introduction of the oral agent miltefosine.	Feasey *et al*.
2	Lymphatic filariasis	1. Phosphoglycerate mutase 2. Aminoacyl-tRNA synthetase 3.Glutathione-s-transferases 4. Transglutaminase.	Diethylcarbamazine (DEC) is the drug of choice. Ivermectin kills only the microfilariae. Adult worms can be killed with doxycycline treatment (200 mg/day for four to 6 weeks)	Sharma *et al*.
3	Schistosomiasis	1. Expression of a specific type of RNA 2. Chromatin regulation 3. Histone Modifying Enzymes	Recommended strategy for schistosomiasis is mass treatment with praziquantel.	Mawson *et al*.
4	Chagas disease	These parasites rely on the second messenger cAMP for many essential functions, such as stage-specific differentiation, proliferation, osmoregulation, oxidative stress, and quorum sensing. Its signalling pathway differs greatly from mammals', with structurally distinct adenylyl cyclases, a deficiency of orthologous effector proteins, and a lack of G-protein-coupled receptors, among other differences. These properties make the proteins that are involved in these transduction pathways desirable targets for therapeutic intervention.	Patients are treated with either benznidazole or nifurtimox.	Mitra *et al*.
5	Trypanosomiasis	The action of known nucleoside analogs such as tubercidin and cordycepin driven to the improvement of a arrangement of C7-substituted nucleoside analogs. Whole-genome RNAi screening uncovered the inclusion of adenosine kinase and 4E interacting protein into the mode-of-action of certain antitrypanosomal nucleoside analogs. Utilizing RNAi lines and gene-deficient parasites, 4E interacting protein was found to be basic for parasite development and infectivity within the vertebrate have.	Combination treatment with oral nifurtimox and low-dose intravenous eflornithine has been placed on WHO's essential drugs list.	Babokhov *et al*.

CONCLUSION

In impoverished nations, tropical and infectious diseases persist as leading causes of death and illness. While cost-effective preventive measures are available, the substantial funding allocated to combat these diseases has not fully translated into improved health outcomes. Despite this financial support, many developing countries grapple with significant challenges in delivering essential services and ensuring financial protection against infectious and tropical diseases for their populations. Given the limited resources in these heavily affected countries, leveraging economic analysis becomes crucial for resource prioritization. The goal is to extract the maximum benefit from the scarce resources at hand. Additionally, employing economic tools such as demand and supply analysis and applying economic principles to issues like government involvement and health-care financing offers a potent means for countries to enhance the design and performance of their health systems. Thus, a multidisciplinary approach is essential for the management, treatment, and eradication of infectious disease.

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