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NEGLECTED TROPICAL DISEASES
What Any Health Professional Should Know About Them

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First Edition

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Foreword

Neglected Tropical Diseases (NTDs) initially occurred between the tropics and overlapped in communities in which social drivers play a significant role. However, climate change has spread them away and unrestricted human development has immersed them into unprecedented places. NTDs can be found almost anywhere, and health professionals should be prepared to help the people who need them the most.

"Neglected Tropical Diseases. What Any Health Professional Should Know About Them" is a book written by and for health professionals to raise awareness about NTDs within our global community. It does not intend to replace any local, national, or international guidelines, but to share essential information that any student or primary care physician should know. Therefore, it should be used for educational purposes and it must not be used as medical advice for professional services. Each health professional should consult the protocols that are in force in their country or region before diagnosing and treating patients. No responsibility will be accepted if damage or death results from ignoring this disclaimer.

The contents of the book follow the list of NTDs recognized by the World Health Organization, but there is more to know. The first chapter provides a perspective of what to expect from the next ones. Readers can look up the index and go directly to the chapter of interest to quickly obtain reader-friendly content. In all chapters, information is organized according to the same sections: introduction, historical background, epidemiology, etiology, risk factors, clinical manifestations, diagnosis, treatment, prevention, and conclusion.

We thank you for the time that you will invest in reading this book and hope it inspires you to play your role within your capacity, knowledge, and professional scope to alleviate the global burden of NTDs.

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We thank our families and friends for sharing and strengthening our principles and values, and for unconditionally supporting us in each step of our careers as health professionals but, above all, as human beings.

We thank our students, colleagues, and professors for sharing their knowledge, motivation, and will to always assist those affected by disease and those most in need.

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We thank the Neglected Tropical Diseases Community for being an inspiration for generations and for their tireless work in this effort to control, eliminate, and eradicate NTDs.

Chapter 1. Neglected Tropical Diseases

Authors

Diego-Abelardo Álvarez-Hernández, Rodolfo García-Rodríguez-Arana, Rosalino Vázquez-López, Héctor Gallardo-Rincón

Introduction

Neglected Tropical Diseases (NTDs) are a diverse group of infectious and non-infectious diseases mainly occurring in tropical and subtropical environments. They affect most severely poor people living in communities deprived of basic infrastructure where inadequate sanitation and health services prevail. In addition to the high morbidity and mortality among those affected by them, these diseases also lead to discrimination and stigmatization.[1]

Historical Background

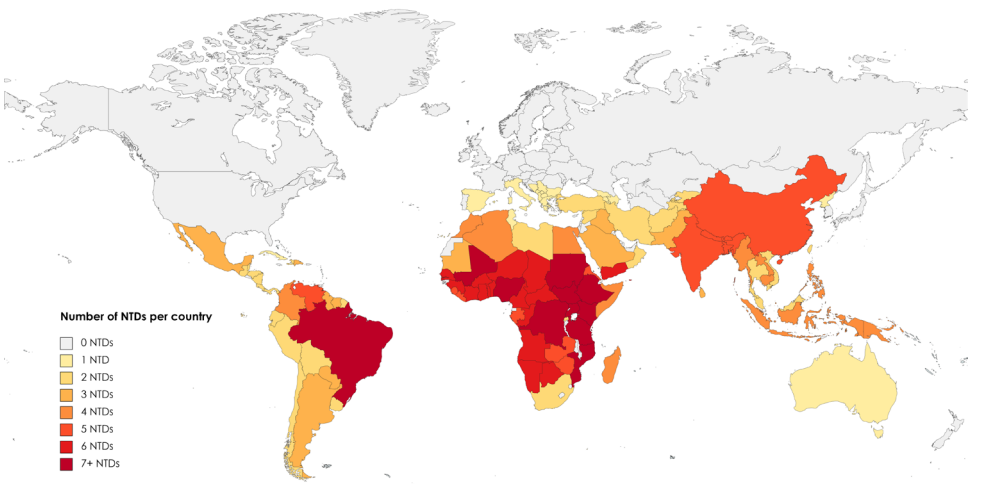
Although the existence of tropical diseases was acknowledged several centuries ago, they remained unnoticed until the 20th century, when several physicians, researchers, and scientists launched multiple initiatives and created networks to bring them to the attention of the world. In the 1970s, Kenneth Warren branded them as "Great Neglected Diseases (GNDs) of Mankind" and launched the GNDs network to unite scientists against the "infectious diseases of the poor." At the same time, the World Health Organization (WHO) launched the Special Programme for Research and Training in Tropical Diseases to study a similar disease portfolio. In the 2000s, Jeffrey Sachs linked the control of these diseases with the economic and social development of countries and even continents, leading to their inclusion into the United Nations Millennium Development Goals (MDGs). However, the MDGs only included a small subset of NTDs, neglecting millions of poor and vulnerable people. David Molyneux, Peter Hotez, and Alan Fenwick identified 13 diseases that demanded immediate attention and branded them "Neglected Tropical Diseases". In the 2010s, the WHO designed a roadmap to control, eliminate, and eradicate 17 NTDs by 2020. Subsequently, the WHO partnered with national

governments, non-governmental organizations, and the pharmaceutical industry to achieve this goal. The London Declaration endorsed this unprecedented effort. Finally, in the 2020s, the WHO restructured the initial roadmap to tackle the burden of 20 NTDs by 2030, and the world celebrated the first-ever World NTDs Day.[2]

Epidemiology

NTDs affect about 1.7 billion people and cause almost 200,000 deaths every year worldwide. They occur in practically every continent but are most prevalent in Africa (sub-Saharan Africa), America (Central and South America), and Asia (Southeast Asia). (Figure 1).[3] They are major disablers rather than killers, leading to a heavy global burden that can be evaluated using various metrics such as disability adjusted-life years (DALYs), years lived with disability (YLDs), and years of life lost (YLLs). The 2010 *Global Burden of Disease Study* estimated that NTDs are responsible for 26.06 million DALYs, 18.22 million YLDs, and 7.90 million YLLs.[4] These metrics do not capture the entire global burden of NTDs, as several of them are both underdiagnosed and underreported. Therefore, epidemiologic surveillance needs to be strengthened to understand the severity of the situation.

FIGURE 1. NUMBER OF ENDEMIC NTDS PER COUNTRY



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Etiology

The WHO recognizes 20 major NTDs:

- **Buruli ulcer.** Bacterial disease caused by *Mycobacterium ulcerans*. Its transmission mechanism is unclear but has been linked to water. Arthropods and mosquitoes have been proposed as vectors.
- **Chagas disease.** Parasitic disease caused by *Trypanosoma cruzi*. Its transmission is mainly vector-borne, with triatomines in the genera *Panstrongylus, Rhodnius*, and *Triatoma* acting as vectors. Transmission through blood transfusion or organ transplantation, from mother to child, by ingesting food or beverages contaminated with trypanosomes, and accidental exposure has also been reported.
- **Dengue and chikungunya.** Viral diseases caused by the dengue virus and chikungunya virus. Transmission is mainly vector-borne, with mosquitoes in the genus *Aedes* acting as vectors. Transmission from mother-to-child has also been reported.
- **Dracunculiasis.** Parasitic disease caused by *Dracunculus medinensis*. Transmission occurs by drinking water contaminated with copepods in the genus *Cyclops* that carry the parasite larvae.
- **Echinococcosis.** Bacterial disease caused by *Echinococcus* spp. (*E. granulosus* and *E. multilocularis*). Transmission occurs mainly by ingesting food or water contaminated with the parasite eggs. Transmission through the fecal-oral route has also been reported.
- **Food-borne trematodiases.** Parasitic diseases caused by *Clonorchis sinensis*, *Fasciola* spp. (*F. gigantica* and *F. hepatica*), *Opisthorchis* spp. (*O. felineus* and *O. viverrini*), and *Paragonimus* spp. (*P. africanus, P. caliensis, P. heterotremus, P. hueitungensis, P. kellicotti, P. mexicanus, P. miyazakii, P. skrjabini, P. uterobilateralis,* and *P. westermani*). Transmission occurs by ingesting fish, plants, or crustaceans contaminated with the parasite eggs.
- **Leishmaniasis.** Parasitic disease caused by *Leishmania* spp. (*L. braziliensis, L. donovani, L. infantum, L, major,* and *L. mexicana*). Transmission is vector-borne, with sandflies in the genera *Lutzomyia* and *Phlebotomus* acting as vectors.
- **Leprosy.** Bacterial disease caused by *Mycobacterium* spp. (*M. leprae* and *M. lepromatosis*). Transmission occurs mainly by breathing the upper respi-

ratory secretions of an infected individual. Transmission through skin erosions and from mother to child has also been reported but are not widely acknowledged.

- **Lymphatic filariasis.** Parasitic disease caused by *Brugia* spp. (*B. malayi* and *B. timori*) and *Wuchereria bancrofti*. Transmission is vector-borne, with mosquitoes in the genera *Aedes, Anopheles, Culex, Mansonia,* and *Ochlerotatus* acting as vectors.
- **Mycetoma and chromoblastomycosis.** Mycetoma is a bacterial and fungal disease caused by *Actinomadura madurae*, *Nocardia* spp. (*N. asteroides* and *N. brasiliensis*), *Madura* spp. (*M. grisea* and *M. mycetomatis*), and *Scedosporium apiospermum*. Chromoblastomycosis is a fungal disease caused by *C. carrionii* and *F. pedrosoi*. Transmission occurs by direct contact between the etiological agent and a trauma injury of an uninfected individual. Other deep mycoses can be included in this category but are not addressed in this book.
- **Onchocerciasis.** Parasitic disease caused by *Onchocerca volvulus*. Transmission is vector-borne, with blackflies in the genus *Simulium* acting as vectors.
- **Rabies.** Viral disease caused by the rabies virus. Transmission occurs primarily by a bite from a rabid animal. Transmission by direct contact with saliva or brain tissue from a rabid animal, through organ transplantation, or accidental exposure has also been reported.
- **Scabies.** Parasitic disease caused by *Sarcoptes scabiei* var. *hominis*. Transmission occurs mainly by direct contact between an infected and an uninfected person. Transmission through fomites has also been reported. Other ectoparasites can be included in this category but are not addressed in this book.
- **Schistosomiasis.** Parasitic disease caused by *Schistosoma* spp. (*S. guineensis*/*S. intercalatum, S. haematobium, S. mansoni,* and *S. mekongi*). Transmission occurs by direct contact with water contaminated with freshwater snails carrying the parasite larvae.
- **Sleeping sickness.** Parasitic disease caused by *Trypanosoma brucei* spp. (*T. brucei gambiense* and *T. brucei rhodesiense*). Transmission is vector-borne, with tsetse flies in the genus *Glossina* acting as vectors. Transmission through blood transfusion or organ transplantation, from mother to

child, through sexual intercourse, and accidental exposure has also been reported.

- **Soil-transmitted helminthiases.** Parasitic diseases caused by *Ancylostoma* spp. (*A. ceylanicum* and *A. duodenale*), *Ascaris* spp. (*A. lumbricoides* and *A. suum*), *Necator americanus,* and *Trichuris trichiura*. Transmission occurs by direct contact between the etiological agent and the barefoot of an uninfected individual, or by ingesting soil, vegetation, or water contaminated with the parasite eggs.
- **Taeniasis/Cysticercosis.** Parasitic diseases caused by *Taenia* spp. (*T. asiatica, T. saginata,* and *T. solium*). Transmission occurs mainly by ingesting beef or pork meat contaminated with the parasite larvae. Transmission through the fecal-oral route, known as autoinfection, is possible.
- **Trachoma.** Bacterial disease caused by *Chlamydia trachomatis*. Transmission occurs mainly by direct contact with discharges from the eyes or nose of an infected person. Indirect transmission through spread on fomites or by eye-seeking flies in the genus *Musca* has also been reported.
- **Yaws.** Bacterial disease caused by *Treponema pallidum* subsp. *pertenue*. Transmission occurs by direct contact between an infected and an uninfected person.
- **Snakebite envenoming.** Non-infectious disease caused by the bite of over 600 venomous snake species, some 200 of which are medically important. It is the only non-transmissible disease that has been included in the NTDs list due to the shortage of antivenom production.[5, 6]

Risk Factors

The major risk factors for acquiring NTDs include climate change, globalization, sociocultural factors, low socioeconomic status, inadequate sanitation, basic infrastructure, crowded conditions, poor hygiene, lack of disease awareness, intake of contaminated food or water, and occupational exposure.[7]

Clinical Manifestations

As NTDs are a diverse group of infectious and non-infectious diseases, they can affect various organs and systems. For example, Buruli ulcer, chromoblastomy-

cosis, dracunculiasis, leishmaniasis, leprosy, mycetoma, onchocerciasis, scabies, yaws, and snakebite envenoming affect the skin and cause from macules to necrosis. Rabies, sleeping sickness, taeniasis/cysticercosis, and snakebite envenoming affect the central nervous system and cause from confusion to coma. Onchocerciasis, taeniasis/cysticercosis, and trachoma affect the eyes and cause sight impairment ranging from blurred vision to blindness. Echinococcosis and soil-transmitted helminthiasis affect the lungs and cause respiratory impairment ranging from cough to dyspnea. Chagas disease affects the heart and cause cardiac disorders ranging from palpitations to heart failure. Chagas disease, echinococcosis, food-borne trematodiases, leishmaniasis, schistosomiasis, soil-transmitted helminthiases, and taeniasis/cysticercosis affect the gastrointestinal tract and cause gastrointestinal disorders ranging from nausea to malnutrition. Chikungunya, dengue, and snakebite envenoming affect the hematological system and cause mild to severe bleeding. Lymphatic filariasis affect the lymphatic system and causes from edema to elephantiasis.

Some of these diseases may remain unnoticed for a long time until life-threatening complications develop. Moreover, some of them can also co-occur in the same individual, making their diagnosis difficult and inaccurate. When acquired, individuals may experience disability, impairment, and disfigurement, affecting their quality of life and productivity. Consequently, individuals, communities, and countries become trapped in a vicious cycle of disease and poverty.[6, 8]

Diagnosis

Diagnosis requires combining several methods and studies. Identifying the epidemiological background is essential to suspect a potential NTD but understanding the stages through which NTDs develop is necessary to know how and where to look. Confirmation of the diagnosis is often necessary and can be done through several methods:

- **Direct methods.** Their objective is to observe the etiological agent by examining samples under the microscope, including light and dark-field microscopy. These methods are commonly used, but require duly trained personnel that know the concentration, flotation, sedimentation, or staining

techniques that must be used to reveal the morphological features of target microorganisms.

- **Culture methods.** Their objective is to culture and grow the etiological agent through cell or blood cultures or xenodiagnosis. These methods have been traditionally employed and require experienced technicians who know the media or animal models necessary to isolate and grow the target microorganisms.
- **Molecular methods.** Their objective is to identify the presence of the etiological agent by detecting their nucleic acids. These methods include loop-mediated isothermal amplification, nucleic acid amplification test, and polymerase chain reaction. They are excellent tools for detecting the presence of microorganisms when their load is low and identifying the infecting species when this is not possible by other means. Nonetheless, these methods are expensive and have not been developed for all the NTDs.
- **Serological methods.** Their objective is to detect antigens of or antibodies against the etiological agent. These methods include chemiluminescent immunoassay, enzyme-linked immunosorbent assay, immunochromatographic test, indirect immunofluorescence assay, indirect hemagglutination assay, Western blot, and others. They are extraordinary tools for detecting the products or reactions elicited by the target microorganisms in cases where other methods fail, as well as for epidemiological surveillance. Still, these methods cannot discriminate whether the individual suffered a previous infection or is currently infected and have not been developed or validated for all the NTDs.

Combining two or more of the methods listed above improves the accuracy and reliability of the diagnosis. Guidelines and recommendations on the most suitable methods for each disease are available.[6, 9, 10] However, as most NTDs occur in resource-limited areas, the lack of affordable, readily available, reliable tests remain a major challenge for health professionals. Investment in the research and development of new diagnostic tests is urgently required.[11]

Complementing examination with laboratory studies, such as complete blood cell count, blood coagulation, blood chemistry, liver function tests, and urine tests, among others, helps to detect alterations. Also, imaging studies such as X-rays, computerized tomography, magnetic resonance imaging, and ultrasonography, among others, help to determine the extent of the damage and assess the prognosis of infected individuals.[6, 12]

Treatment

The management of NTDs depends on etiology and progression. In general, a combination of non-pharmacological, pharmacological, and surgical interventions is required. For example, non-pharmacological treatment, such as wound cleansing, is essential to foster healing and avoid secondary infections in skin diseases. Pharmacological treatment with antimicrobial drugs is necessary to eliminate the etiological agents of infectious NTDs. Surgical treatment may be necessary to improve the health condition or save the lives of individuals affected by late-stage complications. An interdisciplinary team should assess each case, and decisions should be made taking into account the clinical history of each patient and the resources available.[6, 8, 13]

Prevention

The WHO recognizes five essential interventions for controlling and preventing NTDs:

- **Preventive drug therapy.** It aims to prevent further transmission from infected to uninfected individuals by administering antimicrobial drugs. This intervention applies to the following NTDs: lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiases, and trachoma.
- **Innovative and intensified disease management.** It consists of combining interventions for diseases in cases where resources are scarce or where the widespread use of existing resources is limited. NTDs for which this intervention is applicable include Buruli ulcer, Chagas disease, leishmaniasis, leprosy, mycetoma, sleeping sickness, and yaws.
- **Vector ecology and management.** It consists of applying insect repellents to skin, clothes, and bed nets, and spraying insecticides indoors and outdoors. This intervention applies to the following NTDs: Chagas disease, chikungunya, dengue, leishmaniasis, lymphatic filariasis, onchocerciasis, and sleeping sickness.
- **Veterinary public-health services.** It acknowledges that the health of people is linked and related to the health and the environment of animals. NTDs for which this intervention is applicable include echinococcosis, food-borne trematodiases, rabies, and taeniasis/cysticercosis.

- **Safe water, sanitation, and hygiene.** It recognizes that many pathogens live and reproduce in areas where water and sanitation are inadequate. This intervention applies to the following NTDs: schistosomiasis, soil-transmitted helminthiases, and trachoma.[14]

Preventive or therapeutic vaccines approved for NTDs are almost non-existent, and those available are limited to small populations. Nowadays, multiple vaccine candidates are being assessed in various pre-clinical and clinical phases.[15]

Conclusion

NTDs threaten the life of billions of persons worldwide. Their occurrence is related to several social drivers that indicate that countries are failing their people. Control, elimination, and eradication of NTDs can only be achieved by local, national, and international stakeholders working together to alleviate their burden. In parallel, each health professional plays a key role in ensuring that no individual or community is left behind. We must continue making progress towards the goals that the NTD community has set; such goals are achievable.

References

1. World Health Organization. Controlling and eliminating neglected tropical diseases. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who.int/westernpacific/activities/controlling-and-eliminating-neglected-tropical-diseases
2. Molyneux DH, Asamoa-Bah A, Fenwick A, Savioli L, Hotez P. The history of the neglected tropical diseases movement. Trans R Soc Trop Med Hyg 2021; 115: 169-175.
3. Uniting to Combat NTDs. Neglected Tropical Diseases. Internet. United to Combat NTDs. [Updated; June 2020. Reviewed; January 2021]. Available at: https://uniting-tocombatntds.org/ntds/
4. Hotez PJ, Alvarado M, Basáñez MG, Bolliger I, Bourne R, Boussinesq M, et al. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. PLoS Neglected Tropical Diseases 2014; 8 (7): 1-9.
5. Mitra AK, Mawson AR. Neglected Tropical Diseases: Epidemiology and Global Burden. Trop Med Infect Dis 2017; 2: 1-15.

6. World Health Organization. Fact sheets: neglected tropical diseases. [Internet]. World Health Organization. [Updated: 2017; Reviewed: January 2021]. Available at: https://www.who.int/topics/tropical_diseases/factsheets/neglected/en/

7. Aagard-Hansen J, Chaignat CL. Neglected tropical diseases: equity and social determinants. In: Blas E, Kurup S. Equity, social determinants and public health programmes. 1st edition. Geneva; World Health Organization 2010. pp. 135-157.

8. Centers for Disease Control and Prevention. Neglected Tropical Diseases. [Internet]. U.S. Department of Health & Human Services. [Updated: November 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/globalhealth/ntd/diseases/index.html

9. World Health Organization. Strengthening health security by implementing the International Health Regulations. Microbiological methods. [Internet]. World Health Organization. [Updated: 2007; Reviewed: January 2021]. Available at: https://www.who.int/topics/tropical_diseases/factsheets/neglected/en/

10. Taylor Em. NTD Diagnostics for Disease Elimination: A Review. Diagnostics 2020; 10 (6): 375.

11. Hotez PJ, Pecoul B, Rijal S, Boehme C, Aksoy S, Malecela M. Eliminating the Neglected Tropical Diseases: Translational Science and New Technologies. PLos Negl Trop Dis 2016; 10 (3): 1-14.

12. Jones P, Mazal J. Medical Imaging of Neglected Tropical Diseases of the Americas. Radiol Technol 2016; 87 (4): 393-419.

13. Médecins Sans Frontières. Clinical Guidelines. Diagnosis and treatment manual. For curative programmes in hospitals and dispensaries, guidance for prescribing. 1st ed. Geneva: Médecins Sans Frontières; 2021.

14. World Health Organization. Fourth WHO report on neglected tropical diseases. Integrating Neglected Tropical Diseases into Global Health and Development. 1st edition. Geneva; World Health Organization 2017. pp. 1-278.

15. Albuquerque-Luna EJ, Costa-Campos SRSL. Vaccine development against neglected tropical diseases. Cad Saude Publica 2020; 36 (2): 1-14.

Chapter 2. Buruli Ulcer

Authors

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Introduction

Buruli ulcer (BU), also known as Bairnsdale ulcer, is a chronic, debilitating, and necrotizing disease caused by *Mycobacterium ulcerans* that affects mainly the skin and bones.[1] Its clinical presentation encompasses a wide spectrum, which largely depends on the time elapsed between the onset of symptoms and the time when the infected individual seeks medical attention, with the latter being the primary cause of delayed diagnosis. Late diagnosis combined with lack of proper treatment leads to the development of complications that cause disfigurement, disability, impairment, and stigmatization, which limit everyday activities and degrade the life quality of those affected.[2]

Historical Background

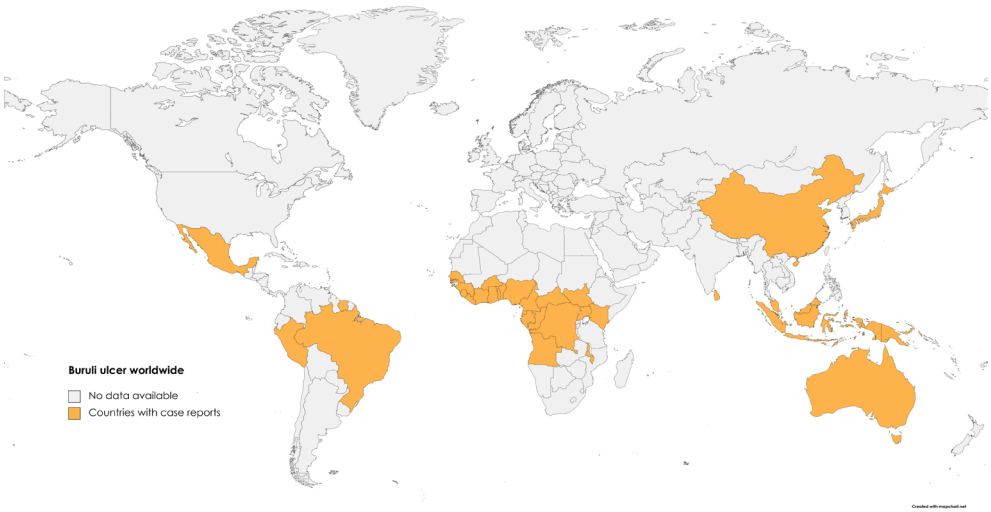
The earliest description of the disease can be traced back to 1897, when Robert Cook observed lesions consistent with BU characteristics in Kampala, Uganda.[3] Later, in 1948, Peter MacCallum reported six patients showing similar ulcers in Bairnsdale, Australia, and coined the disease as Bairnsdale ulcer.[4] And subsequently, during the 1950s and 1960s, a high prevalence of the disease in Buruli, Uganda, gave rise to its current name.[5]

Epidemiology

The precise incidence and prevalence of the disease are currently unknown. Although over 66,215 cases were reported between 2002 and 2019 (Figure 1), the

number of cases has been declining, with a total of 3,245 cases reported in 2002 and 2,027 in 2019. The cases from 2019 were reported in five countries: Nigeria (943 cases), Australia (297 cases), Ghana (296 cases), Côte d'Ivoire (251 cases), and Benin (240 cases).[6] BU is distributed worldwide, but most cases occur in Africa (Central and West Africa), America (Central and South America), Asia (East Asia), and Oceania (Western Pacific).[7] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH BURULI ULCER CASE REPORTS



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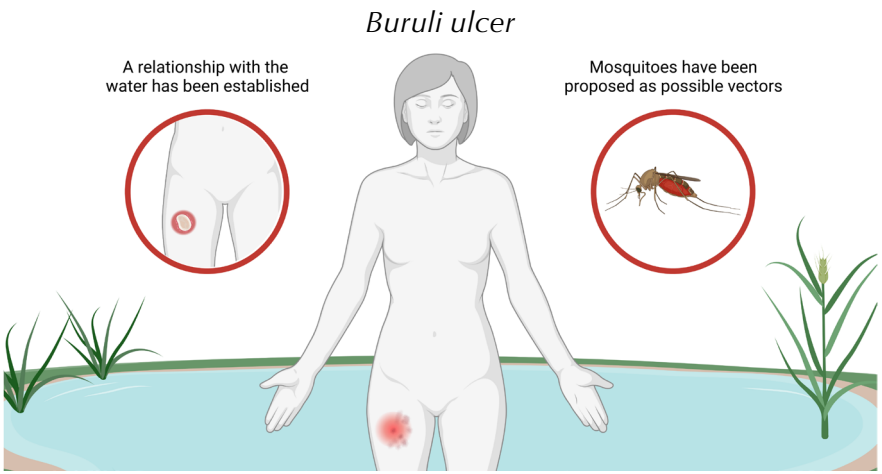
Adapted from: World Health Organization. Global Health Observatory data repository. Neglected tropical diseases. Buruli ulcer. Number of new reported cases. Data by country. [Internet]. World Health Organization. [Updated: January 2021; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.A1631?lang=en

Etiology

BU is caused by a bacterium named *Mycobacterium ulcerans*, which belongs to the phylum Actinobacteria, class Actinomycetia, order Corynebacteriales, family *Mycobacteriaceae*, and genus *Mycobacterium*.[8] *M. ulcerans* is an acid-alcohol resistant bacillus (BAAR) that grows at temperatures between 28 and 33 ºC and oxygen concentrations below 2.5%. Rough, yellowish colonies grow when samples are inoculated in liquid or solid media. The transmission mechanism is unknown,

but a relationship between the disease and water has been clearly established (Figure 2). Cases have been reported following mosquito and water bug bites, through direct contact of the etiological agent with skin lesions, and after floods.[9]

FIGURE 2. MECHANISM OF TRANSMISSION FOR BURULI ULCER



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Risk Factors

In countries where BU is endemic, the main risk factors for acquiring the disease include inadequate sanitation, poor hygiene, bathing, swimming, wading, or washing without wearing protective clothing in slow-flowing water bodies such as lakes, ponds, streams, or swamps, and farming or working near farms. BU affects men and women equally. It is more prevalent in children aged under 15 years in Africa and in adults over 60 years old in Asia.[10, 11]

Clinical Manifestations

Contact with *M. ulcerans* may result in colonization without infection, asymptomatic infection that remains latent, or symptomatic disease that progresses in

stages. The incubation period for this disease ranges between 60 and 90 days for the primary infection and takes 14 days for reactivation. Some authors have reported incubation periods of up to 9 months.[2, 12] Afterward, a papule that gradually progresses into a nodule and a plaque forms at the initial site of infection, mainly on the upper and lower limbs, although it can also occur on other body parts such as the head, neck, breast, and genitalia. Sometimes BU may present with the edematous form in which large body areas are affected. Eventually, ulceration occurs due to necrosis of soft tissues. Deep ulcers with white cotton wool-like appearance and undermining, thickened edges are typical features. Erythema or discoloration may be observed in the surrounding area. The lesions are usually painless unless accompanied by secondary infection. Contractures, disability, and impairment have been reported.[9, 13]

Diagnosis

The epidemiological background and clinical manifestations are sufficient to diagnose this disease in endemic regions. Several laboratory tests are available for confirmation. Samples can be collected with a cotton swab, fine needle aspiration, or by punch biopsy from the center of a papule nodule, plaque, or the undermined edges of an ulcer. Direct microscopic examination of smears stained with auramine-rhodamine, Kinyoun, or Ziehl-Neelsen techniques can demonstrate the presence of BAAR. Histopathology can evidence vascular occlusion, coalescent necrosis, and BAAR during the early stages, and granulomas during the late stages. *In-vitro* cell culture in Brown and Buckle, Löwenstein-Jensen, or Ogawa media produces rough, yellowish colonies. Molecular methods such as polymerase chain reaction can detect *M. ulcerans*-specific DNA sequences. One positive laboratory test suffices to confirm the diagnosis in endemic areas; two positive laboratory tests based on different principles are required in non-endemic areas.[13, 14]

Differential diagnosis should always be made to rule out other causes of ulcers, such as cellulitis, diabetes mellitus, insect bites, leishmaniasis, leprosy, necrotizing fasciitis, onchocerciasis, tropical phagedenic ulcer, a venous ulcer, and yaws, among others.[15, 16]

Treatment

The World Health Organization (WHO) developed a three-category classification system of BU lesions based on size and site to facilitate management and treatment (Table 1):[15]

TABLE 1. CLASSIFICATION AND TREATMENT RECOMMENDATIONS FOR BURULI ULCER

WHO classification of Buruli ulcer		
Category	**Description**	**Treatment**
I	Single lesion less than 5 cm in diameter	• Antibiotic regimen • Maintain normal range of movement when a joint is involved
II	Non-ulcerative and ulcerative plaques, edematous forms, or single ulcerative lesion 5–15 cm in diameter	• Complete course of antibiotic treatment prior to surgery • Maintain normal range of movement when a joint is involved
III	Lesions at critical sites (head, face, neck, breast, or genitalia), a single lesion larger than 15 cm in diameter, multiple lesions and osteomyelitis, and disseminated or mixed forms	• Complete course of antibiotic treatment before surgery • Maintain normal range of movement when a joint is involved

Adapted from: World Health Organization. Treatment of *Mycobacterium ulcerans* disease (Buruli ulcer): guidance for health workers. 1st edition Italy; World Health Organization: 2012. pp. 1-73.

- **Pharmacological treatment.** A combination of two antibiotics is recommended to increase treatment efficacy and reduce the risk of antibiotic resistance. The first-line treatment is rifampicin (10 mg/kg orally once a day) plus clarithromycin (7.5 mg/kg orally twice a day) for 8 weeks. An alternative treatment that has been used in Australia is rifampicin (10 mg/kg orally once a day) plus moxifloxacin (400 mg orally once a day) for 8 weeks.[7, 15] A worsening of the initial BU lesion occurred in one in five patients treated with antibiotics due to a paradoxical reaction. Initial management should exclude antibiotic failure, and the antibiotic regimen should continue at the same dose and duration for mild to moderate reactions. Prednisolone (0.5-1 mg/kg orally once a day for 28 to 56 days) and antibiotics for up to 12 weeks should be considered for severe cases.[17]

- **Surgical interventions.** Surgery is indicated for the debridement of necrotic tissue to improve the wound healing rate and prevent deformity or scarring in lesions with significant necrosis. Surgery should be performed at least 28 days —or preferably 56 days, if possible— after antibiotic treatment. The excision should be made with wide margins through uninvolved tissues, but the extent of the surgery should be as conservative as possible. If left untreated, self-healing may occur but often leads to contractures and bone destruction.[9, 17]

Follow-up over at least 10 months after completing antibiotic treatment is recommended to confirm infection clearance, assess potential complications, and identify any relapses.[15]

Prevention

No vaccine is currently available to prevent BU. The main preventive strategies include wearing protective clothing, using insect repellents and mosquito bed nets, and cleaning wounds after exposure to soil.[18]

Conclusion

BU is a chronic, debilitating, and necrotizing disease that mainly affects the skin and subcutaneous tissues. The precise mode of transmission remains unclear, but an association with water has been established. Clinical manifestations in infected patients can be severe and may lead to disability and impairment. Frequently, infected individuals do not seek immediate medical attention, which delays diagnosis and treatment. The epidemiological background and clinical manifestations are sufficient for diagnosing the disease in endemic countries, but laboratory confirmation is required in non-endemic countries. Developing a point-of-care test to improve disease detection in hard-to-reach areas as well as new treatment options to avoid complications and dropouts must be a priority to control the disease. A stronger commitment of national and international stakeholders to tackle this disease is required.

References

1. Sanyuy-Nsai F, Nambile-Cumber S, Claude-Nkfusai N, Zennobia-Viyoff V, Blake-Afutendem N, Yumumkah-Cumber R, et al. Knowledge and practices of health practitioners on treatment of Buruli ulcer in the Mbonge, Ekondo Titi and Muyuka Health Districts, South West Region, Cameroon. Pan Afr Med J 2018; 31: 228.
2. Boleira M, Lehman L, Kiszewski AE, Lupi O, Asiedu KB. Buruli ulcer. An Bras Dermatol 2010; 85 (3): 281-301.
3. Cook A. Mengo Hospital Notes. Br Med J 1970; 2: 378-379.
4. MacCallum P, Tolhurst JC. A new mycobacterial infection IN Mn. J Pathol Bacteriol 1948; 60 (1): 93-122.
5. Clancey JK, Dodge OG, Lunn HF, Oduori ML. Mycobacterial skin ulcers in Uganda. Lancet 1961; 2 (7209): 951-954.
6. World Health Organization. Global Health Observatory data repository. Neglected tropical diseases. Buruli ulcer. Number of new reported cases. Data by country. [Internet]. World Health Organization. [Updated: January 2021; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.A1631?lang=en
7. World Health Organization. Buruli ulcer (Mycobacterium ulcerans). [Internet]. Ginebra, Switzerland: World Health Organization; [Updated: April 2019; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/buruli-ulcer-(mycobacterium-ulcerans-infection)
8. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
9. Yotsu RR, Murase C, Sugawara M, Suzuki K, Nakanga K, Ishii N, et al. Revisiting Buruli ulcer. J Dermatol 2015; 42: 1033-1041.
10. Röltgen K, Pluschke G. Epidemiology and disease burden of Buruli ulcer: a review. Res Rep Trop Med 2015; 5 (6): 59-73.
11. Röltgen K, Pluschke G. Buruli Ulcer: History and Disease Burden. Buruli Ulcer. In: Pluschke G, Röltgen K. Buruli Ulcer. 1st edition. United States; Springer: 2019. pp. 1-41.
12. Loftus MJ, Trubiano JA, Tay EL, Lavender CJ, Globan M, Fyfe JAM, et al. The incubation period of Buruli ulcer (*Mycobacterium ulcerans* infection) in Victoria, Australia - remains similar despite changing geographic distribution of disease. PLoS Negl Trop Dis 2018; 12 (3): 1-10.
13. Van der Werf T, Stienstra Y, von Reyn CF, ET, Baron EL. Buruli ulcers (Mycobacterium ulcerans infection). [Internet]. UpToDate. Wolters Kluwer. [Updated: December 2021; Reviewed: January 2021]. Available at: https://www.uptodate.

com/contents/buruli-ulcer-mycobacterium-ulcerans-infection?search=Buruli%20ulce&source=search_result&selectedTitle=1~15&usage_type=default&display_rank=1

14. Sakyi SA, Aboagye SY, Otchere ID, Yeboah-Manu D. Clinical and Laboratory Diagnosis of Buruli Ulcer Disease: A Systematic Review. Can J Infect Dis Med Microbiol 2016; 2016; 5310718.

15. World Health Organization. Treatment of *Mycobacterium ulcerans* disease (Buruli ulcer): guidance for health workers. 1st edition Italy; World Health Organization: 2012. pp. 1-73.

16. Junghanss T, Johnson RC, Pluschke G. *Mycobacterium ulcerans* disease. In: Farrar J, Hotez PJ, Junghanss T, Kang G, Lalloo D, White NJ. Manson's tropical diseases. 23rd edition. Edinburgh; Saunders: 2014. pp. 519–531.

17. O'Brien D, Jenkin G, Buntine J, Steffen CM, McDonald A, Horne S, Friedman ND, et al. Treatment and prevention of Mycobacterium ulcerans infection (Buruli ulcer) in Australia: guideline update. Med J Aust 2014; 200 (5): 267-270.

Chapter 3. Chagas Disease

Authors

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Introduction

Chagas disease (CD), also known as American trypanosomiasis, is a chronic, progressive, and silent disease caused by *Trypanosoma cruzi* that primarily affects the heart, esophagus, and colon.[1] CD was initially endemic to Latin American countries, but climate change, urbanization, and globalization have fostered its spread to non-endemic countries, threatening millions of unaware individuals and thousands of unprepared healthcare professionals.[2]

Historical Background

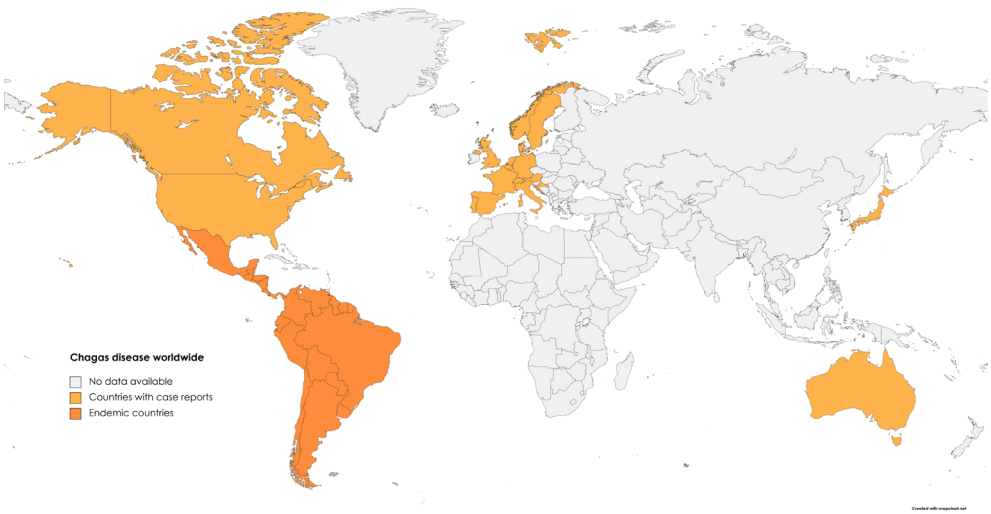
Phylogenetic studies suggest that trypanosomes have been on Earth for almost 100 million years,[3] and the first signs of the disease can be traced back to a 9,000-year-old mummy found in the area between northern Chile and southern Peru.[4] Since then, several explorers, naturalists, and travelers, including Miguel Díaz, Luis Gomes, and Charles Darwin, have described individuals with disease-related symptoms.[5] In 1908, Carlos Chagas first isolated the etiological agent from the hindgut of blood-sucking insects; later, in 1909, he isolated it from the blood of a feverish girl, thus establishing the linkage between the agent, the vector, and the disease.[6]

Epidemiology

Between 6 and 8 million people are estimated to be infected, 65 to 100 million are at risk of acquiring the disease,[7] and nearly 14,000 deaths are caused by CD

each year worldwide.[8] CD is endemic to 21 Latin American countries: Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Guiana, French Guiana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Surinam, Uruguay, and Venezuela.[9] However, the disease has spread to non-endemic countries, such as Australia, Belgium, Canada, France, Japan, Netherlands, Spain, Switzerland, the United Kingdom, and the United States (Figure 1).[10] The 2010 *Global Burden of Disease Study* estimated that CD accounted for 0.55 million disability-adjusted life years, 0.30 years lived with disability, and 0.24 years of life lost.[11]

FIGURE 1. COUNTRIES WITH CHAGAS DISEASE CASE REPORTS



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Adapted from: Chagas Coalition. Learn More About Chagas Disease. [Internet]. Barcelona Institute for Global Health. [Updated: 2019; Reviewed: January 2021]. Available at: http://www.infochagas.org/en/en-que-paises-hay-chagas and Antinori S, Galimberti L, Bianco R, Grande R, Galli M, Corbellino M. Chagas disease in Europe: A review for the internist in the globalized world. Eur J Intern M 2017; 43: 6-15.

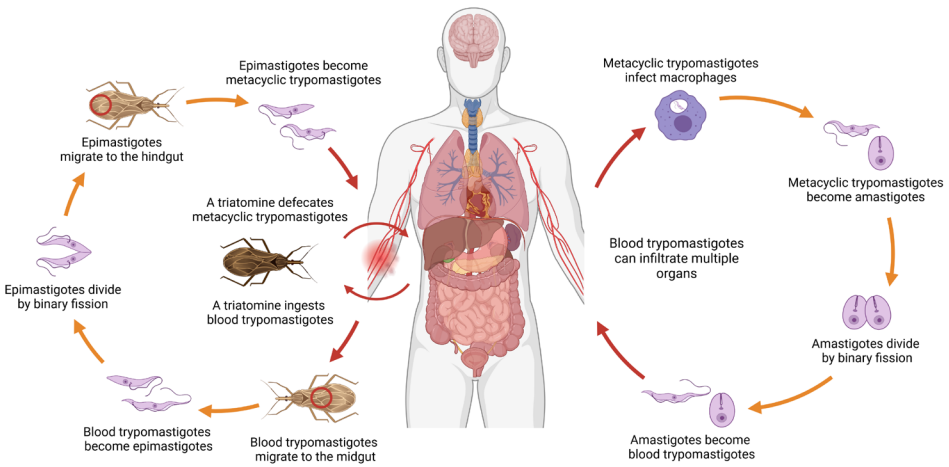
Etiology

CD is caused by a parasite named *Trypanosoma cruzi,* which belongs to the phylum Euglenozoa, class Kinetoplastea, subclass Metakinetoplastina, order Trypanosomatida, family *Trypanosomatidae*, genus *Trypanosoma*, and subgenus

Shizotrypanum.[12] *T. cruzi* is an obligate intracellular protozoan characterized by high genetic diversity, which has led to classifying it into six discrete taxonomic units (DTUs), namely TcI though TcVI, each of which shows different epidemiological and pathogenic characteristics.[13] The disease is mainly vector-borne. Transmission occurs when an infected triatomine takes a blood meal from an uninfected individual, defecates, and releases metacyclic trypomastigotes near the site of the bite. Afterward, metacyclic trypomastigotes enter through the wound and infect cells in the subcutaneous tissues, where they differentiate into amastigotes and replicate by binary fission. Amastigotes then differentiate into bloodstream trypomastigotes and travel through blood vessels to infect new cells. Transmission continues when an uninfected triatomine sucks blood from an infected individual and ingests blood trypomastigotes. Subsequently, blood trypomastigotes migrate through the gastrointestinal tract to reach the midgut, where they differentiate into epimastigotes and replicate by binary fission. Epimastigotes then migrate towards the hindgut, where they transform into metacyclic trypomastigotes. The cycle is completed when an infected triatomine takes a blood meal from an uninfected individual, defecates, and releases metacyclic trypomastigotes near the site of the bite (Figure 2).[14]

FIGURE 2. *TRYPANOSOMA CRUZI* LIFE CYCLE

Chagas disease



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Triatomines in the genera *Panstrongylus, Rhodnius,* and *Triatoma* are currently recognized as vectors; mammals, mainly in the species order *Chiroptera*, *Didelphimorphia*, and *Primates*, have been recognized as reservoirs.[15] Transmission has also been reported through blood transfusion or organ transplantation, from mother to child, by ingesting food or beverages contaminated with trypanosomes, and from accidental exposure.[2]

Risk Factors

In countries where CD is endemic, the main risk factors for acquiring the disease include inadequate sanitation and basic infrastructure, poor hygiene, and cohabitation with animals. CD affects men and women equally, but men tend to seek medical attention less frequently than women. CD is more prevalent in adults than children.[16, 17]

Clinical Manifestations

The incubation period of CD ranges from 7 to 14 days. Afterward, the disease develops through two distinct stages:

- **Acute stage.** Most infected individuals remain asymptomatic. The minority that becomes symptomatic can experience unspecific clinical manifestations such as fever, asthenia, adynamia, myalgia, arthralgia, headache, abdominal pain, hepatomegaly, or splenomegaly. Specific clinical manifestations, such as Romaña sign (painless, unilateral, palpebral, and periocular swelling), may be observed if the route of infection is the eye; chagoma (erythematous, painful, and mobile nodule) may occur when the parasite load is very high. Meningoencephalitis and myocarditis have also been reported.
- **Chronic stage.** Most infected individuals remain in the indeterminate form. The minority that develops the determinate form can experience cardiac, esophageal, or colonic disease:
  - ◊ **Cardiac disease.** It is characterized by arrhythmias, conduction system abnormalities, segmental and general contractility abnormalities, progressive congestive heart failure, thromboembolic phenomena, and sud-

den death. Syncope, dizziness, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, tachypnea, cough, crackles, palpitations, and chest pressure are common.

- ◊ **Esophageal disease.** It is characterized by progressive dysphagia that leads to achalasia and increases the risk of regurgitation and bronchoaspiration. Weight loss, hyporexia, anorexia, nausea, vomiting, dysphagia, regurgitation, and pyrosis can be experienced.
- ◊ **Colonic disease.** It is characterized by progressive constipation that leads to dyschezia and increases the risk of fecaloma, volvulus, and bowel ischemia. Weight loss, hyporexia, anorexia, nausea, vomiting, abdominal pain, distention, constipation, and diarrhea may be experienced.

Reactivation of the disease may lead to encephalitis, meningoencephalitis, myocarditis, or panniculitis. It occurs when immunosuppression is present.[18, 19]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *T. cruzi* is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of smears stained with the Giemsa, Romanowsky, or Wright's techniques can demonstrate the presence of motile trypomastigotes. Concentration techniques such as micro-Strout or Strout may be needed if the parasite load is low. This approach is low-cost, fast, and simple to perform but is only useful during the acute stage of the disease. Culture techniques such as blood culture in Tobie's medium or feeding uninfected triatomines with blood from a potentially infected individual can grow epimastigotes and trypomastigotes. These techniques are reliable indicators of infection but are difficult to perform, and their results become available only weeks to months after the initial infection. Molecular methods such as the polymerase chain reaction can detect *T. cruzi*-specific DNA sequences. These are highly sensitive and specific tests but are also expensive and not widely available in remote areas. When available, they can be used for making the diagnosis during the acute stage of the disease; their use during the chronic stage is still controversial. Serological techniques such as enzyme-linked immunosorbent assay, indirect hemagglutination assay, or indirect immunofluorescence as-

say can recognize antibodies against *T. cruzi* during the chronic stage of the disease.[19, 20] However, their sensitivity and specificity are insufficient for making a diagnosis by themselves. At least two tests with two different principles are required; if their results are discordant, a third test based on a different principle should be performed.[21]

Supplementary patient examination plus cabinet and imaging studies are needed to assess the presence of underlying alterations. If cardiomyopathy is suspected, chest X-ray, electrocardiography, and echocardiography are recommended to rule out cardiac involvement. On the other hand, if megaesophagus is suspected, a barium swallow X-ray, high-resolution esophageal manometry, and upper endoscopy can be performed; if megacolon is suspected, barium enema X-ray and lower colonoscopy are suggested.[22]

Differential diagnosis should always be made to rule out other causes of cardiac disease, such as atrioventricular disturbances, cardiogenic pulmonary edema, dilated cardiomyopathy, hypertrophic cardiomyopathy, myocardial infarction, and pulmonary embolism; other causes of esophageal disease, such as esophageal cancer, esophageal motility disorders, esophageal rupture, esophageal spasms, esophagitis, and gastroesophageal reflux disease; and other causes of colonic disease, such as chronic megacolon, colonic obstruction, Hirschsprung disease, and toxic megacolon.[23]

Treatment

The approach for managing and treating CD depends on the stage of the disease. Trypanosomal drugs such as benznidazole and nifurtimox are indicated for patients undergoing the acute stage of the disease or in the chronic stage with no organ damage.[24] The selection of trypanosomal drug depends upon availability. Dosage regimens by age and their most common adverse effects are summarized in Table 1.[25]

TABLE 1. RECOMMENDED DOSAGE AND ADVERSE REACTIONS OF TREATMENT OPTIONS FOR CHAGAS DISEASE

	Treatment of Chagas disease	
Drug	**Benznidazole**	**Nifurtimox**
Dose	• Newborns: 5 mg/kg orally, divided into two doses per day for 30 days • Infants: 10 mg/kg orally, divided into two doses per day for 60 days • Children: 5–8 mg/kg orally, divided into two doses per day for 60 days • Adults: 5–7 mg/kg orally, divided into two doses per day for 60 days	• Children: 15–20 mg/kg orally, divided into three doses per day for 60, 90, or 120 days • Adults: 8–10 mg/kg orally, divided into three doses per day for 60, 90, or 120 days
Adverse reactions	Skin reactions, anorexia, nausea, vomiting, weight loss, peripheral neuropathy, and leukopenia are the most common adverse reactions. Insomnia, paresthesia, headache, and bone marrow suppression have also been reported	Anorexia, nausea, vomiting, weight loss, peripheral neuropathy, and leukopenia are the most common adverse reactions. Fatigue, disorientation, amnesia, insomnia, seizures, vertigo, paresthesia, polyneuritis, and headache have also been reported

Adapted from: Kawaguchi WH. Bonancio-Cerqueira L. Millan-Fachi M, Campos ML, Messias-Reason IJ, Pontarolo R. Efficacy and Safety of Chagas Disease Drug Therapy and Treatment Perspectives. In: Nissapatorn V, Helieh S. Chagas Disease – Basic Investigations and Challenges. 1st Ed. United Kingdom: IntechOpen; 2018, 121-152.

Management of CD cardiomyopathy includes pharmacological treatment (anticoagulants, antiarrhythmics, antihypertensives, β-blockers, cardiac glycosides, and diuretics), implantation of assistive devices (pacemakers and implantable cardiac defibrillators), and surgical procedures (cardiac bridging and heart transplantation).[26] Management of CD megaesophagus consists in the administration of pharmacological treatment (sphincter relaxants and botulinum toxin injections), implementation of non-pharmacological therapy (pneumatic dilatation), and surgical procedures (laparoscopic cardiomyotomy and esophagectomy). Management of CD megacolon consists in the administration of pharmacological treatment (laxatives), implementation of non-pharmacological therapy (colon enemas), and surgical procedures (anterior rectosigmoidoscopy, hemicolectomy, or total colectomy).[20, 27]

Prevention

No vaccine is currently available to prevent CD. The main preventive strategies involve using insect repellents and bed nets, spraying insecticide indoors and outdoors, and improving household flooring and dwelling.[2]

Conclusions

CD is a chronic and deteriorating disease that affects mainly the heart and gastrointestinal tract. Transmission is primarily vector-borne in endemic countries and non-vector-borne in non-endemic countries. Once infected, most patients remain asymptomatic during the acute stage, but nearly one-third develop cardiac or digestive complications over the chronic stage. CD poses a challenge for healthcare professionals because diagnosis is usually made during the chronic stage when organ damage has already occurred. Treatment options are limited and, when administered, several adverse effects may occur, increasing the possibility of patient dropout. Assessing the efficacy and safety of other molecules and drug candidates is crucial for controlling the disease; the development of prophylactic or therapeutic vaccines is essential for reducing its burden.

References

1. Lynn MK, Bossak BH, Sandifer PA, Watson A, Nolan MS. Contemporary autochthonous human Chagas disease in the USA. Acta Trop 2020; 205: 105361.
2. World Health Organization. Chagas disease (also known as American trypanosomiasis). [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis)
3. Stevens JR, Noyes HA, Dover GA, Gibson WC. The ancient and divergent origins of the human pathogenic trypanosomes, Trypanosoma brucei and T. cruzi. Parasitol 199; 118 (1): 107-116.
4. Aufderheide AC, Salo W, Madden M, Streitz J, Buikstra J, Guhl F, et al. A 9,000-year record of Chagas' disease. Proc Natl Acad Sci USA 2004; 101 (7): 2034-2039.
5. Steverding D. The history of Chagas disease. Parasit Vectors 2014; 7: 317.
6. Chagas C. Nova tripanozomiaze humana. Estudos sobre a morfolojia e o ciclo evolutivo de Schizotrypanum cruzi n. gen., n. sp., ajente etiolojico de nova entidade morbida do homem. Mem Inst Oswaldo Cruz 1909; 1: 159–218.

7. Freitas-Lidani KC, Antunes-Andrade F, Bavia L, Silva-Damasceno F, Holsbach-Beltrame M, Messias-Reason IJ, Lucas-Sandri T. Chagas Disease: From Discovery to a Worldwide Health Problem. Front Public Health 2019; 7: 166.

8. World Health Organization. General Information - Chagas Disease. [Internet]. World Health Organization. [Updated: 2017; Reviewed: January 2021]. Available at: https://www.paho.org/hq/index.php?option=com_content&view=article&id=5856&Itemid=41506&lang=es

9. Chagas Coalition. Learn More About Chagas Disease. [Internet]. Barcelona Institute for Global Health. [Updated: 2019; Reviewed: January 2021]. Available at: http://www.infochagas.org/en/en-que-paises-hay-chagas

10. Antinori S, Galimberti L, Bianco R, Grande R, Galli M, Corbellino M. Chagas disease in Europe: A review for the internist in the globalized world. Eur J Intern M 2017; 43: 6-15.

11. Hotez PJ, Alvarado M, Basáñez MG, Bolliger I, Bourne R, Boussinesq M, et al. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. PLoS Neglected Tropical Diseases 2014; 8 (7): 1-9.

12. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford). 2020; 2020: baaa062.

13. Kirchhoff L. Chagas Disease (American Trypanosomiasis). [Internet]. Medscape [Updated: April 2019; Reviewed: January 2021]. Available at: https://emedicine.medscape.com/article/214581-overview

14. Centers for Disease Control and Prevention. Parasites - American Trypanosomiasis (also known as Chagas Disease). Biology. [Internet]. U.S. Department of Health & Human Services. [Updated: March 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/chagas/epi.html

15. Jansen AM, Xavier SCDC, Roque ALR. Trypanosoma cruzi transmission in the wild and its most important reservoir hosts in Brazil. Parasit Vectors 2018; 11 (1): 502.

16. Ventura-García L, Roura M, Pell C, Posada E, Gascón J, Aldasoro E, et al. Socio-cultural aspects of Chagas Disease: a systematic review of qualitative research. PLoS Negl Trop Dis 2013; 7 (9): 1–9.

17. Hernandez S, Forsyth CJ, Flores CA, Meymandi SK. Prevalence of Chagas Disease Among Family Members of Previously Diagnosed Patients in Los Angeles, California. Clin Infect Dis 2019; 69 (7): 1226-1228.

18. Bern C. Chagas disease. Engl J Med 2015; 373: 456-466.

19. Álvarez-Hernández DA, Frantyuti-Kelly GA, Díaz-López-Silva R, González-Chávez AM, González-Hermosillo-Cornejo D, Vázquez-López R. Chagas disease:

Current perspectives on a forgotten disease. Rev Med Hosp Gen Mex 2018; 81 (3): 154-164.

20. Kann S, Kunz M, Hansen J, Sieversten J, Crespo JJ, Loperena A, et al. Chagas Disease: Detection of Trypanosoma cruzi by a New, High-Specific Real Time PCR. J Clin Med 2020; 9 (5): 1517.

21. Centers for Disease Control and Prevention. Parasites - American Trypanosomiasis (also known as Chagas Disease). Diagnosis. [Internet]. U.S. Department of Health & Human Services. [Updated: March 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/chagas/health_professionals/dx.html

22. Gómez YM, Lorena VMB, Luquetti AO. Diagnosis of Chagas disease: what has been achieved? What remains to be done with regard to diagnosis and follow up studies? Mem Inst Oswaldo Cruz 2009; 104 (1): 115-121.

23. Kirchoff LV, Talavera F, King JW, Chandrasekar PH. Chagas Disease (American Trypanosomiasis) Differential Diagnoses. [Internet]. Medscape. [Updated: January 2021; Reviewed: January 2021]. Available at: https://emedicine.medscape.com/article/214581-differential#1

24. Pan American Health Organization, World Health Organization. Guidelines for the Diagnosis and Treatment of Chagas Disease. 1st edition. Geneva; Pan American Health Organization, World Health Organization: 2020.

25. Kawaguchi WH. Bonancio-Cerqueira L. Millan-Fachi M, Campos ML, Messias-Reason IJ, Pontarolo R. Efficacy and Safety of Chagas Disease Drug Therapy and Treatment Perspectives. In: Nissapatorn V, Helieh S. Chagas Disease – Basic Investigations and Challenges. 1st Ed. United Kingdom: IntechOpen; 2018. pp 121-152.

26. Pereira-Nunes MC, Acquatella H, Bern C, Bolger AF, Echeverría LE, Ditra WO, Gascon J, et al. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management. Circulation 2018; 138: 169-209.

27. Álvarez-Hernández DA, Castro-Rico ZL, García-Rodríguez-Arana R, González-Chávez AM, González-Chávez MA, Martínez-Juárez LA, Ferreira C, Vázquez-López R. Current Treatment of Chagas Disease. Current Treat Options Infect Dis 2020; 2020: 1-20.

Chapter 4. Dengue and Chikungunya

Authors

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Dengue and chikungunya are infections caused by viruses in the genera *Flavivirus* and *Alphavirus,* respectively. They occur mainly in tropical countries, but climate change and globalization have spread them throughout the world. Transmission is primarily vector-borne, with mosquitoes in the genus *Aedes* acting as vectors. The incubation period is short but variable. Infected individuals can experience similar clinical manifestations, including fever, myalgia, arthralgia, headache, and maculopapular rash. However, dengue can lead to life-threatening hemorrhagic complications. Diagnosis requires laboratory confirmation using molecular or serological methods, depending on the time when infected individuals seek medical attention. Treatment mainly consists of administering supportive measures to control or palliate the symptoms, but close monitoring of the health status of the patient is necessary to prevent complications. A vaccine is available for dengue, but not for chikungunya. Integrated vector management continues to be the most effective approach to control these diseases.

DENGUE

Introduction

Dengue, also known as breakbone fever, is a vector-borne disease caused by the dengue virus (DENV) that primarily affects bones and joints. The distribution of dengue was initially restricted to Africa and Asia but has spread to America, Europe, and Oceania, where local transmission has been identified, and outbreaks have increased over the past decade. Dengue shows a high prevalence in poor and marginalized communities, but this disease has become a global threat with potentially devastating consequences.[1]

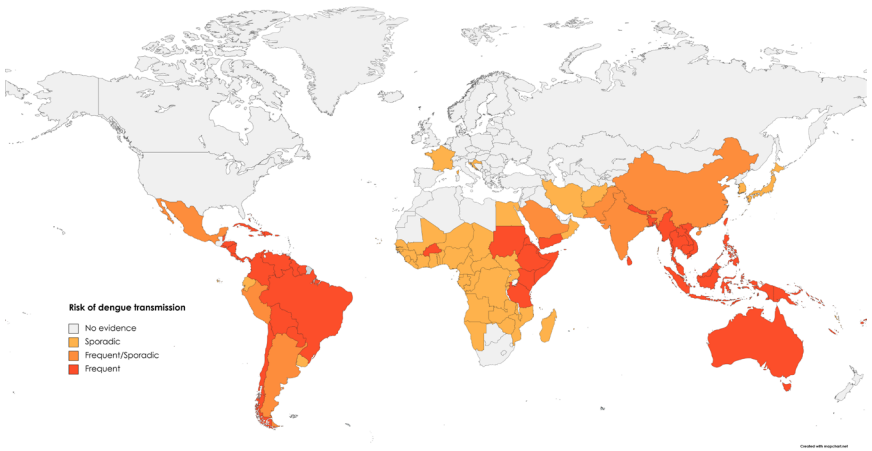
Historical Background

The earliest evidence of the disease can be traced back to the *Chinese Encyclopaedia of Disease Symptoms and Remedies* (3rd century AD), in which the term "water poison" was used to link it with flying insects thriving in association with water bodies.[2] Migration and trade spread the disease to other geographic areas, with several outbreaks reported in other continents, including Africa and America in the 17th–20th centuries.[3] However, it was until 1903 that Graham documented the route of transmission[4] and until 1943 that Ren Kimura and Susumu Hotta first isolated the DENV.[5]

Epidemiology

About 390 million persons are estimated to be infected, almost 3.9 billion are at risk of acquiring the disease, and nearly 4,000 deaths are caused by dengue each year worldwide.[1] It is endemic to more than 100 countries in Africa (sub-Saharan Africa), America (Central and South America), Asia (Southeast Asia), and Oceania (Western Pacific). Southeast Asia is the most affected region, bearing nearly 70% of the global burden of the disease. In addition to the endemic areas, more than 130 countries currently face the risk of dengue transmission and outbreaks (Figure 1).[1, 6]

FIGURE 1. RISK OF DENGUE TRANSMISSION WORLDWIDE



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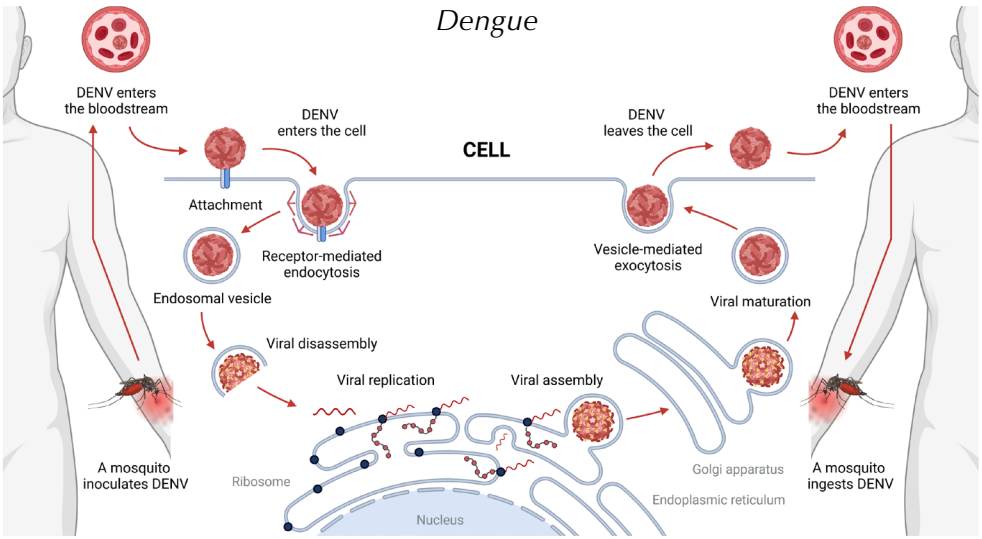
Adapted from: Centers for Disease Control and Prevention. Dengue - Dengue Around the World. [Internet]. Centers for Disease Control and Prevention. [Updated: January 2020; Consulted: January 2021]. Available at: https://www.cdc.gov/dengue/areaswithrisk/around-the-world.html

The 2010 *Global Burden of Disease Study* estimated that dengue accounted for 0.83 million disability-adjusted life years, 0.01 years lived with disability, and 0.81 years of life lost.[7]

Etiology

Dengue is caused by a virus named dengue virus, which belongs to the phylum Kitrinoviricota, class Flasuviricetes, order Amarillovirales, family *Flaviviridae*, and genus *Flavivirus*.[8] It is a positive-sense single-stranded RNA virus that encompasses four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Each serotype initially belonged to a distinct geographic region, but the four currently circulate worldwide.[9] Transmission is mainly vector-borne. Transmission occurs when an infected mosquito sucks blood from an uninfected individual and injects the virus. Afterward, the virus is transported through the bloodstream, enters cells, and hijacks their machinery to replicate. Transmission continues when an uninfected mosquito takes a blood meal from an infected individual and ingests the virus. Subsequently, the virus migrates to the midgut, where it replicates and disseminates to secondary tissues, including the salivary glands. The cycle is completed when an infected mosquito sucks blood from an uninfected individual and injects the virus (Figure 2).

FIGURE 2. DENGUE VIRUS LIFE CYCLE



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Mosquitoes in the genus *Aedes* have been recognized as vectors: *A. aegypti,* an anthropophilic species restricted to warm climates, is the primary vector of DENV; *A. albopictus*, an anthropophilic enzootic species widely spread in cold, temperate, and warm climates, is the secondary vector of DENV. Humans are the main reservoirs of the virus, but other primates and rodents are also reservoirs. Transmission from mother to child has also been reported but it is not widely acknowledged.[1, 9]

Risk Factors

In countries where dengue is endemic, the main risk factors for acquiring the disease include low socioeconomic status, open water-storage containers, wearing non-protective clothing, sleeping with no bed nets during the daytime, and being in close contact with infected individuals. The disease is more prevalent in men than women and in adults than children.[1, 10]

Clinical Manifestations

The incubation period of the disease ranges from 4 to 10 days. Afterward, the disease develops through three distinct stages:

- **Febrile stage.** It is characterized by abrupt high-grade fever with or without generalized aches (myalgia, arthralgia, headache, and retro-orbital pain), hyporexia, nausea, vomiting, and maculopapular rash. Mild mucocutaneous hemorrhages (petechiae, epistaxis, and gingivorrhagia) can also be experienced. The febrile stage lasts between 2 and 7 days.
- **Critical stage.** It is characterized by a decrease in body temperature and either decrease or increase in capillary permeability that leads to improvement or worsening of the disease, respectively. If the health condition of the infected individual improves, it progresses towards the recovery phase; if it worsens, the patient may experience plasma leakage that may lead to fluid accumulation (pleural effusion and ascites), severe mucocutaneous hemorrhages, hypovolemic shock, and multiorgan failure. Assessment helps to determine the severity of the disease (Table 1). This stage lasts between 2

and 3 days and occurs between the third and seventh day after the onset of symptoms.

TABLE 1. CLINICAL MANIFESTATIONS AND PARACLINICAL VARIABLES USED FOR CLASSIFICATION OF DENGUE

	WHO classification of dengue		
Category	Dengue with no warning signs	Dengue involving warning signs	Severe dengue
Criteria	Fever plus two of the following: • Generalized aches • Nausea or vomiting • Maculopapular rash • Mild mucocutaneous bleeding • Leukopenia	At least one of the following: • Agitation or lethargy • Persistent vomiting • Abdominal pain • Hepatomegaly • Fluid accumulation • Mild to moderate mucocutaneous bleeding • Increased HTC with decreased PLT count	Severe plasma leakage with: • Fluid accumulation + respiratory distress • Severe mucocutaneous bleeding • Compensated shock • Decompensated shock • Multiorgan failure

HTC: hematocrit; PLT: platelet.

Adapted from: World Health Organization, Special Programme for Research and Training in Tropical Diseases. Dengue. Guidelines for Diagnosis, Treatment, Prevention, and Control. 1st ed: Geneve, Switzerland; WHO Library Cataloguing-in-Publication Data: 2009.

- **Convalescent stage.** It is characterized by resorption of leaked plasma, improvement of the overall health condition, resolution of gastrointestinal symptoms, and normalization of the hemodynamic status. Rash, pruritus, and bradycardia can also be experienced.[11, 12]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis. However, the detection of DENV is required for confirma-

tion, and several laboratory tests are available for this purpose. Molecular methods such as polymerase chain reaction or nucleic acid amplification tests can detect DENV-specific RNA sequences. Serological methods can detect antigens produced by DENV or antibodies against it produced by the host. Antigen detection techniques such as NS1 antigen lateral-flow immunoassay or NS1 enzyme-linked immunosorbent assay (ELISA) and antibody detection techniques such as DENV IgM ELISA or E/M-specific capture IgM or IgG ELISA are used for this purpose.[13, 14] Molecular and serological techniques are recommended for diagnosis if the sample is collected before the seventh day after the onset of disease; serological methods should be preferred if the sample is collected on or after the seventh day.[15]

Differential diagnosis should be conducted to rule out other causes of fever and hemorrhage, including chikungunya, hemorrhagic fever, idiopathic thrombocytopenic purpura, influenza, leptospirosis, malaria, meningococcemia, rickettsiosis, roseola infantum, Ross river fever, West Nile encephalitis, yellow fever, and Zika.[12, 16]

Treatment

There is no specific drug to treat dengue, and supportive treatment should be administered according to the severity of the disease:

- **Dengue with no warning signs.** Patients can be treated at home. Relative rest, oral hydration, and antipyretics should be prescribed. The first-line treatment to control fever is acetaminophen (10 mg/kg per dose orally every 4 to 6 hours in newborns, 15 mg/kg per dose orally every 4 to 6 hours in children over one month, and 1 g per dose orally every 4 to 6 hours in adults). Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates should be avoided.
- **Dengue evidenced by warning signs.** Patients should be hospitalized and placed under a bed net to avoid further contagion. Mandatory rest, intravenous hydration, and antipyretics must be indicated. Invasive procedures should be avoided to minimize the risk of bleeding. Clinical signs, fluid balance, urine output, hematocrit, and platelet count should be monitored every 4 hours until vital signs are stable.

- **Severe dengue.** Patients require to be hospitalized in the intensive care unit and placed under a bed net to avoid further contagion. Mandatory rest, oxygen supplementation, intravenous hydration, and antipyretics should be administered. Invasive procedures should be avoided to minimize the risk of bleeding. Clinical signs, fluid balance, urine output, hematocrit, and platelet count should be monitored every 4 hours until vital signs are stable. Fresh whole blood must be transfused in case of severe bleeding or decreased hematocrit.[12]

Prevention

A prophylactic dengue vaccine is available. However, it should only be administered to 9–45 years old persons with confirmed prior DENV infection.[17] The main preventive strategies include wearing protective clothing, using insect repellents and bed nets, spraying insecticide indoors and outdoors, and eliminating mosquito breeding sites.[1, 18]

Conclusion

Dengue is a vector-borne disease that can be acquired in more than 130 countries, and new cases in unusual places are reported each year. Mosquitoes in the genus *Aedes* can adapt to various climates and environmental conditions, and can transmit other viral infections too, which makes them a threat to global health. Integrated vector management continues being the best strategies to control its transmission. Dengue may cause severe symptoms, but it is rarely life-threatening if patients are promptly diagnosed and adequately treated. Research and development of novel drugs and effective vaccines are increasingly needed to reduce the burden of this disease.

References

1. World Health Organization. Dengue and severe dengue. [Internet]. World Health Organization. [Updated: June 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

2. Nobuchi H. The symptoms of a dengue-like illness recorded in a Chinese medical encyclopedia (in Japanese). Kanpo Rinsho 1979; 26: 422-425.

3. Gubler DJ. Dengue/dengue haemorrhagic fever: history and current status. Novartis Found Symp 2006; 277: 3-16; discussion 16-22, 71-3, 251-253.

4. Graham H. The dengue: a study of its pathology and mode of propagation. J Trop Med 1903: 6: 209–214.

5. Kimura R, Hotta S. Studies on dengue fever (VI). On the inoculation of dengue virus into mice (in Japanese). Nippon Igaku 1944; 3379: 629–633.

6. Centers for Disease Control and Prevention. Dengue - Dengue Around the World. [Internet]. U.S. Department of Health & Human Services. [Updated: January 2020; Reviewed: January 2021]. Available at: hhttps://www.cdc.gov/dengue/areaswithrisk/around-the-world.html

7. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.

8. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

9. Scitable. Dengue Viruses. [Internet]. Nature Education. [Updated: 2018; Reviewed: January 2021]. Available at: https://www.nature.com/scitable/topicpage/dengue-viruses-22400925/

10. Centers for Disease Control and Prevention. Dengue - Prevent Mosquito Bites. [Internet]. U.S. Department of Health & Human Services. [Updated: December 2020; Consulted: Reviewed 2021]. Available at: https://www.cdc.gov/dengue/prevention/prevent-mosquito-bites.html

11. Médecins Sans Frontières. Clinical guidelines / Chapter 8. Viral diseases Dengue. [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/dengue-16690007.html

12. World Health Organization, Special Programme for Research and Training in Tropical Diseases. Dengue. Guidelines for Diagnosis, Treatment, Prevention, and Control. 1st ed: Geneve, Switzerland; WHO Library Cataloguing-in-Publication Data: 2009.

13. Centers for Disease Control and Prevention. Dengue - Testing Guidance. [Internet]. U.S. Department of Health & Human Services. [Updated: January 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/dengue/healthcare-providers/testing/testing-guidance.html

14. Casenghi M, Kosack C, Li R, Bastard M, Ford N. NS1 antigen detecting assays for diagnosing acute dengue infection in people living in or returning from endemic countries. Cochrane Database Syst Rev 2018; 2018 (5): CD011155.

15. Muller DA, Depelsenaire AC, Young PR. Clinical and Laboratory Diagnosis of Dengue Virus Infection. J Infect Dis 2017; 215 (2): 89-95.

16. Smith DS, Bronze MS. What are the differential diagnoses for dengue?. [Internet]. Medscape. [Updated: May 2019; Reviewed: January 2021]. Available at: https://www.medscape.com/answers/215840-52396/what-are-the-differential-diagnoses-for-dengue#qna

17. Centers for Disease Control and Prevention. Dengue - Prevention. [Internet]. Centers for Disease Control and Prevention. [Updated: January 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/dengue/healthcare-providers/hc-providers-prevention.html

18. Rather IA, Parray HA, Lone JB, Paek WK, Lim J, Baipai VK, et al. Prevention and Control Strategies to Counter Dengue Virus Infection. Front Cel Infect Microbiol 2017; 7: 336.

CHIKUNGUNYA

Introduction

Chikungunya, also known as chikungunya fever, is a vector-borne disease caused by the chikungunya virus (CHIKV) that primarily affects bones and joints. Most cases occur in Africa and Asia, but it is becoming a significant health issue in the Americas, where sporadic outbreaks have occurred, and in Europe, where local transmission has been reported. Chikungunya is frequently misdiagnosed as symptoms resemble those of other mosquito-borne diseases, such as dengue and Zika. This issue hinders control and facilitates its spread.[1]

Historical Background

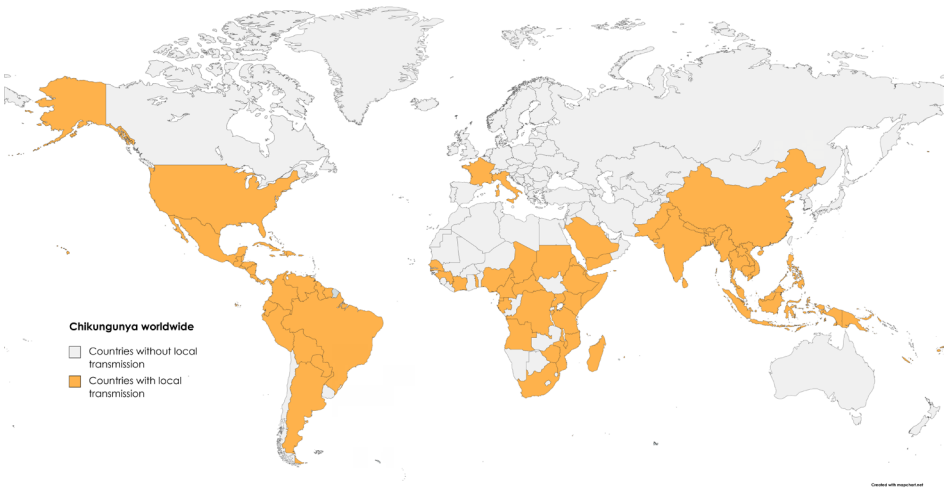
The earliest evidence of the disease can be traced back to 1952 when an epidemic of an acute disease characterized by high fever, joint swelling, and rash occurred in former Tanganyika (current Tanzania).[2] The disease was initially thought to be caused by the dengue virus; however, one year later, CHIKV was isolated from the blood of several febrile patients and mosquito species. Since then, the disease has spread out, and several outbreaks have been documented around the

world. The first outbreak in Asia was reported in Thailand in 1963; in Europe, in Italy in 2007; in Oceania, in New Caledonia in 2013; and in America, in St. Martin Island in 2013.[3]

Epidemiology

The precise incidence and prevalence of the disease are currently unknown. The number of cases varies from hundreds of thousands to millions each year, depending on the number of outbreaks, and misdiagnosis and underreporting are common. Almost 1.3 billion people are estimated to be at risk of acquiring the disease[1, 4]. Chikungunya has been reported in more than 100 countries in Africa (Central and East Africa), America (Central and South America), Asia (Southeast Asia), Europe (Central Europe), and Oceania (Pacific islands) (Figure 1).[5] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH LOCAL TRANSMISSION OF CHIKUNGUNYA



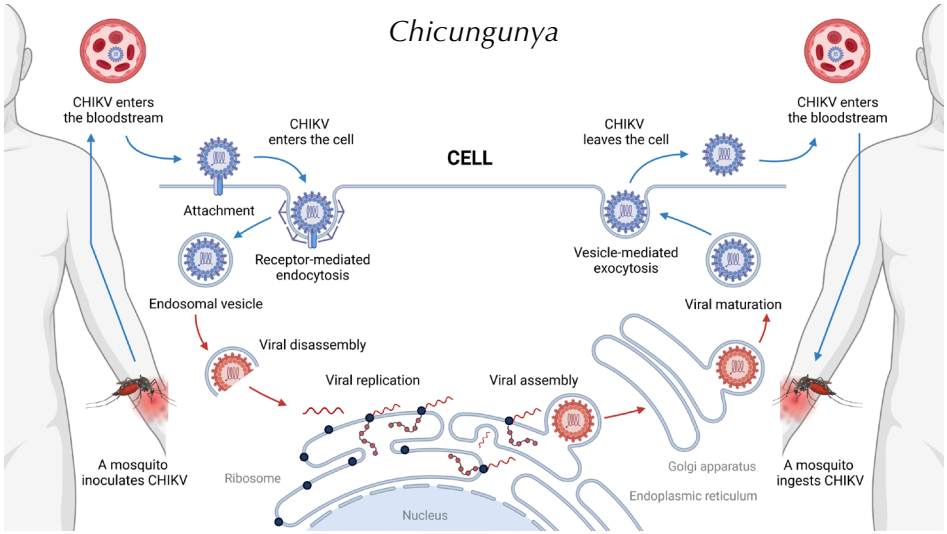
Created with MapChart.net

Adapted from: Centers for Disease Control and Prevention. Chikungunya Virus - Geographic Distribution. [Internet]. U.S. Department of Health & Human Services. [Updated: November 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/chikungunya/geo/index.html

Etiology

Chikungunya is caused by a virus named chikungunya virus, which belongs to the phylum Kitrinoviricota, class Alsuviricetes, order Martellivirales, family *Togaviridae*, and genus *Alphavirus*.[6] It is a positive-sense single-stranded RNA virus that encompasses three genotypes, named after their geographic distribution: Asia, East-Central-South African, and West African.[7, 8] Transmission is mainly vector-borne. Transmission occurs when an infected mosquito sucks blood from an uninfected individual and injects the virus. Afterward, the virus is transported through the bloodstream, enters cells, and hijacks their machinery to replicate. Transmission continues when an uninfected mosquito takes a blood meal from an infected individual and ingests the virus. Subsequently, the virus migrates to the midgut, where it replicates and disseminates to secondary tissues, including the salivary glands. The cycle is completed when an infected mosquito sucks blood from an uninfected individual and injects the virus (Figure 2). Mosquitoes in the genus *Aedes* are currently recognized as vectors: *A. aegypti*, an anthropophilic species restricted to warm climates, and *A. albopictus,* an anthropophilic and enzootic species widespread in cold, temperate, and warm climates, are the primary vectors for CHIKV. Exclusively enzootic mosquito species such as *A. africanus, A. furcifer, A. luteocephalus, A. neoaphricanus*, and *A. taylori* can also transmit the disease to non-human primates and rodents.[1, 9]

FIGURE 2. CHIKUNGUNYA VIRUS LIFE CYCLE



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Risk Factors

In countries where chikungunya is endemic, the main risk factors for acquiring the disease include low socioeconomic status, keeping water-storage containers open, wearing non-protective clothing, sleeping without bed nets during the daytime, and being in close contact with an infected individual. The disease is more prevalent in women than men and in adults than children.[10, 11]

Clinical Manifestations

The incubation period of the disease ranges between 2 and 4 days, but there are reports of infected individuals developing symptoms of the disease in 1 to 12 days. Afterward, the disease develops through two distinct stages:

- **Acute stage.** It is characterized by an abrupt onset of fever and arthralgia (bilateral, symmetric, debilitating, and disabling) that affects mainly the face, torso, and upper and lower extremities. Confusion, fatigue, malaise, myalgia, headache, lumbalgia, nausea, vomiting, abdominal pain, diarrhea, maculopapular rash, and pruritus can also be experienced. Most symptoms resolve over the course of 2 weeks, except for arthralgia, which may last for months or years.
- **Chronic stage.** It is characterized by the persistence of inflammatory conditions in joints and bones, such as arthritis, bursitis, enthesitis, synovitis, and tenosynovitis. Edema, entrapment, joint stiffness, worsening of pre-existing or traumatic arthropathies, and neuropathic pain can also be experienced. Symptoms may resolve spontaneously or after treatment or may persist for prolonged periods.

Newborns, adults over 65 years old, and people with comorbidities tend to develop a severe form of the disease (encephalitis, myocarditis, hepatitis, or multiorgan failure), which can be life-threatening.[7, 9, 12]

Diagnosis

Epidemiological background and clinical manifestations should be considered for diagnosis, but detection of CHIKV is required for confirmation, and several laboratory tests are available for this purpose. Molecular methods such as polymerase chain reaction can detect CHIKV-specific RNA sequences, and serological techniques such as CHIKV IgM enzyme-linked immunosorbent assay (ELISA) or E/M-specific capture IgM and IgG ELISA can recognize antibodies against CHIKV.[9, 13] Molecular methods are recommended for diagnosis on samples collected before the sixth day after the onset of the disease; serological techniques should be preferred for samples collected on or after the sixth day or when molecular methods tested negative. Simultaneous testing for dengue and Zika is strongly recommended.[9, 13]

Differential diagnosis should rule out other causes of fever and arthralgia such as dengue, leptospirosis, lupus erythematosus systemic, malaria, Mayaro, measles, mononucleosis, O'nyong-nyong, reiter arthritis, rheumatoid arthritis, systemic arthritis, yellow fever, and Zika.[13]

Treatment

There is no specific drug for the treatment of chikungunya. Supportive treatment with relative rest to avoid fatigue, hydration to prevent dehydration, and symptomatic treatment with antipyretics to control fever are recommended. The first-line treatment to control fever is acetaminophen (10 mg/kg per dose orally every 4 to 6 hours in newborns, 15 mg/kg per dose orally every 4 to 6 hours in children over one month, and 1 g per dose orally every 4 to 6 hours in adults). Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates should be avoided during the acute stage of the disease or until a differential diagnosis has ruled out dengue because of the increased risk of bleeding. Afterward, NSAIDs or other drugs can be administered.[1, 12]

Prevention

No vaccine is currently available to prevent chikungunya. The main preventive strategies include wearing protective clothing, using insect repellents and bed

nets, spraying insecticide indoors and outdoors, and eliminating mosquito breeding sites.[9, 12]

Conclusion

Chikungunya is a crippling and disabling vector-borne disease that has spread worldwide due to climate change and globalization. Epidemiological surveillance needs to be strengthened to better understand the distribution and burden of this disease. Infected individuals may experience chronic and relapsing symptoms that impair their productivity; proper pain management is essential to improve life quality. Vaccines are under development, but several years may still have to pass before a vaccine is given final approval based on efficacy and safety. Until then, integrated vector management strategies should be strengthened to prevent the occurrence of outbreaks and epidemics.

References

1. World Health Organization. Chikungunya. [Internet]. orld Health Organization. [Updated: September 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/chikungunya
2. Weaver SC, Forrester NL Chikungunya: Evolutionary history and recent epidemic spread. Antiviral Res 2015; 3628: 1-8.
3. Zeller H, Van Bortel W, Sudre B. Chikungunya: Its History in Africa and Asia and Its Spread to New Regions in 2013-2014. J Infect Dis 2016; 214 (5): 436-440.
4. Nsoesie EO, Kraemer MU, Golding N, et al. Global distribution and environmental suitability for chikungunya virus, 1952 to 2015. Euro Surveill 2016; 21 (20): 1-22.
5. Centers for Disease Control and Prevention. Chikungunya Virus - Geographic Distribution. [Internet]. U.S. Department of Health & Human Services. [Updated: November 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/chikungunya/geo/index.html
6. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
7. Ganesan VK, Duan B, Reid SP. Chikungunya Virus: Pathophysiology, Mechanism, and Modeling. Viruses. 2017; 9 (12): 368.

8. Silva LA, Dermody TS. Chikungunya virus: epidemiology, replication, disease mechanisms, and prospective intervention strategies. J Clin Invest 2017; 127 (3): 737-749.

9. Galán-Huerta KA, Rivas-Estilla AM, Fernández-Salas I, Farfan-Ale JA, Ramos-Jiménez J. Chikungunya virus: A general overview. Med Universit 2015; 17 (68): 175-183.

10. Alayu M, Teshome T, Amare H, Kinde S, Belay D, Assefa Z. Risk Factors fot Chikungunya Outbreak in Kebridhar City, Somali Ethiopia, 2019. Unmatched Case-Control Study. BioRxiv 2020; 1: 1-20.

11. Bhagwati C, M M, Mehta KD, Y S G. Profile of The Chikungunya Infection: A Neglected Vector Borne Disease which is Prevalent In The Rajkot District. J Clin Diagn Res 2013; 7 (6): 1008-1011.

12. Vairo F, Haider N, Kock R, Ntoumi F, Ippolito G, Zumla A. Chikungunya: Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention. Infect Dis Clin North Am 2019; 33 (4): 1003-1025.

13. Álvarez-Argüelles ME, Rojo-Alva S, Rodríguez-Pérez M, Boga-Riveiro JA, Melón-García S. Diagnosis and Molecular Characterization of Chikungunya Virus Infections. In: Rodríguez-Morales AJ. Current Topics in Neglected Tropical Diseases. 4th edition. London, United Kingdom; IntechOpen: 2019.

Chapter 5. Dracunculiasis

Authors

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Introduction

Dracunculiasis, also known as Guinea-worm disease, is a debilitating and disabling disease caused by *Dracunculus medinensis* that primarily affects the skin and subcutaneous tissues. The persons most affected live in rural, deprived, and marginalized areas and rely on surface water sources for drinking.[1] Infected individuals usually remain asymptomatic over the first year, but then an adult worm emerges through the skin, causing damage and pain. Complete emergence of the worm can last up to a few months and, if left untreated, can cause permanent disability and impairment.[2]

Historical Background

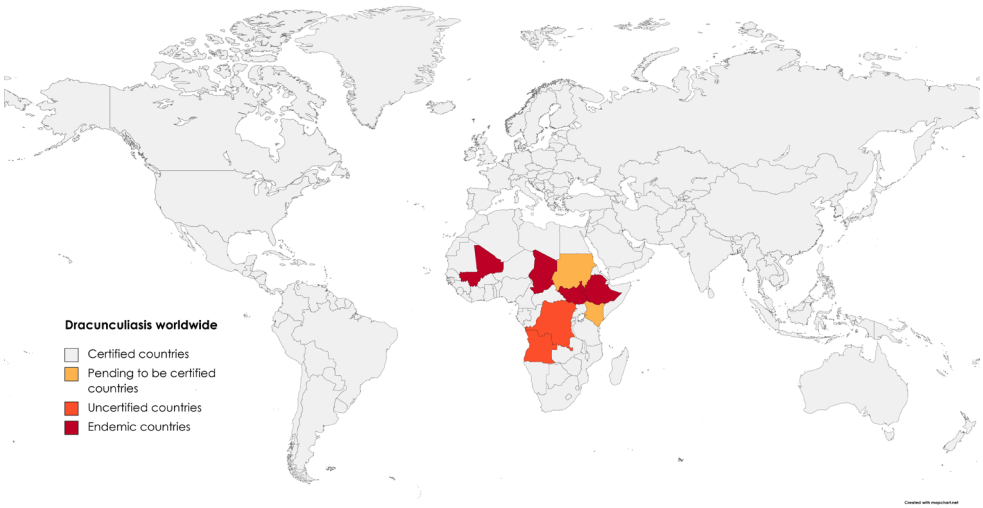
The earliest evidence of the disease can be traced back to the *Eber papyrus* (15th century BC). Archeologists and paleontologists discovered calcified Guinea-worms in Egyptian mummies, demonstrating that this disease has been afflicting humans since then.[3] Philosophers such as Galen and Plutarch acknowledged its presence, and physicians such as Avicenna and Rhazes described its characteristics (10th–11th century AD).[4] However, it was until 1819 that Carl Rudolphi isolated the etiological agent; until 1870 that Alesej Fedchenko identified the intermediate host; and until 1913 that Dyneshvar Turkhud described its life cycle.[5]

Epidemiology

The precise prevalence and incidence of the disease are unknown. Although more than 270,000 cases were reported between 2000 and 2020 (Figure 1)[6, 7],

the number of cases has been declining, with 75,223 cases reported in 2000 and 27 in 2020. The cases from 2020 were reported in 6 countries: Chad (12 cases), Ethiopia (11 cases), Angola (1 case), Cameroon (1 case), Mali (1 case), and South Sudan (1 case). Dracunculiasis occurs throughout Africa, but most cases have been found in Central and East Africa.[8] In 2016, Elizabeth Cromwell et al. estimated that 1.9 million disability-adjusted life years had been averted since the launch of the Guinea-worm Eradication Program.[9]

FIGURE 1. CERTIFICATION STATUS OF DRACUNCULIASIS ERADICATION



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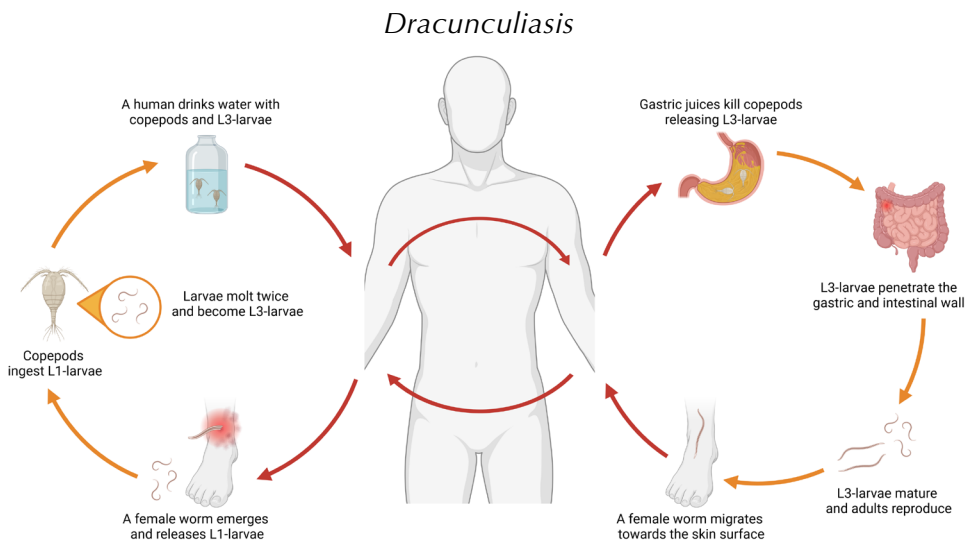
Adapted from: World Health Organization. Certification status of dracunculiasis eradication. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/dracunculiasis/dradata/html/report_Countries_i1.html

Etiology

Dracunculiasis is caused by a parasite named *Dracunculus medinensis,* which belongs to the phylum Nematoda, class Chromadorea, order Rhabditida, suborder Spirurina, superfamily *Dracunculoidea*, family *Dracunculideae,* and genus *Dracunculus*.[10] *D. medinensis* is a long, thread-like nematode that can reach up to 60–100 cm in length.[11] The disease is water-borne. Transmission occurs when an uninfected individual drinks unfiltered water containing freshwater copepods carrying infective larvae. Copepods die in the stomach and release infective lar-

vae. These larvae penetrate the intestinal walls to enter the peritoneal and retroperitoneal space, where they grow into adult worms and undergo sexual reproduction. Male worms die, while females migrate to the subcutaneous tissues towards the skin surface. About one year after the initial infection, the female worms induce a painful blister on the skin. When the blister bursts, infected individuals seek relief by coming in contact with water, which triggers the emergence of the female worms and release of non-infective larvae. Copepods ingest these larvae, where they molt twice to develop into infective larvae. The cycle is completed when an uninfected individual drinks unfiltered water containing copepods carrying infective larvae (Figure 2).[12] Copepods in the genus *Cyclops* have been recognized as the main intermediate host.[13] Since *D. medinensis* has no definitive hosts, it must pass from one host to another to survive.[14]

FIGURE 2. DRACUNCULUS MEDINENSIS LIFE CYCLE



Risk Factors

In countries where dracunculiasis is endemic, the main risk factors for acquiring the disease include drinking unfiltered water and using stagnant water sources for human consumption.[15] The disease affects men and women equally and is more prevalent in adults than children.[16]

Clinical Manifestations

The incubation period of the disease ranges from 10 to 14 months. Afterward, an unspecified allergic reaction may occur before evident signs of the disease appear. The emergence of a female worm through the skin induces papules and swelling, mainly in the lower limbs. Sometimes it is possible to observe and palpate the Guinea-worm. Papules become blisters that cause itching and intense burning pain, leading to temporary or even permanent disability.[15] Blisters may grow in diameter before they burst, producing shallow ulcers. The expulsion of the female worm from the affected body part is usually completed within 14 to 28 days —some authors have reported up to a few months; the sore heals up quickly thereafter.[14] Each infection lasts only one year, but more than one worm may emerge simultaneously or sequentially over the course of several weeks.[17] If left untreated, acute and late-stage complications may develop, including abscesses, cellulitis, septic arthritis, and septic shock. Chronic complications include worm calcification and joint deformation.[18]

Diagnosis

Epidemiological background and clinical manifestations are sufficient to make a diagnosis in endemic areas. Laboratory confirmation is not required, but histopathology techniques are useful when in doubt.[8] Supplementary examination with imaging studies can demonstrate the presence of female worms in soft tissues; these appear as long, linear, serpiginous, or coiled, whorled chain mail types of calcifications in X-rays. The typical clinical picture is easy to diagnose, but atypical presentations may require histopathology testing to improve accuracy and reliability.[18]

Differential diagnosis should always be made to rule out other worm-related diseases, such as loiasis and onchocerciasis.[18]

Treatment

Every positive case detected should be contained and treated to prevent further transmission:

- **Case containment.** It can be achieved through isolation and education of each patient to prevent contamination of water sources.[19]
- **Pharmacological treatment.** It consists of administering anti-histamine drugs to control the pruritus, non-steroidal anti-inflammatory drugs to relieve the pain and reduce the swelling, and antimicrobials to prevent secondary infections.[20]
- **Non-surgical treatment.** It consists of immersing the affected body parts in hot water to induce the female worm to migrate towards the skin surface. The protruding part can then be attached to and twisted around a small stick until the worm is completely removed. If the worm breaks during extraction, the remainder part retracts into the body and spills larvae into the tissues, causing severe inflammation and abscess formation.[20]
- **Surgical treatment.** It may be possible where adequately trained healthcare professionals and proper medical facilities are available.[1]

Prevention

No vaccine to prevent dracunculiasis is currently available. The main preventive strategies include treating potentially contaminated surface water bodies with an organophosphate larvicide to kill copepods, filtering potentially contaminated drinking water through a cloth filter to remove copepods, and providing safe drinking water from protected hand-dug wells.[21]

Conclusions

Dracunculiasis is a preventable water-borne disease that mainly affects people in developing countries. The number of human cases has decreased by over 99% during recent decades, with a few countries still pending to be certified as free of transmission. Dracunculiasis has been set as the first neglected tropical disease to be eradicated and, as we move towards reaching this goal by 2030, efforts to complete the task should be strengthened. Dracunculiasis continues to be a health problem in hard-to-reach communities. No patient should be left behind, and reemergence should be prevented.

References

1. World Health Organization. Dracunculiasis (guinea-worm disease). [Internet]. Ginebra, Switzerland; WHO: [Updated: March 2019; Reviewed: December 2020]. Available at: http://www.who.int/mediacentre/factsheets/fs359/en/
2. Rawla P, Jan A. Dracunculiasis. In: StatPearls [Internet]. Florida, United States; StatPearls Publishing: [Updated: June 2019; Reviewed: December 2020]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538231/#article-20696.s1
3. Nunn JF, Trap E. Tropical diseases in ancient Egypt. Trans R Soc Trop Med Hyg 2000; 94: 147-153.
4. World Health Organization. Dracunculiasis Historical background. [Internet]. Ginebra, Switzerland; WHO: [Updated: August 2014; Reviewed: December 2020]. Available at: https://www.who.int/dracunculiasis/background/en/
5. Cox FEG. History of Human Parasitology. Clin Microbiol Rev 2002; 2002: 595-612.
6. World Health Organization. Dracunculiasis eradication: global surveillance summary, 2017. Wkly Epidemiol Rec 2018; 93: 305-320.
7. World Health Organization. Certification status of dracunculiasis eradication. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/dracunculiasis/dradata/html/report_Countries_i1.html
8. The Carter Center. Guinea Worm Case Totals. [Internet]. Atlanta, United States; CC [Updated: December 2020; Reviewed: December 2020]. Available at: https://www.cartercenter.org/health/guinea_worm/case-totals.html
9. Cromwell EA, Roy S, Sankara, DP, Weiss A, Stanaway J, Goldberg E, et al. Slaying little dragons: the impact of the Guinea Worm Eradication Program on dracunculiasis disability averted from 1990 to 2016. Gates Open Res 2018; 2: 1-14.
10. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
11. Biswas G, Sankara DP, Agua-Agum J, Maiga A. Dracunculiasis (guinea worm disease): eradication without a drug or a vaccine. Phil Trans R Soc B Biol Sci 2013; 368 (1623): 1-13.
12. Muller R. Life cycle of Dracunculus medinensis. [Internet]. Washington, DC: National Academy Press; 1985 [Reviewed in: December 2020]. Available at: https://www.ircwash.org/sites/default/files/245.3-85WO-6448.pdf
13. Johnson M, Atting I, Boxshall GA, Braide EI. Copepod vectors of guinea worm: A review of West African records and a local scale study relevant to eradication programmes. Nigerian J of Parasitol 1990; 9 (11): 33-39.

14. Mbong EM, Sume GE, Danbe F, Kum WK, Mbi VO, Bita-Fouda AA, et al. Not every worm wrapped around a stick is a guinea worm: a case of Onchocerca volvulus mimicking Dracunculus medinensis. Parasit Vectors 2015; 8: 1-8.

15. Dada EO. Prevalence of Dracunculiasis in Parts of Akoko Land, Ondo State, Nigeria. JALSI 2015; 4 (1): 1-10.

16. Rawla P, Jan A. Dracunculiasis. [Internet]. StatPearls Publishing. [Updated: June 2020; Revised: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538231/

17. Miri ES, Hopkins DR, Ruiz-Tiben E, Keana AS, Withers Jr. PC, Anangbogu IN, et al. Nigeria's Triumph: Dracunculiasis Eradicated. Am J Trop Med Hyg 2010; 83 (2): 215-225.

18. Gulanikar A. Dracunculiasis: Two Cases with Rare Presentations. J Cutan Aesthet Surg 2012; 5 (4): 281-283.

19. Hopkins DR, Weiss AJ, Roy SL, Zingeser J, Guagliardo SA. Progress Toward Global Eradication of Dracunculiasis - January 2018–June 2019. MMWR Morb Mortal Wkly Rep 2019; 68: 979-984.

20. Kim SM. Dracunculiasis in oral and maxillofacial surgery. J Korean Assoc Oral Maxillofac Surg 2016; 42 (2): 67-76.

21. Ruiz-Tiben E, Hopkins DR. Dracunculiasis (Guinea worm disease) eradication. Adv Parasitol 2006; 61: 275-309.

Chapter 6. Echinococcosis

Authors

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Introduction

Echinococcosis is a complex, parasitic, zoonotic disease caused by *Echinococcus* spp. that primarily affects the liver and lungs. It can occur in two forms: cystic echinococcosis (CE), which is widely distributed, and alveolar echinococcosis (AE), most prevalent in the Northern Hemisphere. The incubation period is highly variable; it can take decades for cysts to grow to the extent that their mass triggers clinical manifestations. Treatment is complex since it depends on the clinical setting and expertise of the healthcare personnel. Complete disease clearance seems unlikely as high relapse rates have been reported.[1]

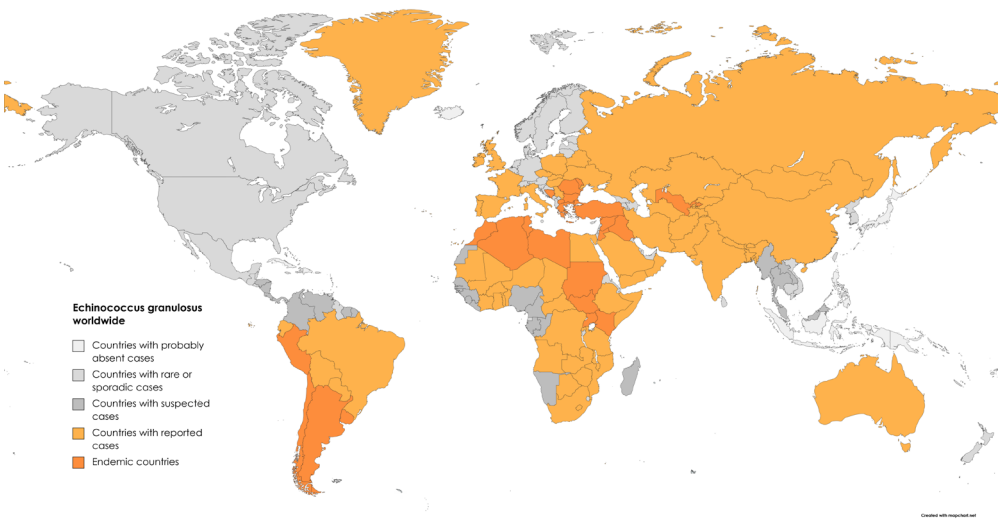
Historical Background

The earliest report of the disease can be traced back to the aphorisms of Hippocrates (4th century BC), in which the clinical manifestations of echinococcosis were described. Several philosophers, including Arateus (1st century AD) and Galenus (2nd century AD), described the presence of cysts in the abdomen. However, their contents remained unknown until 1648, when Francisco Redi showed that they contained parasites, and until 1766, when German Simon suggested that those were the larval stage of tapeworms. The main etiological agents were isolated in the 18th and 19th centuries; August Batsch isolated *Echinococcus granulosus* in 1786, and Rudolf Leuckart isolated *Echinococcus multilocularis* in 1863.[2]

Epidemiology

About 4 million people are estimated to be infected, and almost 40 million are at risk of acquiring the disease.[3] The annual incidence rate ranges between 1 and 200 cases per 100,000 inhabitants for CE and between 0.03 and 1.2 cases per 100,000 inhabitants for AE.[4] CE is endemic to Africa (East Africa), America (South America), Asia (Central Asia), and Europe (Eastern Europe); AE is endemic to Asia (North and East Asia), America (North America), and Europe (Central and Eastern Europe). (Figures 1 and 2).[1, 4, 5] The 2010 *Global Burden of Disease Study* estimated that echinococcosis accounted for 0.14 million disability-adjusted life years, 0.11 years lived with disability, and 0.03 years of life lost.[6]

FIGURE 1. DISTRIBUTION OF *ECHINOCOCCUS GRANULOSUS*



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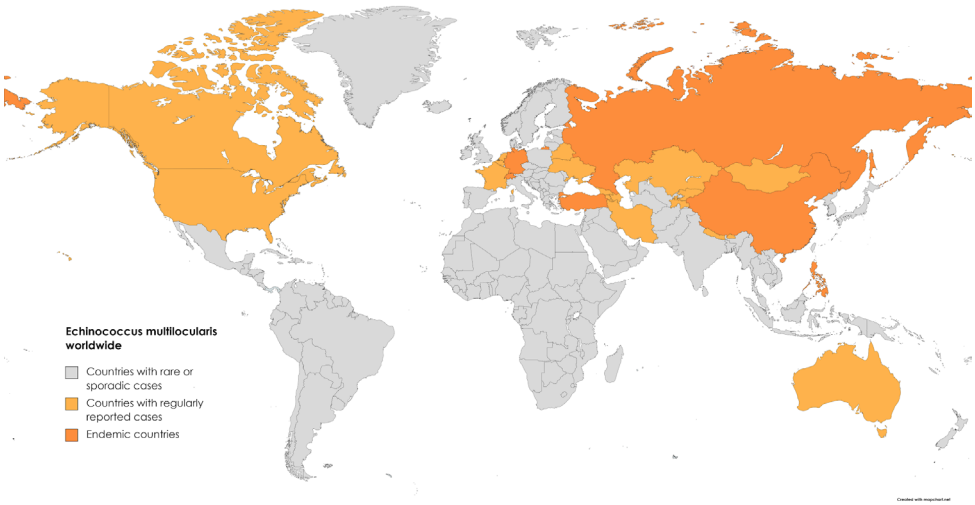
Adapted from: Rodríguez-Morales AJ, Calvo-Betancourt LS, Alarcón-Olave C, Bolívar-Mejía A. Echinococcosis in Colombia - A Neglected Zoonosis? In: Rodríguez-Morales AJ. Current Topics in Echinococcosis. 1st edition. London; IntechOpen: 2015.

FIGURE 2. DISTRIBUTION OF *ECHINOCOCCUS MULTILOCULARIS*



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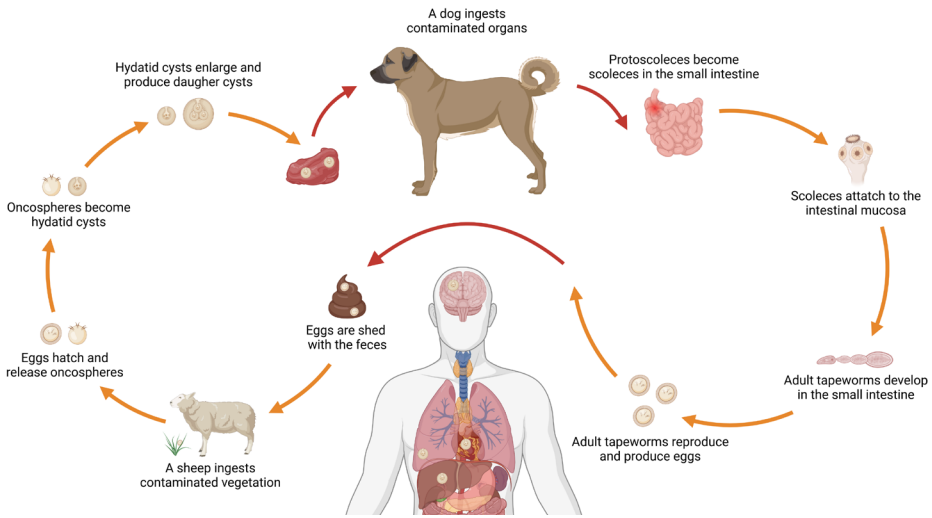
Etiology

Echinococcosis is caused by parasites from the *Echinococcus granulosus* complex, which belongs to the phylum Platyhelminthes, class Cestoda, order Cyclophyllidea, family *Taeniidae*, and genus *Echinococcus*.[7] This complex includes several species, but *E. granulosus* and *E. multilocularis* are responsible for most cases of echinococcosis in humans. *E. granulosus* causes CE and *E. multilocularis* causes AE. In addition, *E. oligarthus* and *E. vogeli* are the cause of neotropical echinococcosis.[8] The disease is food-borne. Transmission occurs when an uninfected intermediate host ingests *Echinococcus* spp. eggs. Afterward, the eggs travel through the gastrointestinal tract to reach the stomach, where they hatch and release oncospheres. Oncospheres penetrate the intestinal wall and travel through the bloodstream to the liver and lungs, where they develop into hydatid cysts that grow and produce protoscoleces and daughter cysts within them. Transmission continues when an uninfected definitive host ingests the infected organs of an intermediate host. Subsequently, the hydatid cysts travel through the gastrointestinal tract to reach the small intestine, where their protoscoleces evaginate, develop into scoleces, attach to the intestinal mucosa, mature into adults, and un-

dergo sexual reproduction to produce eggs that are excreted with the feces. The cycle is completed when an uninfected intermediate host ingests *Echinococcus* spp. eggs. (Figure 3).[9] Intermediate hosts of *E. granulosus* include cattle, camels, goats, horses, swine, sheep, and yaks; dogs are the definitive host. Intermediate hosts of *E. multilocularis* are rodents; canids and foxes are the definitive hors. Humans are regarded as aberrant, atypical, or incidental hosts of both species.[10]

FIGURE 3. *ECHINOCOCCUS GRANULOSUS* LIFE CYCLE

Echinococcosis



Created with BioRender.com

Humans are not properly part of the *E. granulosus* life cycle. However, they can get infected if they ingest the parasite eggs. That is why they are known as "aberrant hosts".

*This is a schematization of the *E. granulosus* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where echinococcosis is endemic, the major risk factors for acquiring the disease include low socioeconomic status, inadequate sanitation, poor hygiene, raising livestock along with domestic animals, feeding dogs home-butchered viscera, consuming undercooked meat and other animal products, and lack of control programs.[1, 11, 12] The disease is more prevalent in women than men and in adults than children.[13]

Clinical Manifestations

The incubation period of the disease can last up to 50 years before cysts grow to the extent that their mass triggers clinical manifestations; this depends on the infecting species and the location, number, and size of cysts (Table 1). Most of them can be found in the liver or lungs, but their presence in other organs, such as the brain, heart, pancreas, kidneys, muscles, and bones, has also been observed.[14] The typical presentation consists of a single cyst in a single organ; however, a single cyst in multiple organs, multiple cysts in a single organ, or multiple cysts in multiple organs have also been reported.[15] The growth rate ranges from 1 to 10 mm per year for hepatic cysts[16] and from 1 to 20 cm per year for alveolar cysts.[17] The loss of cyst integrity due to spontaneous or traumatic rupture may lead to dissemination and secondary implantation, along with allergic reactions that may cause anaphylaxis.[18]

TABLE 1. COMPARISON OF THE LOCALIZATION, CLINICAL MANIFESTATIONS, AND COMPLICATIONS OF CYSTIC AND ALVEOLAR ECHINOCOCCOSIS

Comparison between cystic and alveolar echinococcosis		
Disease	**Cystic echinococcosis**	**Alveolar echinococcosis**
Location	Cysts are more frequently located in the liver than the lungs. Other organs such as the brain, heart, spleen, kidneys, muscles, and bones are rarely affected	Cysts are located in the liver but can rarely disseminate to other organs such as the brain, lungs, and spleen
Clinical manifestations	Anorexia, nausea, vomiting, abdominal pain, and hepatomegaly when the liver is involved. Dyspnea, chest pain, cough, and hemoptysis when the lungs are involved	Anorexia, nausea, vomiting, abdominal pain, and hepatomegaly. Clinical presentation can resemble that of hepatocellular carcinoma
Complications	Cholangitis, biliary obstruction, and Budd-Chiari syndrome when the liver is involved. Pleural effusion, empyema, and pneumothorax when the lungs are involved. Secondary seeding, abscess formation, and anaphylaxis when cysts rupture and spill their content	

Adapted from: Moro PL, Weller PF, Baron EL. Clinical manifestations and diagnosis of echinococcosis. Internet, UpToDate. Wolters Kluwer [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-echinococcosis?search=echinococcosis&source=search_result&selectedTitle=1~55&usage_type=default&display_rank=1#H2.

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of hydatid cysts is required for confirmation; several imaging studies and laboratory tests are available for this purpose:

- **Imaging studies.** They can demonstrate the presence of cysts in multiple organs. Cysts appear as a mass with irregular margins in X-rays.[19] In computerized tomography imaging (CT), cysts look like a mass of irregular margins and heterogenous content with scattered areas of hypodensity (necrosis) and hyperdensity (calcifications).[20] In magnetic resonance imaging (MRI), cysts look like a mass of irregular margins and heterogeneous content with scattered areas of hypo- or iso-intensity on T1-weighted images (necrosis) and hypo-, iso-, or hyper-intensity on T2-weighted images (necrosis).[19, 20] In ultrasonography (US), cysts look like a mass of irregular margins and heterogeneous echogenic patterns with scattered hypoechoic (necrosis) and hyperechoic (calcifications) areas. A "hailstorm pattern" with multiple areas of hyperechoic solid lesions may also be present.[20] US is the recommended imaging study as it is widely available and relatively inexpensive.[13] For diagnosis and treatment purposes, cysts can be classified based on their metabolic activity using the standardized classification of CE developed by the 1995 *World Health Organization Informal Working Group on Echinococcosis* (WHO/IWGE) (Table 2).[21] CT and MRI must be used when significant details of cysts and their extent are required. For diagnosis, treatment, and prognosis purposes, cysts can be classified based on their dissemination stage using the 2006 WHO/IWGE classification of AE (Tables 3 and 4).[22]

TABLE 2. ULTRASOUND CLASSIFICATION OF CYSTIC ECHINOCOCCOSIS INCLUDING LABEL, FEATURES, AND STAGES

WHO/IWGE ultrasound classification of cystic echinococcosis		
Label	**Features**	**Stage**
CE1	Univesicular cyst	Active
CE2	Multivesicular multiseptated cysts with daughter cysts Can be identified by a "honeycomb" or "wheel" appearance	Active

WHO/IWGE ultrasound classification of cystic echinococcosis		
Label	**Features**	**Stage**
CE3a	Cysts with a detached laminated membrane Can be recognized by a "water lily sign"	Transitional
CE3b	Cysts with daughter cysts in a solid matrix	Transitional
CE4	Cysts with a heterogeneous matrix without daughter cysts Degenerating membranes may resemble a "ball of wool"	Inactive
CE5	Cysts with a solid calcified wall	Inactive

Adapted from: WHO Informal Working Group. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Tropica 2003; 85 (2): 253-261.

TABLE 3. CLASSIFICATION OF ALVEOLAR ECHINOCOCCOSIS, INCLUDING PNM AND FEATURES

WHO/IWGE PNM* classification of alveolar echinococcosis	
PNM	**Features**
P	Primary lesion located in the liver
PX	Cannot be assessed
P0	No detectable lesions in the liver
P1	Peripheral lesions without proximal vascular and/or biliary involvement
P2	Central lesions with proximal vascular and/or biliary involvement of one lobe
P3	Central lesions with hilar, vascular, or biliary involvement of both lobes and/or with involvement of two hepatic veins
P4	Any liver lesion with extension along the portal vein, inferior vena cava, or hepatic arteries and the biliary tree
N	Extrahepatic involvement of contiguous organs
N0	Cannot be assessed
N1	Regional involvement of contiguous organs
M	Absence or presence of distant metastasis

WHO/IWGE PNM* classification of alveolar echinococcosis	
PNM	**Features**
MX	Cannot be assessed
M0	No metastasis
M1	Metastasis

*PNM: Parasitic liver lesion, infiltration of Neighboring organs and Metastases.

Adapted from: Kern P, Wen H, Vuitton DA, Gruener B, Shao Y, Delabrousse E, et al. WHO classification of alveolar echinococcosis: principles and application. Parasitol Int 2006; 55: 283-287.

TABLE 4. WHO/IWGE CLASSIFICATION OF ALVEOLAR ECHINOCOCCOSIS, INCLUDING STAGES AND PNM

WHO/IWGE classification of alveolar echinococcosis			
Stage	**P**	**N**	**M**
I	P1	N0	M0
II	P2	N0	M0
IIIa	P3	N0	M0
IIIb	P4P1-P3 P4	N1 N0	M0 M0
IV	P1-P4 P4	N1 N1	M1 M0

Adapted from: Kern P, Wen H, Vuitton DA, Gruener B, Shao Y, Delabrousse E, et al. WHO classification of alveolar echinococcosis: principles and application. Parasitol Int 2006; 55: 283-287.

- **Laboratory tests.** They can demonstrate the presence of *Echinococcus* spp. in biological samples. Serological techniques can detect antigens produced by *Echinococcus* spp. or antibodies produced by the host against it. Techniques should be combined to increase sensitivity and specificity. Screening can be done with an enzyme-linked immunosorbent assay or an indirect hemagglutination assay; then, confirmation should be performed with immunoblot or immunoelectrophoresis. A negative result is insufficient to

issue a negative diagnosis as some patients may not show an immunological response. Instead, cyst samples should be obtained by percutaneous aspiration guided by CT or US, or by biopsy. Direct microscopic examination of smears stained with the Baxby or Ziehl-Neelsen techniques can demonstrate the presence of protoscoleces or scoleces. Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect DNA sequences specific to *E. granulosus* and *E. multilocularis*, but are used mainly for research.[14, 23]

Differential diagnosis should be made to rule out other causes of cysts, such as abscess, hemangioma, hepatocellular carcinoma, and tuberculosis, among others.[14]

Treatment

The approach to manage and treat the disease depends on the localization and number of cysts, organ involvement, and presence of complications:

- **Surgical management.** It is indicated for cysts located in the brain, lungs, or kidneys; when hepatic cysts are superficial and susceptible to traumatic rupture or are large and include multiple daughter cysts; in cases where cysts compromise adjacent organs or structures; or when cysts become secondarily infected. Surgery is contraindicated when cysts are inactive, inaccessible, or very small. Prophylactic treatment with albendazole or mebendazole should be started 4 days prior to surgery and continued for 4 weeks (albendazole) or 12 weeks (mebendazole). Surgery may involve partial cystectomy, closed total pericystectomy, or total open pericystectomy, depending on the skill of the surgeon and the equipment available.[4, 15] If the cyst content is spilled, anaphylactic treatment may be necessary. Relapse rates are highly variable and may occur over the course of months to years after the initial procedure.[18, 24]
- **Pharmacological treatment.** It is indicated in inoperable cases of primary CE and AE; when two or more cysts are present in two or more organs; or in case of secondary seeding, peritoneal involvement, or risk of recurrence. Pharmacological treatment is contraindicated when there is the risk of cystic rupture and during early pregnancy. The first-line treatment is al-

bendazole (10–15 mg/kg orally, divided into two doses per day for at least 3 months). The second-line treatment is mebendazole (40–50 mg/kg orally, divided into three doses per day for at least 3 months).[4, 15]

- **Puncture, aspiration, injection, and re-aspiration (PAIR).** It is indicated in inoperable cases of primary CE and AE; when multiple cysts are present in the liver, spleen, abdominal cavity, kidneys, or bones; in case of failure of pharmacological treatment; and in case of post-surgery relapse. PAIR is contraindicated when cysts are located in the lungs; when they fall in the CE2, CE3b, CE4, or CE5 categories of the WHO/IWGE US classification; and in case of biliary fistula because of protoscolices.[4, 15] Prophylactic treatment with albendazole or mebendazole should be started 4 days prior to PAIR and continued for 4 weeks (albendazole) or 12 weeks (mebendazole). The technique includes a percutaneous puncture of the cysts guided by US, aspiration of the fluid, injection of a protoscolices agent (20% sodium chloride or 95% ethanol), and re-aspiration. If the cyst content is spilled, anaphylactic treatment may be necessary.[18, 21]
- **Observation without treatment.** It is indicated for cysts that fall in the CE4 or CE5 categories of the WHO/IWGE US classification because they remain inactive. However, close monitoring and long-term follow-up of these cases is needed.[4, 15]

Since any of the previous methods require a controlled setting, adequate facilities, advanced skilled practitioners, and proper equipment, any suspected or diagnosed patients should be referred to specialists. Furthermore, regardless of the treatment administered, patients should be monitored every 6 months for the first 2 years and every year thereafter, depending on the clinical setting.[25]

Prevention

No vaccine is currently available to prevent echinococcosis. The main preventive strategies include regular deworming of dogs and domestic carnivores that may come in contact with wild rodents and improvement of hygiene practices while slaughtering livestock.[1]

Conclusions

Echinococcosis is a highly complex zoonotic disease that affects millions of people worldwide. The incubation period is highly variable, and clinical manifestations only appear when complications have arisen. Diagnosis requires a combination of methods and techniques that are not readily available in remote communities. Prompt referral to adequate healthcare facilities is necessary for optimal management. Treatment depends on the localization, number, and size of cysts, organ involvement, and complications. Most patients undergo extensive surgery or prolonged drug therapy with no guarantee of clearing the infection. New drugs with improved efficacy and safety profiles are needed to achieve treatment success. An integrated healthcare approach is more necessary than ever.

References

1. World Health Organization. Echinococcosis. [Internet]. Ginebra, Switzerland; WHO: [Updated: March 2020; Reviewed: January 2021]. Available at: http://www.who.int/mediacentre/factsheets/fs377/en/
2. Eckert J, Thompson RCA. Historical Aspects of Echinococcosis. Advances in Parasitol 2017; 95: 1-64.
3. Yang S, Zhao Y, McManus DP, Yang Y. Current Research Advance on Echinococcosis. In: Inceboz T. Echinococcosis. 1st edition. London; IntechOpen: 2017.
4. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop 2010; 114: 1-16.
5. Rodríguez-Morales AJ, Calvo-Betancourt LS, Alarcón-Olave C, Bolívar-Mejía A. Echinococcosis in Colombia - A Neglected Zoonosis? In: Rodríguez-Morales AJ. Current Topics in Echinococcosis. 1st edition. London; IntechOpen: 2015.
6. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.
7. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
8. Álvarez-Rojas CA, Romig T, Lightowlers MW. *Echinococcus granulosus* sensu lato genotypes infecting humans-review of current knowledge. Int J Parasitol 2014; 44: 9-18.

9. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Parasites of Public Health Concern. Echinococcosis. Parasite Biology. Internet. U.S. Department of Health & Human Services. [Updated: July 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/dpdx/echinococcosis/index.html

10. Romig T, Deplazes P, Jenkins D, Giraudoux P, Massolo A, Craig PS, et al. Ecology and Life Cycle Patterns of Echinococcus Species. Advances Parasitol 2017; 95: 213-314.

11. Al-Ani AM. Pulmonary Echinococcosis. Ann Clin Pathol 2016; 4 (1): 1062.

12. Al-Ani AM, Khan FY, Elzouki AN, Hajri MA, Ibrahim W. Epidemiology of hydatid disease in Qatar: a hospital-based study from 2000 to 2013. Asian Pac J Trop Med 2014; 7: 8587.

13. Vahedi A, Vahedi L. Demographics of Patients with Surgical and Nonsurgical Echinococcosis in East Azerbaijan from 2001 to 2012. Pak J Biol Sci 2012; 14 (4): 186-191.

14. Moro PL, Weller PF, Baron EL. Clinical manifestations and diagnosis of echinococcosis. Internet, UpToDate. Wolters Kluwer [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-echinococcosis?search=echinococcosis&source=search_result&selectedTitle=1~55&usage_type=default&display_rank=1#H2

15. Moro PL, Schantz PM. Echinococcosis: a review. Int J Infect Dis 2009; 13: 125-133.

16. Demircan O, Baymus M, Seydaoglu G, Akinoglu A, Sakman G. Occult cystobiliary communication presenting as postoperative biliary leakage after hydatid liver surgery: are there significant preoperative clinical predictors? Can J Surg 2006; 49: 177-184.

17. Ammann RW, Eckert J. Cestodes. Echinococcus. Gastroenterol Clin North Am 1996; 25: 655-689.

18. Morar R, Feldman C. Pulmonary echinococcosis. Eur Respir J 2003; 21: 1069-1077.

19. Bulakci M, Gülbiz-Kartal M, Yilmaz S, Yilmaz E, Yilmaz R, Sahin Murat-Asik, et al. Multimodality imaging in diagnosis and management of alveolar echinococcosis: an update. Diagn Interv Radiol 2016; 22 (3): 247-256.

20. Liu W, Delabrousse E, Blagosklonov O, Wang J, Zeng H, Jiang Y, et al. Innovation in hepatic alveolar echinococcosis imaging: best use of old tools, and necessary evaluation of new ones. Parasite 2014; 21: 74.

21. WHO Informal Working Group. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Tropica 2003; 85 (2): 253-261.

22. Kern P, Wen H, Vuitton DA, Gruener B, Shao Y, Delabrousse E, et al. WHO classification of alveolar echinococcosis: principles and application. Parasitol Int 2006; 55: 283-287.

23. Eckert J, Gemmell MA, Meslin F-X, Pawłowski ZS (ed). 2001. WHO/ OIE manual on echinococcosis in humans and animals: a public health problem of global concern. World Organization for Animal Health (Office International des Epizooties), Paris, France, and the World Health Organization, Geneva, Switzerland.

24. Chautems R, Bühler LH, Gold B, Giostra E, Poletti P, Chilcott M, et al. Surgical management, and long-term outcome of complicated liver hydatid cysts caused by *Echinococcus granulosus*. Surgery 2005; 137: 312-316.

25. Bhutani N, Kajal P. Hepatic echinococcosis: A review. Ann Med Surg (Lond) 2018; 36: 99-105.

Chapter 7. Food-Borne Trematodiases

Authors

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Food-borne trematodiases are a group of parasitic diseases that include clonorchiasis, fascioliasis, opisthorchiasis, and paragonimiasis. They occur mainly in South America and East Asia, imposing a substantial burden on fragile healthcare systems. Transmission occurs when an uninfected individual ingests fish, plants, or crustaceans contaminated with parasite eggs. The incubation period is variable. Clinical manifestations depend on the parasite load and the stage of the disease, but all of them can potentially cause life-threatening complications. Diagnosis requires considering the epidemiological background and clinical manifestations, but confirmation through direct microscopic examination is necessary. Molecular methods can help with species identification, and serological methods are used to assess antibodies against the etiological agent, but they cannot distinguish between past and current infections. Pharmacological treatment with anthelmintic drugs is widely available and highly effective, but recurrence is common. No prophylactic or therapeutic vaccines are currently available for any of these diseases.

CLONORCHIASIS

Introduction

Clonorchiasis, also known as liver fluke disease, is a parasitic food-borne disease caused by *Clonorchis sinensis* that primarily affects the hepatobiliary tract. It is endemic to Asia, where it affects people who eat fish contaminated with the parasite eggs. Infected individuals may remain asymptomatic or develop mild to moderate gastrointestinal manifestations, depending on the parasite load. Consequently, these persons do not seek medical attention until the hepatobiliary disease has reached an advanced stage, limiting their everyday activities and threatening their life.[1]

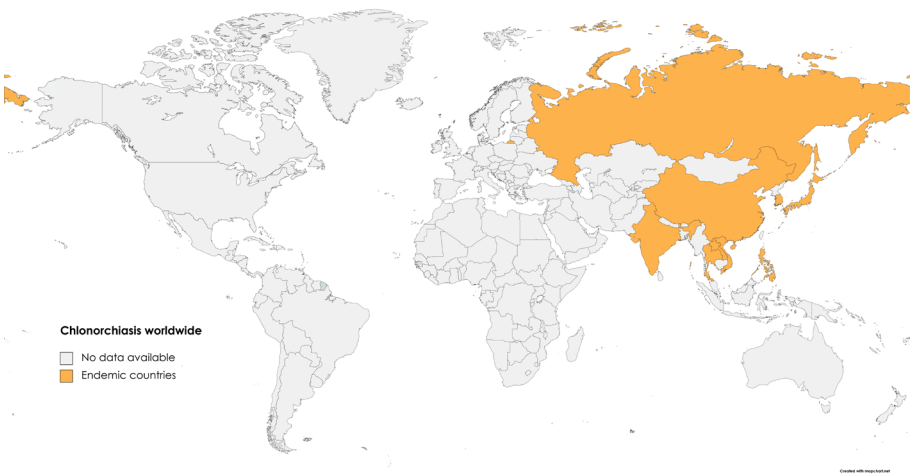
Historical Background

The earliest evidence of the disease can be traced back to Chinese mummies (5th to 3rd century BC), in which *C. sinensis* eggs were found. Since then, several archeologists and paleontologists have also identified *C. sinensis* eggs in personal hygiene sticks used after defecation in endemic and non-endemic countries (1st century BC to 1st century AD).[2] The etiological agent and intermediate hosts were identified several centuries later. James MacConnell found flukes in the bile ducts of a carpenter while performing his autopsy in 1874; Harujiro Kobayashi identified freshwater fish as the second intermediate host in 1911; and Masatomo Muto identified freshwater snails as the first intermediate hosts in 1917.[3]

Epidemiology

About 35 million individuals are estimated to be infected, almost 200 million are at risk of acquiring the disease, and nearly 6,000 deaths are caused by clonorchiasis each year worldwide.[4] Clonorchiasis is endemic to Asian countries, including China, Hong Kong, Japan, Lao People's Democratic Republic, Philippines, Republic of Korea, Russia, Taiwan, and Vietnam (Figure 1).

FIGURE 1. CLONORCHIASIS ENDEMIC COUNTRIES



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Adapted from: Lu XT, Gu QY, Limpanont Y, Song LG, Wu ZD, Okanurak K, Lv ZY. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. Infect Dis Poverty 2018; 7 (1): 28.

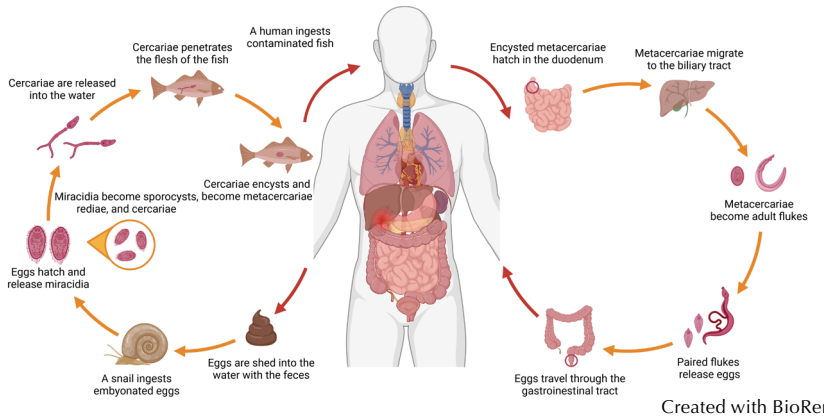
However, it has also been reported in non-endemic countries, such as the United States[5], due to exports of contaminated food and migration of infected individuals. In 2010, Tang Ze-Li et al. estimated that clonorchiasis accounted for 0.275 million disability-adjusted life years.[6]

Etiology

Clonorchiasis is caused by a parasite named *Clonorchis sinensis,* which belongs to the phylum Platyhelminthes, class Trematoda, subclass Digenea, order Opisthorchiida, suborder Opisthorchiata, superfamily Opisthorchioidea, family *Opisthorchiidae*, and genus *Chlonorchis*.[7] The disease is food-borne. Transmission occurs when a freshwater snail ingests *C. sinensis* eggs. Upon reaching the gastrointestinal tract, they hatch to release miracidia, which penetrates the intestinal wall. The miracidia then differentiate into sporocysts, rediae, and cercariae, which are shed into the water, where they swim and penetrate the scales and flesh of freshwater fish. Once the cercariae reach the muscles, they become encysted and mature into metacercariae. Transmission to humans occurs when an uninfected individual ingests pickled, salted, smoked, or undercooked fish containing encysted metacercariae. Upon reaching the duodenum, the metacercariae emerge from the cysts and migrate to the biliary tract, where they mature into adult flukes, undergo sexual reproduction, and produce fertilized eggs, which are excreted with feces into water. The cycle is completed when a freshwater snail ingests *C. sinensis* eggs (Figure 2).[8]

FIGURE 2. *CLONORCHIS* SINENSIS LIFE CYCLE

Clonorchiasis



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*This is a schematization of the *C. sinensis* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Several freshwater snails, mainly in the genera *Bithynia* and *Parafossarulus*, and freshwater fish, mostly in the family *Cyprinidae*, have been identified as intermediate hosts. Several mammalian species, mainly *Homo sapiens*, have been recognized as reservoirs. Other reservoirs include cats, buffaloes, dogs, foxes, pigs, rats, and weasels.[9]

Risk Factors

In countries where clonorchiasis is endemic, particularly in areas adjacent to water bodies, the main risk factors for acquiring the disease include lack of sanitation and open defecation, as well as consuming pickled, salted, smoked, or undercooked fish.[10] Clonorchiasis affects men more frequently than women, but prevalence is apparently unrelated to age.[11]

Clinical Manifestations

The incubation period of the disease is highly variable; it can range from weeks to months or even years. Afterward, some infected individuals can remain asymptomatic when the parasite load is low or may become symptomatic when the parasite load is high. Clinically, the disease develops through two distinct stages:

- **Acute stage.** It is characterized by acute inflammation of the biliary tract. Fever, malaise, fatigue, anorexia, nausea, vomiting, abdominal distention, abdominal discomfort, abdominal pain, and diarrhea can be experienced.[9] Portal hypertension, hematemesis, ascites, hepatomegaly, splenomegaly, and melena have also been reported.[12]
- **Chronic stage.** It is characterized by chronic inflammation of the biliary tract leading to fibrosis and necrosis of the liver parenchyma. Clinical manifestations of the acute stage can also be experienced. Malnutrition, hepatitis, hepatic abscesses, pancreatitis, and biliary complications such as cholelithiasis, cholecystitis, pyogenic cholangitis, cholangiohepatitis, and cholangiocarcinoma have also been reported.[12]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *C. sinensis* is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of stool samples or biliary or duodenal aspirates can demonstrate the presence of *C. sinensis* eggs.[13] Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low. Quantitative methods such as the Kato-Katz technique (KKT) may be used to estimate the infection intensity.[13, 14] Direct microscopic examination combined with FECT or KKT is the preferred approach for detection, but it is not useful in the acute stage of the disease, and *C. sinensis* eggs are indistinguishable from those of *Opisthorchis spp.* at any time. Epidemiological background or identification of adult flukes is required for elucidation.[4] Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect *C. sinensis*-specific DNA sequences, and can be used to diagnose the disease during the acute stage or to differentiate the infecting species. However, they are expensive and not widely available.[2] Serological techniques can detect antigens produced by *C. sinensis* or antibodies produced by the host against it. The enzyme-linked immunosorbent assay and immunoblot have been used with varying success, but there is cross-reactivity with antibodies produced against other parasites, and these methods cannot distinguish between previous and current infections. Besides, most of these techniques are still in the experimental stage.[4, 15]

Supplementary examination with X-rays, computer tomography, magnetic resonance imaging, ultrasonography, or endoscopic retrograde cholangiopancreatography should be carried out to detect structural abnormalities, evaluate the extent of damage, and monitor disease progression.[1, 2]

Differential diagnosis should always be made to rule out other causes of hepatobiliary inflammation and obstruction such as ascariasis, cholangiocarcinoma, choledocholithiasis, cholecystitis, fascioliasis, hepatitis, opisthorchiasis, primary sclerosing cholangitis, schistosomiasis, and strongyloidiasis.[4]

Treatment

Treatment depends on the disease progression. Patients may require a combination of anthelmintic treatment and surgical interventions:

- **Anthelmintic treatment.** Praziquantel (25 mg/kg orally three times a day for 2 to 3 days) is the anthelmintic drug of choice to treat all the disease stages;[1] its cure rate is of almost 100%.[4] Albendazole (10 mg/kg orally once a day for 7 days) can be used in cases where praziquantel is contraindicated or not available;[16] its cure rate is over 90%.[15]
- **Surgical interventions.** Surgery is indicated when patients experience chronic complications of the disease. Adequate assessment by an experienced surgeon should be performed when available.[4, 15]

Prevention

No vaccine to prevent clonorchiasis is currently available. The main preventive strategies include improving sanitation, implementing snail control strategies, consuming well-cooked freshwater fish, and administering preventive drug therapy (praziquantel 40 mg/kg orally in a single dose) in high-risk populations.[1, 5]

Conclusion

Clonorchiasis is a parasitic food-borne disease endemic to Asian countries, but migration has led to the spread of infected individuals worldwide. The lack of symptomatology during the acute stage of the disease deters patients from seeking medical attention. Chronic complications are related to organ damage produced by the migration of flukes. Some individuals may develop cholangiocarcinoma over time. Diagnosis can be performed with simple laboratory tests, but supplementary examination with more advanced studies is strongly recommended to assess subclinical alterations or underlying complications in the hepatobiliary tract. Anthelmintic therapy cures almost 100% of the patients, and secondary effects are well-tolerated. However, reinfections occur frequently, warranting close follow-up. Investing time in disease awareness contributes to prevent further cases and mitigate further consequences.

References

1. World Health Organization. Foodborne trematode infections - Clonorchiasis. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.who.int/foodborne_trematode_infections/clonorchiasis/en/
2. Na BK, Pak JH, Hong SJ. Clonorchis sinensis and clonorchiasis. Acta Trop 2020; 203: 105309.
3. Yeh HY, Mitchel PD. Ancient Human Parasites in Ethnic Chinese Populations. Korean J Parasitol 2016; 54 (5): 1-8.
4. Locke V, Richardson MS. Clonorchis Sinensis. [Internet]. StatPearls Publishing. [Updated: December 2020; Revised: January 2021]. Available at: https://www.statpearls.com/ArticleLibrary/viewarticle/19619
5. Lu XT, Gu QY, Limpanont Y, Song LG, Wu ZD, Okanurak K, Lv ZY. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. Infect Dis Poverty 2018; 7 (1): 28.
6. Tang ZL, Huang Y, Yu XB. Current status and perspectives of Clonorchis sinensis and clonorchiasis: epidemiology, pathogenesis, omics, prevention and control. Infect Dis Poverty 2016; 5 (1): 71.
7. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
8. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Parasites of Public Health Concern - Clonorchiasis. [Internet]. U.S. Department of Health & Human Services. [Updated: June 2019; Revised: January 2021]. Available at: https://www.cdc.gov/dpdx/clonorchiasis/index.html
9. Choi BI, Han JK, Hong ST, Lee KH. Clonorchiasis and cholangiocarcinoma: etiologic relationship and imaging diagnosis. Clin Microbiol Rev 2004; 17 (3): 540-552.
10. Centers for Disease Control and Prevention. Parasites - Clonorchis. Epidemiology & Risk Factors. [Internet]. U.S. Department of Health & Human Services. [Updated: February 2020; Revised: January 2021]. Available at: https://www.cdc.gov/parasites/clonorchis/epi.html
11. June KJ, Cho SH, Lee WJ, Kim C, Park KS. Prevalence and Risk Factors of Clonorchiasis among the Populations Served by Primary Healthcare Posts along Five Major Rivers in South Korea. Osong Public Health Res Perspect 2013; 4 (1): 21-26.
12. Pal M. Clonorchiasis: An emerging foodborne disease of public health concern. J Nutrition and Food Processing 2020; 3 (1): 1-10.
13. Asare KK, Boampong JN, Ameyaw EO, Thomford AK, Afoakwah R, Kwayke-Nuako G, et al. Microscopic identification of possible Clonorchis/Opisthorchis infection in

two Ghanaian women with undiagnosed abdominal discomfort: two case reports. J Med Case Rep 2014; 8: 369.

14. World Health Organization. Bench aids for the diagnosis of intestinal parasites. 1st edition. Geneva; World Health Organization: 1994.

15. Leder K, Weller P, Ryan E, Baron EL. Liver flukes: Clonorchis, Opisthorchis, and Metorchis. Internet. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/liver-flukes-clonorchis-opisthorchis-and-metorchis?search=chlonorchis&source=search_result&selectedTitle=1~19&usage_type=default&display_rank=1

16. Centers for Disease Control and Prevention. Parasites - Clonorchiasis. Resources for Health Professionals. [Internet]. U.S. Department of Health & Human Services. [Updated: May 2020; Revised: January 2021]. Available at: https://www.cdc.gov/parasites/clonorchis/health_professionals/index.html

FASCIOLIASIS

Introduction

Fascioliasis, also known as hepatic distomatosis, is a parasitic food-borne disease caused by *Fasciola* spp. that primarily affects the hepatobiliary tract. It is widely distributed and mostly infects persons who eat vegetables contaminated with the parasite eggs. Although fascioliasis is more common in animals than humans, case reports in humans have increased over the past decades, especially in temperate climates and where herding communities prevail.[1]

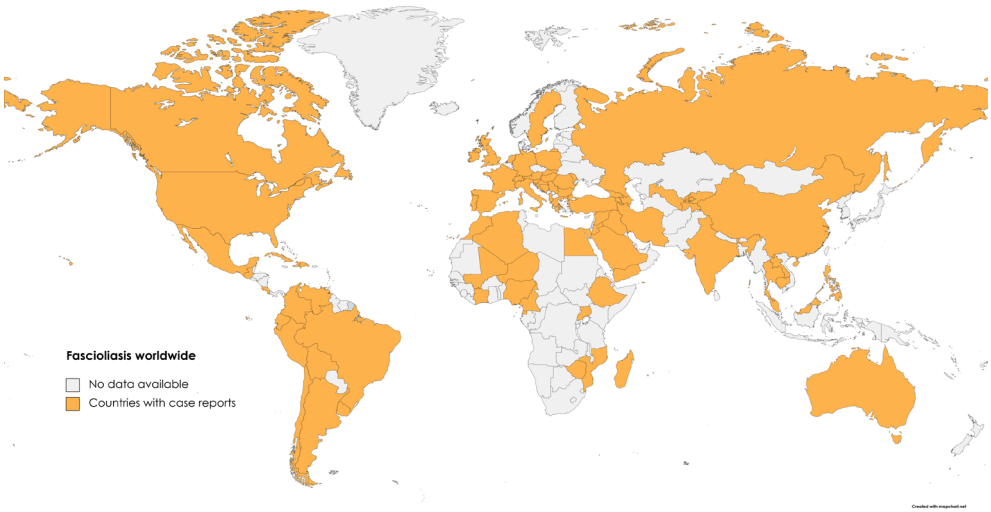
Historical Background

The earliest report of the disease can be traced back to 1379 when Jehan de Brie described the etiological agent. Later, Francesco Redi accurately illustrated it in a 1686 paper, Jan Swammerdam described the larval stages in 1737, and Carl Linnaeus formally classified it in the genus *Fasciola* in 1758. Subsequently, Rudolph Leukart and Algeron Thomas described the transmission route to the intermediate host in 1883, and Adolph Lutz described the transmission mechanism to the definitive host in 1892.[2]

Epidemiology

Some 50 million people are estimated to be infected, and almost 180 million are at risk of acquiring the disease worldwide.[3] Fascioliasis occurs across Africa, America, Asia, Europe, and Oceania, being endemic to more than 70 countries. Bolivia, China, Cuba, Egypt, Ethiopia, Iran, Iraq, Peru, Saudi Arabia, Spain, Syria, and Vietnam are the countries with most cases reported (Figure 1).[3, 4] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH FASCIOLIASIS CASE REPORTS



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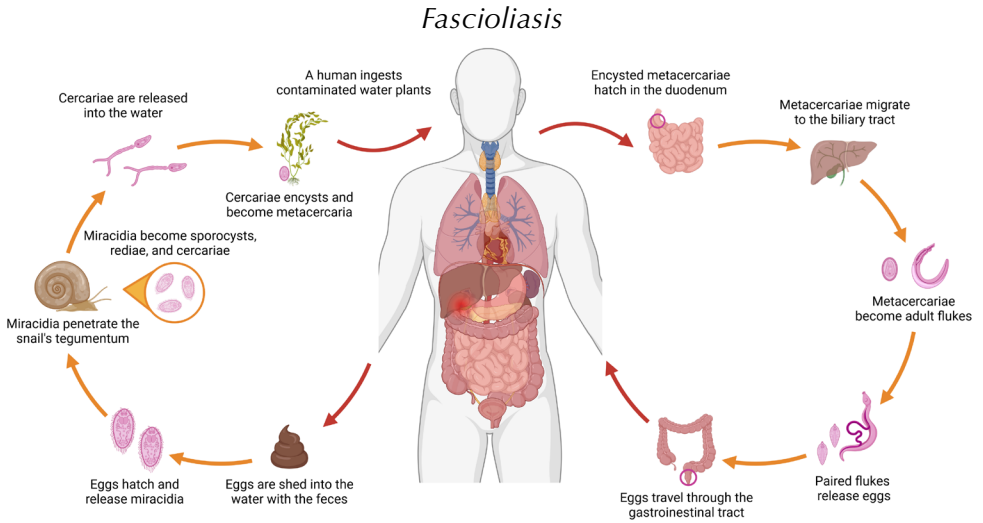
Adapted from: Ebenezer T, Taiye-Lawal O. Fascioliasis: A Foodborne Disease of Veterinary and Zoonotic Importance. In: Bacha U. Rural Health. 1st edition. London, United Kingdom; IntechOpen: 2020.

Etiology

Fascioliasis is caused by the parasites *Fasciola gigantica* and *Fasciola hepatica,* which belong to the phylum Platyhelminthes, class Trematoda, subclass Digenea, order Plagiorchiida, suborder Echinostomata, superfamily *Echinostomatoidea*, family *Fasciolidae*, and genus *Fasciola*.[5] The disease is food-borne. Transmission occurs when immature *Fasciola* spp. eggs are excreted with feces into water. After a couple of weeks, they hatch and release miracidia, which

swim and penetrate the tegmentum of freshwater snails. Upon reaching the gastrointestinal tract, they penetrate the intestinal wall. The miracidia then differentiate into sporocysts, rediae, and cercariae, which are shed into the water, where they become encysted and differentiate into metacercariae on riparian vegetation. Transmission to humans occurs when an uninfected individual ingests aquatic plants or raw vegetables carrying encysted metacercariae. Upon reaching the duodenum, the metacercariae emerge from the cysts and migrate to the biliary tract, where they mature into adult flukes, undergo sexual reproduction, and produce immature eggs. The cycle is completed when immature *Fasciola* spp. eggs are excreted with feces into water (Figure 2).[6] Several freshwater snails, mainly in the genera *Galba, Fossaria, Lymnaea, Pseudosuccinea,* and *Radix*, are currently recognized as intermediate hosts.[6, 7] Several mammalian species such as buffaloes, cattle, deer, goats, equines, sheep, and swine, are recognized as definitive hosts. Buffalo is the primary definitive host for *F. gigantica*, and cattle for *F. hepatica*.[2, 6]

FIGURE 2. *FASCIOLA* SPP. LIFE CYCLE



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*This is a schematization of the *Fasciola* spp. life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where fascioliasis is endemic, particularly in areas adjacent to water bodies, the main risk factors for acquiring the disease include raising livestock and consuming contaminated aquatic plants or raw vegetables.[8] Fascioliasis is more prevalent in women than men and in children than adults.[4, 9]

Clinical Manifestations

The incubation period of the disease ranges from weeks to months. Afterward, some infected individuals can remain asymptomatic when the parasite load is low or may become symptomatic when the parasite load is high. Clinically, the disease develops through two distinct stages:

- **Acute stage.** The onset starts between 6 and 12 weeks after the initial infection.[10] In this stage, metacercariae penetrate the liver and migrate towards bile ducts, producing inflammation and internal bleeding.[11] Fever, malaise, fatigue, anorexia, nausea, vomiting, abdominal pain, hepatomegaly, pruritus, and urticaria may be experienced. Anemia and eosinophilia may be observed in paraclinical examination. Extrahepatic manifestations are uncommon, but Loeffler-like syndrome, cardiac conduction abnormalities, and pericarditis have been reported.[10, 11]
- **Chronic stage.** The onset starts around 6 months after the initial infection.[10] In this stage, the flukes invade and reproduce in the biliary tract, causing inflammation and fibrosis.[11] Clinical manifestations of the acute stage may also be experienced. Anemia is frequent, but eosinophilia may or may not be evident in paraclinical examination. Cholestasis, cholangitis, cholelithiasis, cholecystitis, pancreatitis, and secondary infections may develop. Extrahepatic fascioliasis involving the brain, eyes, heart, genitourinary tract, muscles, and subcutaneous tissues has also been reported.[10, 11]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Fasciola* spp. is required for confirma-

tion and several laboratory tests are available for this purpose. Direct microscopic examination of stool or biliary or duodenal aspirates can demonstrate the presence of *Fasciola* spp. eggs.[12] Concentration methods such as the formalin-ether concentration technique (FECT) and simple-ether concentration technique (SECT) may be necessary when the parasite load is low. Quantitative methods such as the Kato-Katz technique (KKT) can be used to estimate the infection intensity.[12, 13] Direct microscopic examination combined with FECT, SECT, or KKT is the preferred approach for detection, but this is not useful during the acute stage of the disease or when there is extrahepatic location. Furthermore, the eggs of *Fasciola* spp. are indistinguishable from those of *Clonorchis sinensis* at any time, and the eggs of *F. gigantica, F. hepatica,* and *Fasciolopsis buski* are difficult to differentiate.[14] Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect *Fasciola* spp.-specific DNA sequences, but they are novel tests still not commercially available. Serological techniques can detect antigens produced by *Fasciola* spp. or antibodies produced by the host against it. Counterimmunoelectrophoresis, enzyme-linked immunosorbent assay, indirect hemagglutination assay, and indirect immunofluorescence assay have been used with varying success. Although these assays have shown good sensitivity, the specificity is suboptimal;[14, 15] there is cross-reactivity with antibodies produced against other parasites, and they cannot distinguish between previous and current infections. However, these assays can be performed for diagnosis during the subacute stage of the disease and can evaluate the parasite load based on its correlation with antigen levels.[11, 15]

Supplementary examination with X-rays, computer tomography, magnetic resonance imaging, ultrasonography, cholangiography, or endoscopic retrograde cholangiopancreatography should be performed to detect structural abnormalities, evaluate the extent of the damage, and monitor disease progression.[16, 17]

Differential diagnosis should always be made to rule out other causes of hepatobiliary disease such as amebiasis, ascariasis, brucellosis, clonorchiasis, cholangiocarcinoma, cholangitis, choledocholithiasis, cholecystitis, cholelithiasis, echinococcosis, hepatitis, opisthorchiasis, pancreatitis, primary and secondary hepatobiliary malignancies, pyogenic abscesses, schistosomiasis, strongyloidiasis, and toxocariasis.[11, 18]

Treatment

Treatment depends on the disease progression. Patients may require a combination of anthelmintic treatment and surgical interventions:

- **Anthelmintic treatment.** Triclabendazole (10 mg/kg orally in a single dose) is the anthelmintic drug recommended to treat the disease at all stages;[19] its cure rate is over 90%.[10] If the first regimen of triclabendazole fails, a second dosage regimen (20 mg/kg orally, divided into two doses administered 12 to 24 hours apart) must be administered.[19] Other anthelmintic drugs such as nitazoxanide or praziquantel have been administered with varying success, so they cannot be endorsed as an alternative treatment until further research is performed.[10]
- **Surgical interventions.** These are indicated when patients experience chronic complications of the disease. Adequate assessment by an experienced surgeon should be performed when available.[11, 15]

Prevention

No vaccine to prevent fascioliasis is currently available. The main preventive strategies include improving sanitation, cultivating vegetables with clean water, cooking vegetables before consumption, implementing veterinary public-health strategies, and administering preventive drug therapy (triclabendazole 10 mg/kg orally in a single dose) in high-risk populations.[1, 4]

Conclusion

Fascioliasis is a parasitic food-borne disease distributed worldwide. The disease develops in stages, with the liver affected during the acute stage and the biliary tract in the chronic stage. Clinical manifestations are directly correlated with the parasite load. Most infected individuals develop mild clinical manifestations, but others may experience chronic complications that increase morbidity and mortality. Diagnosis requires the combination of epidemiological background, clinical manifestations, and laboratory confirmation. Anthelmintic treatment cures over 90% of patients, but recurrence is common. Surgery may be needed to man-

age chronic complications. Prevention through adequate sanitation is key for controlling this disease.

References

1. World Health Organization. Foodborne trematode infections - Fascioliasis. [Internet]. World Health Organization [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.who.int/foodborne_trematode_infections/fascioliasis/en/
2. Gupta SC. Fasciolosis in man and animals: An overview retrospecto to historical perspective. XXIV National Congress of Veterinary Parasitology & National Symposium on "Towards Food Security through Sustainable Animal Production and Integrated Parasite Management" 2014; 1: 164-174.
3. Nyindo M, Lukambagire AH. Fascioliasis: An Ongoing Zoonotic Trematode Infection. BioMed Research Int 2015; 2015 (1): 786195.
4. Ebenezer T, Taiye-Lawal O. Fascioliasis: A Foodborne Disease of Veterinary and Zoonotic Importance. In: Bacha U. Rural Health. 1st edition. London, United Kingdom; IntechOpen: 2020.
5. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
6. Centers for Disease Control and Prevention. Parasites - Fascioliasis. Biology. [Internet]. U.S. Department of Health & Human Services. [Updated: December 2018; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/fasciola/biology.html
7. Caravedo MA, Cabada MM. Human Fascioliasis: Current Epidemiological Status and Strategies for Diagnosis, Treatment, and Control. Research Reports Trop Med 2020; 11: 149-158.
8. Centers for Disease Control and Prevention. Parasites - Fascioliasis. Epidemiology & Risk Factors. [Internet]. U.S. Department of Health & Human Services. [Updated: December 2018; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/fasciola/epi.html
9. Ai L, Chen JX, Cai YC, Lu Y, Chu YH, Chen SH, Li H, Song P, Chen MX, Zhou XN. Prevalence and risk factors of Fascioliasis in China. Acta Trop 2019; 196: 180-188.
10. Leder K, Weller P, Ryan E, Baron EL. Liver flukes: Fascioliasis. Internet. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/liver-flukes-fascioliasis?search=fascioliasis&source=search_result&selectedTitle=1~21&usage_type=default&display_rank=1#H6
11. World Health Organization, Pan American Health Organization. General Information - Fascioliasis. [Internet]. World Health Organization, Pan American Health Or-

ganization. [Updated: 2018; Reviewed: January 2021]. Available at: https://www.paho.org/hq/index.php?option=com_content&view=article&id=5758:2011-general-information-fascioliasis&Itemid=4153&lang=en

12. Mas-Coma S, Bargues MD, Valero MA. Diagnosis of human fascioliasis by stool and blood techniques: update for the present global scenario. Parasitol 2014; 141 (14): 1-29.
13. World Health Organization. Bench aids for the diagnosis of intestinal parasites. 1st edition. Geneva; World Health Organization: 1994.
14. Centers for Disease Control and Prevention. Parasites - Resources for Health Professionals. Fascioliasis. Biology. [Internet]. CDC. [Updated: September 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/fasciola/health_professionals/index.html#dx
15. Good R, Scherbak D. Fascioliasis. Internet. StatPearls. [Updated: May 2020; Reviewed January 2021]. Available at: https://www.statpearls.com/ArticleLibrary/viewarticle/21628
16. Kabaalioglu A, Ceken K, Alimoglu E, Saba R, Cubuk M, Arslan G, Apaydin A. Hepatobiliary fascioliasis: sonographic and CT findings in 87 patients during the initial phase and long-term follow-up. AJR Am J Roentgenol 2007; 189 (4): 824-828.
17. Kaya M, Beştaş R, Cetin S. Clinical presentation and management of Fasciola hepatica infection: single-center experience. World J Gastroenterol 2011; 17 (44): 4899-4904.
18. World Health Organization. Foodborne trematode infections. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/foodborne-trematode-infections

OPISTHORCHIASIS

Introduction

Opisthorchiasis, also known as Siberian liver fluke disease, is a parasitic foodborne disease caused by *Opisthorchis* spp. that primarily affects the hepatobiliary tract. It is endemic to Asia and Europe, where it mainly infects people who eat fish contaminated with the parasite eggs. Opisthorchiasis is a significant public health issue in countries where it is endemic, but case reports in non-endemic countries have increased over the past decades due to migration of infected individuals and exports of raw fish.[1]

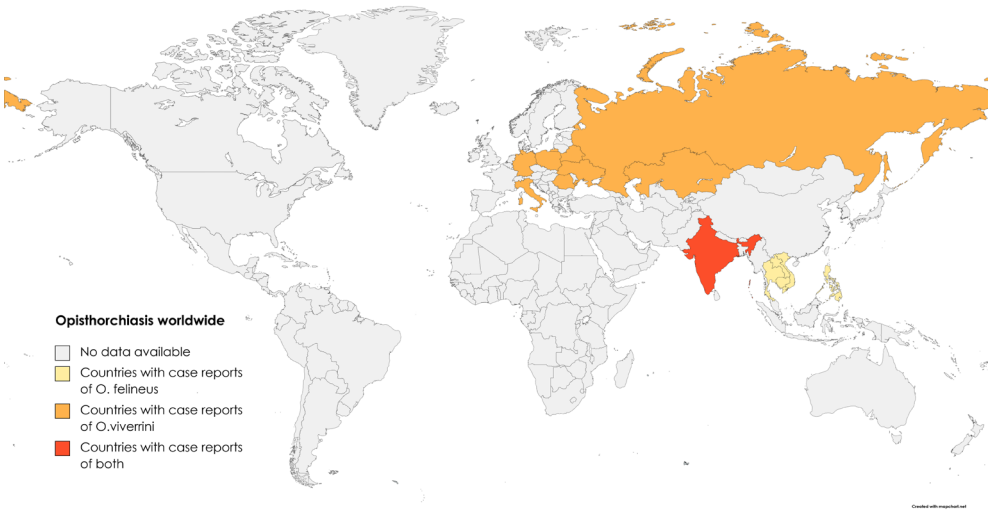
Historical Background

The earliest report of the disease can be traced back to 1884, when Sebastiano Rivolta isolated *Opisthorchis felineus* from a cat and a dog;[2] and to 1886, when Jules Poirier isolated *Opisthorchis viverrini* from the liver of a civet cat.[3] The mechanism of transmission was proposed by Brown in 1893 and confirmed by Askanazy in 1891.[2] The first case report of *O. viverrini* in man was described by Robert Leiper in 1915, when he identified the disease in two prisoners in Chang Mail, Thailand.[4] The first case report of *O. felineus* in humans was described by Prommas in 1927 when he identified the disease in a resident of northeastern Thailand.[5]

Epidemiology

About 50 million people are estimated to be infected, and almost 180 million are at risk of acquiring opisthorchiasis worldwide.[6] Opisthorchiasis is endemic to Asia and Europe: *O. felineus* occurs mainly in Belarus, Germany, Kazakhstan, Poland, Romania, Russia, and Ukraine; *O. viverrini* primarily occurs in Cambodia, Lao People's Democratic Republic, Philippines, Thailand, and Vietnam. Both parasite species occur in India (Figure 1).[7, 8] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH OPISTHORCHIASIS CASE REPORTS

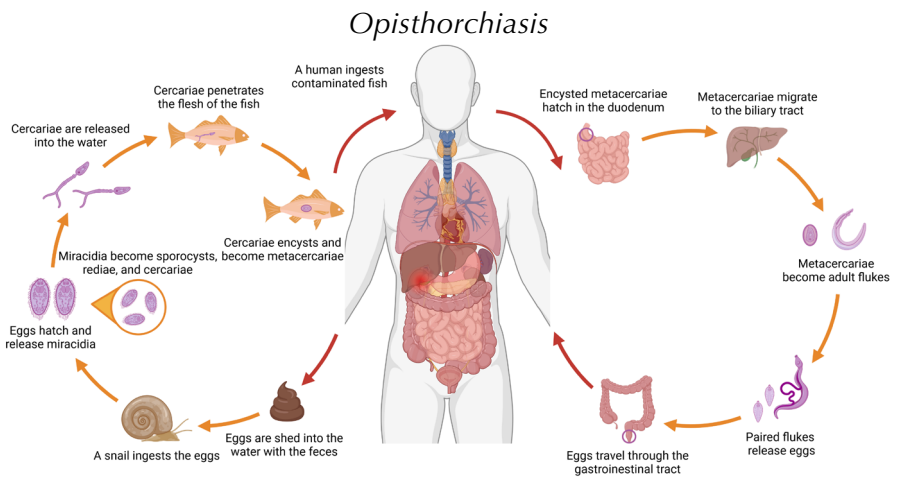


Adapted from: Lu XT, Gu QY, Limpanont Y, Song LG, Wu ZD, Okanurak K, Lv ZY. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. Infect Dis Poverty 2018; 7 (1): 28.

Etiology

Opisthorchiasis is caused by the parasites *Opisthorchis felineus* and *Opisthorchis viverrine,* which belong to the phylum Platyhelminthes, class Trematoda, subclass Digenea, order Opisthorchiida, suborder Opisthorchiata, family *Opisthorchiidae*, and genus *Opisthorchis*.[9] The disease is food-borne. Transmission occurs when a freshwater snail ingests *Opisthorchis* spp. eggs. Upon reaching the gastrointestinal tract, they hatch and release miracidia, which penetrate the intestinal wall. The miracidia then differentiate into sporocysts, rediae, and cercariae, which are released into the water, where they swim and penetrate the scales and skin of freshwater fish. Once the cercariae reach the muscles, they become encysted and mature into metacercariae. Transmission to humans occurs when an uninfected individual ingests pickled, salted, smoked, or undercooked fish carrying encysted metacercariae. Upon reaching the duodenum, the metacercariae emerge from the cysts and migrate to the biliary tract, where they mature into adult flukes, undergo sexual reproduction, and produce fertilized eggs, which are excreted with feces into water. The cycle is completed when a freshwater snail ingests *Opisthorchis* spp. eggs (Figure 2).[7] Several freshwater snails, mainly in the genus *Bithynia*, and freshwater fish, mostly in the genus *Cyprinus*, have been acknowledged as intermediate hosts. Humans have been recognized as the main reservoir for the disease. Other reservoir species include cats, dogs, and pigs, among others.[10]

FIGURE 2. *OPISTHORCHIS* SPP. LIFE CYCLE



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*This is a schematization of the *Opisthorchis* spp. life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where opisthorchiasis is endemic, particularly in areas adjacent to water bodies, the main risk factors for acquiring the disease include lack of sanitation, open defecation, and consuming pickled, salted, smoked, or undercooked fish.[11] Opisthorchiasis is more prevalent in men than women and in persons under 25 years or over 55 years old.[12]

Clinical Manifestations

The incubation period of the disease ranges from 2 to 4 weeks. Afterward, some infected individuals can remain asymptomatic when the parasite load is low or may become symptomatic when the parasite load is high. Clinically, the disease develops through two distinct stages:

- **Acute stage.** The onset of symptoms usually begins between 10 and 30 days after the initial infection.[13] Individuals infected with *O. viverrini* tend to remain asymptomatic, whereas those infected with *O. felineu*s tend to become symptomatic. Infected persons may experience fever, malaise, fatigue, myalgia, arthralgia, anorexia, nausea, vomiting, abdominal discomfort, diarrhea, constipation, pruritus, urticaria, and lymph node enlargement. The Katayama-like syndrome has also been reported. Eosinophilia, along with increased alkaline phosphatase and liver enzymes, can be detected in paraclinical examination. This stage lasts between 4 and 8 weeks.[1, 2]
- **Chronic stage.** This stage usually begins 6 months after the initial infection.[13] The clinical manifestations of the acute stage can be experienced, but malnutrition and weight loss are common. Chronic complications such as hepatitis, cirrhosis, hepatic abscesses, acalculous cholecystitis, suppurative cholangitis, pyogenic cholangitis, and cholangiohepatitis may develop. Individuals infected with *O. viverrini* have an increased risk of cholangiocarcinoma, whereas those infected with *O. felineus* have an increased risk of pancreatitis. This stage lasts from 10 to 20 or more years.[1, 2]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Opisthorchis* spp. is required for confirmation,

and several laboratory tests are available for this purpose. Direct microscopic examination of stool or biliary or duodenal aspirates can demonstrate the presence of *Opisthorchis* spp. eggs.[14] Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low. Quantitative methods such as the Kato-Katz technique (KKT) may be used to evaluate the infection intensity.[15, 16] Direct microscopic examination combined with FECT or KKT is the preferred approach for detection, but this is not useful during the acute stage of the disease. Moreover, the eggs of *Opisthorchis* spp. are indistinguishable from those of *Clonorchis sinensis*. Epidemiological background or identification of adult flukes is required for elucidation.[1] Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect *Opisthorchis* spp.-specific DNA sequences and are useful to diagnose the disease during the acute stage or to differentiate the infecting species. However, these methods are used mainly for research. Serological techniques can detect antigens produced by *Opisthorchis* spp. or antibodies produced by the host against it. The enzyme-linked immunosorbent assay, indirect hemagglutination assay, and indirect immunofluorescence assay have been used with varying success as there is cross-reactivity with the antibodies produced against other parasites. Besides, these assays cannot distinguish between previous and current infections, and most of them are still in the experimental stage.[17, 18]

Supplementary examination with X-rays, computer tomography, magnetic resonance imaging, ultrasonography, or endoscopic retrograde cholangiopancreatography should be performed to detect structural alterations, evaluate the extent of the infection, and monitor disease progression.[13, 19]

Differential diagnosis should always be conducted to rule out other causes of hepatobiliary inflammation and obstruction, such as ascariasis, clonorchiasis, cholangiocarcinoma, choledocholithiasis, cholecystitis, fascioliasis, hepatitis, primary sclerosing cholangitis, schistosomiasis, and strongyloidiasis.[13, 19]

Treatment

Treatment depends on the disease progression. Patients may require a combination of anthelmintic treatment and surgical interventions:

- **Anthelmintic treatment.** Praziquantel (25 mg/kg orally three times a day for 2 to 3 days) is the anthelmintic drug recommended to treat the disease at

any stage;[20] its cure rate is over 90%.[19] Albendazole (10 mg/kg orally once a day for 7 days) can be used as an alternative treatment when praziquantel is contraindicated or not available;[15] its cure rate is over 60%.[21]

- **Surgical interventions.** Surgery is indicated when patients experience chronic complications of the disease. Adequate assessment by an experienced surgeon should be performed when available.[2, 10]

Prevention

No vaccine to prevent opisthorchiasis is currently available. The main preventive strategies include improving sanitation, implementing snail control strategies, consuming well-cooked freshwater fish, and administering preventive drug therapy (praziquantel 40 mg/kg orally in a single dose) in high-risk populations.[8, 20]

Conclusion

Opisthorchiasis is a parasitic food-borne disease endemic to Asian and European countries. The clinical manifestations depend on the infecting species, the parasite load, and the stage of the disease. Individuals infected with *O. viverrini* usually remain asymptomatic during the acute stage but have an increased risk of developing cholangiocarcinoma during the chronic stage. Individuals infected with *O. felineus* usually become symptomatic during the acute stage and have an increased risk of developing pancreatitis during the chronic stage. Diagnosis requires the combination of epidemiological background, clinical manifestations, laboratory tests, and imaging studies for confirmation. New diagnostic tools that are affordable, widely available, and reliable are required to detect new cases. Anthelmintic treatment cures over 90% of patients, but recurrence is common, and close follow-up is needed. Strengthening prevention campaigns may reduce the burden of the disease.

References

1. Yossepowitch O, Gotesman T, Assous M, Marva E, Zimlichman R, Dan M. Opisthorchiasis from imported raw fish. Emerg Infect Dis 2004; 10 (12): 2122-2126.

2. Simakova V, Poltoratskaya NV, Babkina IB, Poltoratskaya TN, Shikhin AV, Pankina TM. The World Largest Focus of the Opisthorchiasis in the Ob-Irtysh Basin, Russia,

Caused by Opisthorchis felineus. In: Bacha U. Rural Health. 1st edition. London, United Kingdom; IntechOpen. pp.

3. Poirier MJ. Trematodes nouvelles ou peu connus. Bull Soc Philomath Ser 1886; 10 (7): 27–29.
4. Leiper RT. Notes of the occurrence of parasites presumably rare in man. J R Army Med Corps 1915; 24: 569–75.
5. Prommas C. Report of a case of Opisthorchis felineus in Siam. Ann Trop Med Parasitol 1927; 21: 9–10.
6. Nyindo M, Lukambagire AH. Fascioliasis: An Ongoing Zoonotic Trematode Infection. Biomed Res Int 2015; 2015: 786195.
7. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Parasites of Public Health Concern. Opisthorchiasis. [Internet]. U.S. Department of Health & Human Services. [Updated: February 2018; Reviewed: January 2021]. Available at: https://www.cdc.gov/dpdx/opisthorchiasis/index.html
8. Lu XT, Gu QY, Limpanont Y, Song LG, Wu ZD, Okanurak K, Lv ZY. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. Infect Dis Poverty 2018; 7 (1): 28.
9. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
10. Sripa B, Bethony JM, Sithithaworn P, et al. Opisthorchiasis and Opisthorchis-associated cholangiocarcinoma in Thailand and Laos. Acta Trop 2011; 120 (1): S158-S168.
11. Food and Agriculture Organization of the United Nations, World Organization for Animal Health, World Health Organization. Foodborne parasitic infections. Clonorchiasis and Opisthorchiasis. [Internet]. Food and Agriculture Organization of the United Nations, World Organization for Animal Health, World Health Organization. [Updated: 2018; Reviewed: January 2021]. Available at: https://www.who.int/docs/default-source/ntds/foodborne-trematode-infections/clonorchiasis-and-opisthorchiasis.pdf?sfvrsn=13f264d2_4
12. Pengput A, Schwartz DG. Risk Factors for Opisthorchis Viverrini Infection: A Systematic Review. J Infect Public Health. 2020; 13 (9): 1265-1273.
13. Locke V, Richardson MS. StatPearls. Clonorchis Sinensis. [Internet]. Treasure Island. StatPearls Publishing. [Updated: September 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK532892/
14. Lukambagire, AH.S., Mchaile, D.N. & Nyindo, M. Diagnosis of human fascioliasis in Arusha region, northern Tanzania by microscopy and clinical manifestations in patients. BMC Infect Dis 2015; 15: 578.

15. World Health Organization. Fascioliasis diagnosis, treatment and control strategy. Internet. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who.int/foodborne_trematode_infections/fascioliasis/fascioliasis_diagnosis/en/

16. World Health Organization. Bench aids for the diagnosis of intestinal parasites. 1st edition. Geneva; World Health Organization: 1994.

17. Upatham ES, Viyanant V. Opisthorchis viverrini and opisthorchiasis: a historical review and future perspective. Acta Tropica 2003; 171-176.

18. Khuntikeo N, Titapun A, Loilome W, Yongvanit P, Thinkhamrop B, Chamadol N, Boonmars T, Nethanomsak T, Andrews RH, Petney TN, Sithithaworn P. Current Perspectives on Opisthorchiasis Control and Cholangiocarcinoma Detection in Southeast Asia. Front Med (Lausanne) 2018; 5: 117.

19. Leder K, Weller P, Ryan E, Baron EL. Liver flukes: Clonorchis, Opisthorchis, and Metorchis. Internet. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/liver-flukes-clonorchis-opisthorchis-and-metorchis?search=chlonorchis&source=search_result&selectedTitle=1~19&usage_type=default&display_rank=1

20. World Health Organization. Foodborne trematode infections [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/opisthorchis/health_professionals/index.html

21. Centers for Disease Control and Prevention. Parasites - Opisthorchis Infection - Resources for Health Professionals. [Internet]. U.S. Department of Health & Human Services. [Updated: May 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/opisthorchis/health_professionals/index.html

PARAGONIMIASIS

Introduction

Paragonimiasis, also known as lung fluke disease, is a parasitic food-borne disease caused by *Paragonimus* spp. that primarily affects the lungs. It is endemic to Africa, America, and Asia, where it mostly affects people who eat crustaceans contaminated with the parasite eggs. Disease progression is slow and is frequently misdiagnosed as other respiratory infectious diseases, thus compromising the diagnosis, treatment, and prognosis.[1]

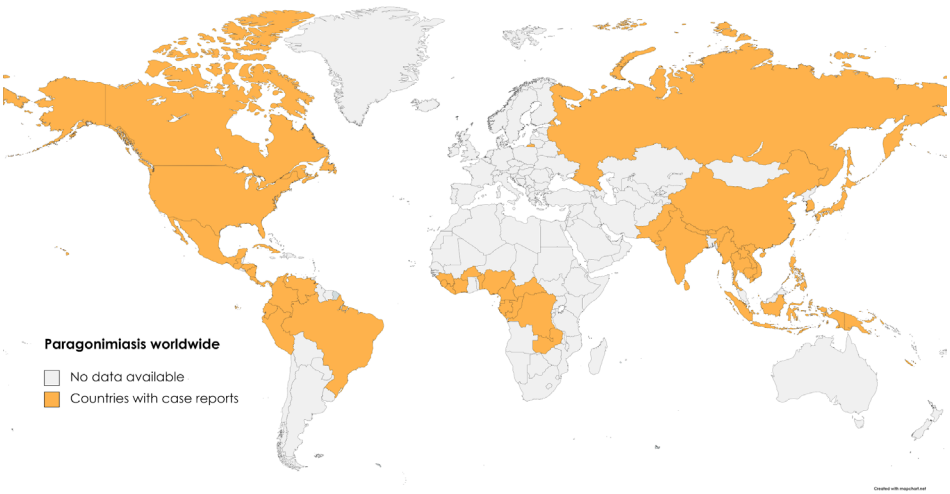
Historical Background

The earliest report of the disease can be traced back to 1878 when Coenraad Kerbert isolated flukes from the lungs of a Bengal tiger; he named the parasite *Paragonimus westermani* after Peter Westerman, the tiger zookeeper.[2] The first case report in humans was described by Ringer in 1879;[3] the etiological agent was isolated by Erwin von Baetz and Patrick Manson in 1880;[4] and its life cycle was described by Harujiro Kobayashi, Keinosuke Miyairi, Koan Nakagawa, and Sadamu Yokogawa between 1916 and 1922.[5]

Epidemiology

About 23 million people are estimated to be infected, and almost 293 million are at risk of acquiring the disease worldwide.[6] Paragonimiasis is endemic to Africa (*P. africanus, P. uterobilateralis*), America (*P. caliensis, P. kellicotti,* and *P. mexicanus*), and Asia (*P. heterotremus, P. hueitungensis, P. miyazakii, P. skrjabini,* and *P. westermani*) (Figure 1).[2, 7] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH PARAGONIMIASIS CASE REPORTS



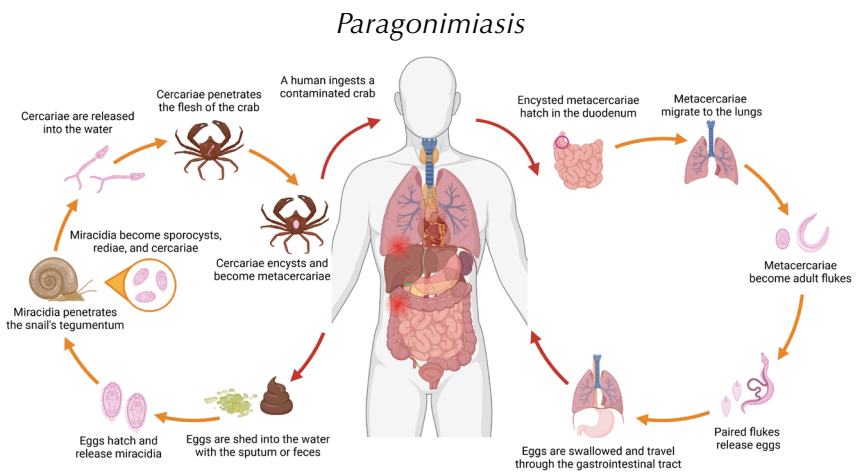
Created with MapChart.net

Adapted from: Lu XT, Gu QY, Limpanont Y, Song LG, Wu ZD, Okanurak K, Lv ZY. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. Infect Dis Poverty 2018; 7 (1): 28.

Etiology

Paragonimiasis is caused the parasites *P. africanus, P. caliensis, P. heterotremus, P. hueitungensis, P. kellicotti, P. mexicanus, P. miyazakii, P. skrjabini, P. uterobilateralis,* and *P. westermani,* which belong to the phylum Platyhelminthes, class Trematoda, subclass Digenea, order Plagiorchiida, suborder Troglotremata, family *Troglotrematidae*, and genus *Paragonimus*.[8] *P. westermani* is responsible for most human cases. The disease is food-borne. Transmission occurs when immature *Paragonimus* spp. eggs are excreted with feces into water. After a couple of weeks, they hatch and release miracidia, which swim and penetrate the tegmentum of freshwater snails. Upon reaching the gastrointestinal tract, they penetrate the intestinal wall. The miracidia then differentiate into sporocysts, rediae, and cercariae, which are shed into the water, where they swim and penetrate the flesh of crabs or crayfish. Once the cercariae reach the muscles, they become encysted and differentiate into metacercariae. Transmission to humans occurs when an uninfected individual ingests pickled, salted, smoked, or undercooked crabs or crayfish carrying encysted metacercariae. Upon reaching the duodenum, the metacercariae emerge from the cysts and migrate to the lungs, where they mature into adult flukes, undergo sexual reproduction, and produce immature eggs. Once the eggs are expelled with the sputum, they are swallowed into the gastrointestinal tract. The cycle is completed when immature *Paragonimus* spp. eggs are excreted with feces into water (Figure 2).[9]

FIGURE 2. *PARAGONIMUS* SPP. LIFE CYCLE



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*This is a schematization of the *Paragonimus* spp. life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Several species of freshwater snails, mainly in the genera *Brotia, Melanoides, Semisulcospira, Tarebia,* and *Thiara*, and freshwater crustaceans, mostly in the genera *Eriocheir, Potamon,* and *Potamiscus*, have been acknowledged as intermediate hosts.[2] Cats, dogs, leopards, mongooses, monkeys, opossums, pigs, and tigers have been recognized as reservoirs.[1]

Risk Factors

In countries where paragonimiasis is endemic, particularly in areas adjacent to water bodies, the main risk factors for acquiring the disease include lack of sanitation, open defecation, and consuming pickled, salted, smoked, or undercooked crustaceans.[1] Paragonimiasis is more prevalent in men than women, but there is no apparent relationship with age.[2]

Clinical Manifestations

The incubation period of the disease ranges from 2 to 16 weeks. Afterward, some infected individuals can remain asymptomatic when the parasite load is low or may become symptomatic when the parasite load is high. Clinically, the disease develops through two distinct stages:

- **Acute stage.** The onset of symptoms begins within 2 to 10 days after the initial infection.[10] In this stage, metacercariae migrate from the duodenum to the lungs, causing irritation and inflammation.[11] Fever, fatigue, malaise, nausea, vomiting, abdominal discomfort, abdominal pain, diarrhea, and urticaria are common. Dyspnea, dry cough, chest pain, hepatomegaly, and splenomegaly may also be experienced. Leukocytosis and eosinophilia can be detected in paraclinical examination.[10, 11]
- **Chronic stage.** This stage usually begins 2 months after the initial infection.[13] In this stage, the flukes reach the pulmonary tract and other parts of the body where they reproduce, causing inflammation and fibrosis.[11] Dyspnea, dry and wet cough with blood-tinged or brown-colored sputum, wheezing, chest pain, and finger clubbing are common. Extrapulmonary clinical manifestations are rare but may also be experienced if eggs or flukes migrate to other parts of the body:

- **Cerebral paragonimiasis.** Fever, headache, and vomiting are common. Seizures, visual disturbances, and sensory or motor disturbances may occur. Meningitis, encephalitis, brain hemorrhage, and space-occupying lesions have been reported.
- **Abdominal paragonimiasis.** Nausea, vomiting, and melena or hematochezia are common. Cysts and abscess formation in organs located in the peritoneal cavity, such as the liver or spleen, or the retroperitoneal cavity, such as the kidneys, may occur.
- **Subcutaneous paragonimiasis.** Painless migratory swelling or firm and mobile nodules that contain immature flukes, mainly in the abdominal wall, inguinal region, and lower extremities, are common.[11, 13]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Paragonimus* spp. is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of smears of sputum, bronchoalveolar lavage, or stool stained with the Kinyoun or Ziehl-Neelsen techniques can demonstrate the presence of *Paragonimus* spp. eggs.[11] Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low. Quantitative methods such as the Kato-Katz technique (KKT) may be used to estimate the infection intensity.[11, 14] Direct microscopic examination combined with FECT or KKT is the preferred approach for detection but is not useful during the acute stage of the disease. Molecular methods such as the polymerase chain reaction can detect *Paragonimus* spp.-specific DNA sequences, but these are emerging tests that are not commercially available yet. Serological techniques can detect antigens produced by *Paragonimus* spp. or antibodies produced by the host against it. Countercurrent immunoelectrophoresis, immunoblot, and enzyme-linked immunosorbent assays have been used with varying success. These assays have shown good sensitivity but suboptimal specificity as there is cross-reactivity with antibodies produced against other parasites. Furthermore, they are unable to distinguish between previous and current infections. Nonetheless, these assays can be used for diagnosis in the subacute stage of the disease and for estimating the magnitude of the parasite load based on its correlation with antigen levels.[2, 13]

Supplementary examination with X-rays, ultrasonography, computer tomography, or magnetic resonance imaging should be performed to assess the extent of the lesions and make a prognosis of the patient.[11]

Differential diagnosis should always be conducted to rule out other causes of fever, cough, and hemoptysis, such as ascariasis, aspergillosis, bronchitis, bronchiectasis, cysticercosis, eosinophilic lung disease, filarial tropical pulmonary eosinophilia, granulomatous vasculitis, idiopathic hypereosinophilic syndrome, lung cancer, lymphomatoid granulomatosis, paragonimiasis, schistosomiasis, strongyloidiasis, toxocariasis, trichinosis, tuberculosis, and Wegener's granulomatosis.[2]

Treatment

Treatment depends on the disease progression. Patients may require a combination of anthelmintic treatment and surgical interventions:

- **Anthelmintic treatment.** Triclabendazole (20 mg/kg orally divided into two doses administered 12 hours apart) and praziquantel (25 m/kg orally three times a day for 3 days) are the anthelmintic drugs of choice to treat the disease at any stage. Both drugs are equally effective, although triclabendazole is preferred over praziquantel due to its simpler dosage regimen.[1, 15] Other anthelmintic drugs such as bithionol and niclosamide have been administered; however, significant side effects have been reported and, thus, these cannot be endorsed as an alternative treatment.[11]
- **Surgical interventions.** Surgery is indicated when patients experience chronic complications of the disease. Adequate assessment by an experienced surgeon should be performed when available.[16, 17]

Prevention

No vaccine to prevent paragonimiasis is currently available. The main preventive strategies include improving sanitation, implementing snail control strategies, consuming only well-cooked crustaceans, and administering preventive drug therapy (triclabendazole 20 mg/kg orally in a single dose) in high-risk populations.[1, 15]

Conclusion

Paragonimiasis is a widely distributed parasitic food-borne disease. It is a significant public-health issue in Africa, America, and Asia, but cases can be found worldwide. Infected individuals experience clinical manifestations related to the migration of flukes from the gastrointestinal to the pulmonary tract. Chronic inflammation of the affected organs leads to fibrosis and the development of life-threatening complications. Diagnosis is difficult during the acute stage, and the disease is frequently misdiagnosed as pulmonary tuberculosis. Approval and distribution of molecular and serological methods to assist diagnosis during the acute stage are needed. Treatment with anthelmintics is effective, but reinfection is common. Vector control and veterinary public-health strategies play a significant role in prevention.

References

1. World Health Organization. Paragonimiasis. [Internet]. World Health Organization. [Updated: 2018; Reviewed: January 2021]. Available at: https://www.who.int/food-borne_trematode_infections/paragonimiasis/en/
2. Diaz JH. Paragonimiasis acquired in the United States: native and nonnative species. Clin Microbiol Rev. 2013 Jul;26(3):493-504. https://doi.org/10.1128/CMR.00103-12. Erratum in: Clin Microbiol Rev 2015; 28 (4): 3.
3. Muller R. Liver and lung flukes. In: Cox FEG. The Wellcome Trust illustrated history of tropical diseases. 1st edition. London; The Wellcome Trust: 1996.
4. Cox FEG. History of Human Parasitology. Clin Microbiol Rev 2003; 15 (4): 1-19.
5. Grove DI. A history of human helminthology. 1st edition. Wallingford; CAB International: 1990.
6. Narain K, Devi KR, Bhattacharya S, Negmu K, Rajguru SK, Mahanta J. Declining prevalence of pulmonary paragonimiasis following treatment & community education in a remote tribal population of Arunachal Pradesh, India. Indian J Med Res 2015; 141 (5): 648-652.
7. Lu XT, Gu QY, Limpanont Y, Song LG, Wu ZD, Okanurak K, Lv ZY. Snail-borne parasitic diseases: an update on global epidemiological distribution, transmission interruption and control methods. Infect Dis Poverty 2018; 7 (1): 28.
8. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

9. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Parasites of Public Health Concern. Paragonimiasis. [Internet]. U.S. Department of Health & Human Services. [Updated: November 2020; Revised: January 2021]. Available at: https://www.cdc.gov/dpdx/paragonimiasis/index.html

10. McNulty SN, Fischer PU, Townsend RR, Curtis KC, Weil GJ, Mitreva M. Systems biology studies of adult paragonimus lung flukes facilitate the identification of immunodominant parasite antigens. PLoS Negl Trop Dis 2014; 8 (10): e3242.

11. Ryan ET, Baron EL Paragonimiasis. [Internet]. UpToDate. Wolters Kluwer. [Updated: September 2020; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/paragonimiasis?search=paragonimiasis&source=search_result&selectedTitle=1~24&usage_type=default&display_rank=1#H2725518

12. Centers for Disease Control and Prevention. Parasites - Paragonimiasis. [Internet]. U.S. Department of Health & Human Services. [Updated: May 2020; Revised: January 2021]. Available at: https://www.cdc.gov/parasites/paragonimus/health_professionals/index.html

13. Keiser J, Odermatt P, Becker SL, Utzinger J. Paragonimus species (Paragonimiasis). [Internet]. Antimicrobe. [Updated: 2002; Reviewed: January 2021]. Available at: http://www.antimicrobe.org/b127.asp

14. World Health Organization. Bench aids for the diagnosis of intestinal parasites. 1st edition. Geneva; World Health Organization: 1994.

15. World Health Organization. Foodborne trematode infections [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/opisthorchis/health_professionals/index.html

16. Mukae H, Nakamura-Uchiyama F, Nawa Y. Pulmonary Paragonimiasis and Its Surgical Complications. [Internet]. Thoracic Key. [Updated: June 2016; Reviewed: January 2021]. Available at: https://thoracickey.com/pulmonary-paragonimiasis-and-its-surgical-complications/

17. Choo JD, Suh BS, Lee HS, Lee JS, Song CJ, Shin DW, et al. Chronic cerebral paragonimiasis combined with aneurysmal subarachnoid hemorrhage. Am J Trop Med Hyg 2003; 69 (5): 466-469.

Chapter 8. Leishmaniasis

Authors

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Introduction

Leishmaniasis is a vector-borne parasitic disease caused by *Leishmania* spp. that primarily affects the skin, mucous membranes, and viscera. The persons most affected are those living in rural areas with inadequate housing and limited or no access to adequate healthcare facilities. Case reports have been increasing in endemic countries over the past decades, but climate change, migration, and globalization have also spread the disease to non-endemic countries, posing a significant threat to the entire world.[1]

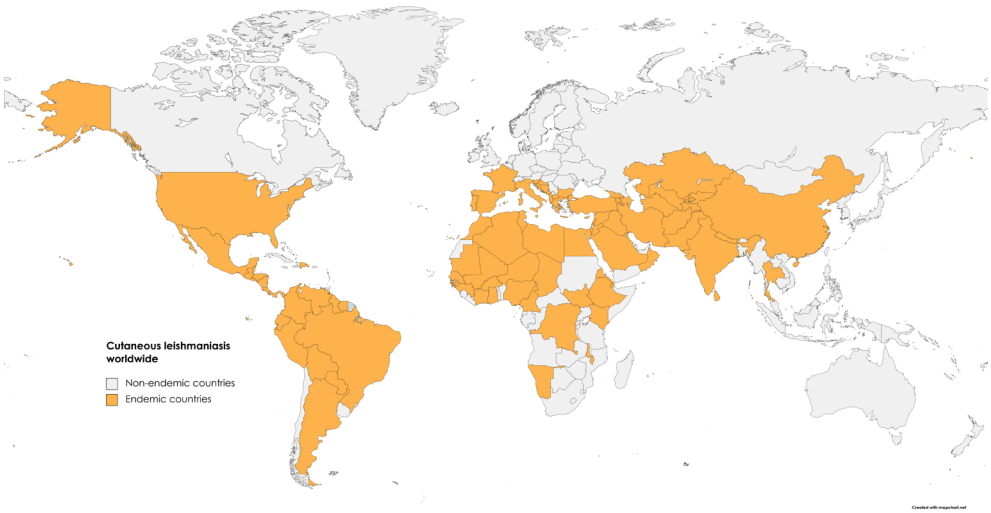
Historical Background

The earliest evidence of the disease can be traced back to the mid-Oligocene–early Miocene, some 100 million years ago, as *Leishmania* fossils were found in the proboscis and alimentary tract of sandflies.[2, 3] Archeological and paleontological studies have discovered mitochondrial DNA of *Leishmania* spp. in Egyptian (2050–1650 BC) and Peruvian (800 BC) mummies.[4, 5] Arabic scientists described the cutaneous form of the disease in medieval times; Spanish colonizers described the mucocutaneous form in the 16th century; and William Twining described the visceral form in the 19th century.[6, 7] Piotr Borovsky isolated the etiological agent in the same century.[8]

Epidemiology

About 12 million people are estimated to be infected, almost 350 million are at risk of acquiring the disease, and nearly 70,000 deaths are caused by leishmaniasis each year worldwide.[9] Some 600,000 to 1 million new cases of cutaneous leishmaniasis (CL) and 50,000 to 90,000 new cases of visceral leishmaniasis (VL) are estimated to occur each year.[10] CL is endemic to Africa (East Africa), America (South America), and Asia (South Asia) (Figure 1), whereas VL is endemic to Africa (East Africa) and America (South America) (Figure 2).[11] The 2010 *Global Burden of Disease Study* estimated that leishmaniasis accounted for 3.32 million disability-adjusted life years, 0.12 years lived with disability, and 3.19 years of life lost.[12]

FIGURE 1. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR CUTANEOUS LEISHMANIASIS



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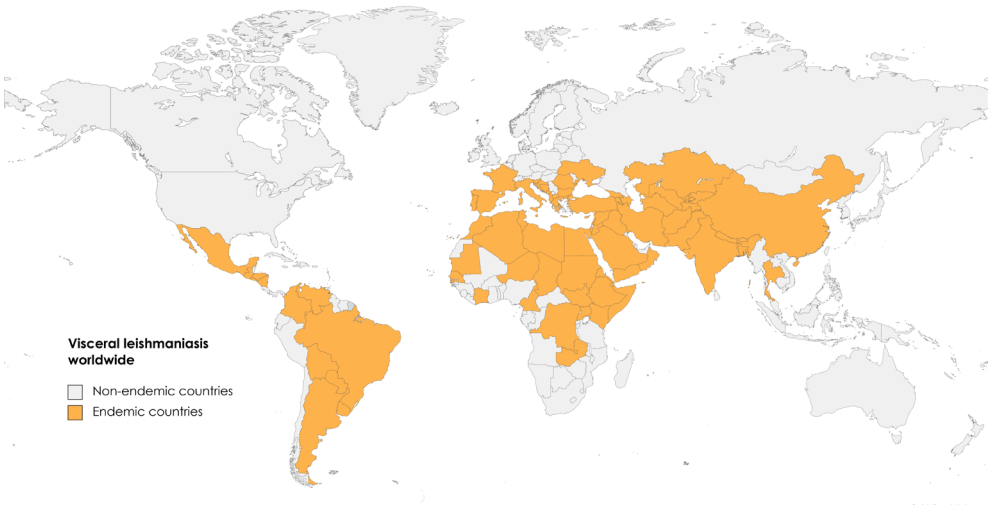
Adapted from: World Health Organization. Global Health Observatory Data Repository. Leishmaniasis. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDLEISH?lang=en

FIGURE 2. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR VISCERAL LEISHMANIASIS



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Adapted from: World Health Organization. Global Health Observatory Data Repository. Leishmaniasis. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDLEISH?lang=en

Etiology

Leishmaniasis is caused by parasites from the *Leishmania* spp., which belong to the phylum Euglenozoa, class Kinetoplastea, subclass Metakinetoplastina, order Trypanosomatida, family *Trypanosomatidae,* subfamily *Leishmaniinae*, and genus *Leishmania*.[13] More than 20 species that can infect humans have been identified and classified based on whether they emerged in the Old or the New World and whether they cause CL, mucocutaneous leishmaniasis (ML), or VL (Table 1).[14] The disease is vector-borne. Transmission occurs when an infected sandfly takes a blood meal from an uninfected individual and introduces promastigotes. Afterward, promastigotes are phagocytosed by macrophages and other phagocytic cells that reside at the subcutaneous tissues, where they differentiate into amastigotes and replicate by binary fission. Amastigotes then differentiate into promastigotes and travel through blood vessels to infect new cells. Transmission continues when an uninfected sandfly sucks blood from

an infected individual and ingests amastigotes from macrophages and other phagocytic cells that reside at the subcutaneous tissues. Subsequently, amastigotes migrate through the gastrointestinal tract to reach either the hindgut or midgut, depending on the infecting species, where they differentiate into promastigotes and replicate by binary fission. Promastigotes then migrate towards the proboscis. The cycle is completed when an infected sandfly takes a blood meal from an uninfected individual and introduces promastigotes (Figure 3).[15] Sandflies in the genera *Phlebotomus* (in the Old World) and *Lutzomyia* (in the New World) have been identified as vectors. Over 70 species of mammals, including anteaters, dogs, foxes, opossums, raccoons, rodents, and sloths, have been recognized as reservoirs.[16]

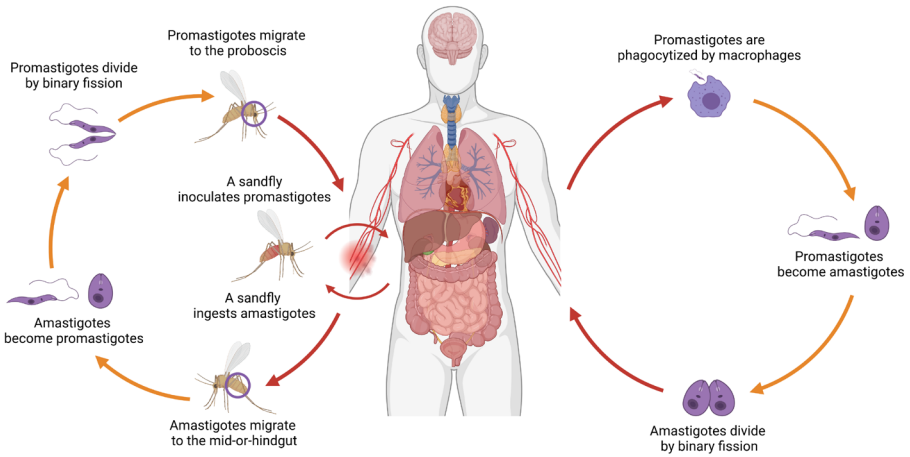
TABLE 1. ORIGINS, VECTORS, AND DISEASES CAUSED BY THE MOST COMMON *LEISHMANIA* SPP.

Etiological agents of leishmaniasis			
Species	**Origin**	**Vector**	**Disease**
L. brazilensis	New World	*Lutzomyia carrerai* *Lutzomyia complexus* *Lutzomyia wellcomei*	Mucocutaneous leishmaniasis
L. donovani	Old World	*Phlebotomus argentipes* *Phlebotomus martini* *Phlebotomus orientalis*	Visceral leishmaniasis
L. chagasi or *L. infantum*	Old and New World	*Lutzomyia longipalpis* *Phlebotomus ariasi* *Phlebotomus perniciosus*	Visceral leishmaniasis
L. major	Old World	*Phlebotomus duboscqi* *Phlebotomus papatasi* *Phlebotomus salehi*	Cutaneous leishmaniasis
L. mexicana	New World	*Lutzomyia olmeca olmeca*	Cutaneous leishmaniasis

Adapted from: Sunter J, Gull K. Shape, form, function and Leishmania pathogenicity: from textbook descriptions to biological understanding. Open Biol 2017; 7 (9): 1-13.

FIGURE 3. *LEISHMANIA* SPP. LIFE CYCLE

Leishmaniasis



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Risk Factors

In countries where leishmaniasis is endemic, the main risk factors for acquiring the disease include climate change, deforestation, migration, low socioeconomic status, inadequate sanitation, poor hygiene, malnutrition, immunosuppression, and occupational exposure.[17] Leishmaniasis is more prevalent in men than women and in adults than children.[18]

Clinical Manifestations

Leishmaniasis has a broad clinical spectrum, ranging from asymptomatic infection to skin, mucous membrane, and visceral disease:

- **Cutaneous leishmaniasis.** The incubation period usually takes 2 to 4 weeks, but infected individuals experiencing symptoms from days to years after exposure have been reported. CL can be sub-classified as localized CL and disseminated CL. Localized CL is characterized by painless erythematous papules 1 to 10 mm in diameter at the inoculation site, mainly on the

head, neck, trunk, or extremities. Papules grow to form well-circumscribed painless ulcers with raised violaceous and indurated borders. Nodules and lymph node enlargement may also occur. Ulcerative lesions heal spontaneously after 1 to 20 years, depending on the infecting species, leaving a depressed or keloid scar.[16] Some *Leishmania* spp. cause specific clinical forms. For example:

- ***L. aethiopica*** produces slow-growing ulcers mainly on the face that can co-occur with nodules and plaques to form a unique lesion. They heal slowly.
- ***L. brazilensis*** produces large ulcers frequently associated with papules, nodules, and lymph node enlargement. They heal after months.
- ***L. guyanensis*** produces multiple ulcers that spread along lymphatic vessels. They do not heal spontaneously and are also known as "Pianbois."
- ***L. mexicana*** produces small, slow-growing ulcers mainly on the face and ears. They heal rapidly and are also known as "Chiclero's ulcers."
- ***L. panamensis*** produces shallow ulcers that spread along lymphatic vessels. They do not heal spontaneously and are also known as "Bejuco's ulcers."
- ***L. peruviana*** produces few small ulcers that can involve mucous membranes by contagious spread. They heal quickly and are also known as "Uta."
- ***L. tropica*** produces small ulcers with a clustered appearance, mainly on the forehead and nose. They heal slowly.[16, 19]

Any individual can be infected by two or more *Leishmania* spp. at any time. On the other hand, disseminated CL is characterized by painless nodules that spread slowly to cover most of the skin surface, mainly on the face, ears, elbows, and knees. Occasionally, it can be accompanied by a rash with verrucous or xanthomatous appearance. Secondary infections are common.[19]

- **Mucocutaneous leishmaniasis.** The incubation period usually takes 2 to 4 years, but patients experiencing symptoms up to 30 years after exposure have been reported. It is characterized by ulcerative lesions predominantly in mucous membranes of the nose, mouth, and throat. Ulcerative lesions do not heal spontaneously and can be severely disfiguring and potentially life-threatening.[16, 20]

- **Visceral leishmaniasis.** The incubation period usually takes 2 to 6 months after inoculation, but patients experiencing symptoms from weeks to years after exposure have been reported. It is characterized by fever, asthenia, fatigue (irregular and relapsing), weakness, anorexia, hepatomegaly, splenomegaly (firm and painful), and weight loss (progressing and wasting). Anemia (normocytic and normochromic), leukopenia (increased risk of secondary infections), and thrombocytopenia (increased risk of spontaneous bleeding) can be seen upon paraclinical examination. Other clinical manifestations that have been reported include pallor, seizures, respiratory distress, cough, nausea, vomiting, ascites, abdominal pain, distention, diarrhea, lower limb edema, and lymph node enlargement, especially in children. Moreover, a well-described complication known as Post-Kala-Azar dermal leishmaniasis (PKDL) may arise after disease resolution; it is characterized by macular, nodular, or papular rash, mainly on the face, trunk, and limbs.[20, 21]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Leishmania* spp. is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of smears of tissue aspirates or biopsy specimens stained with Giemsa or hematoxylin and eosin can demonstrate the presence of amastigotes. Histopathological analysis may detect chronic inflammation of the dermis associated with lymphocytes, macrophages, and plasma cells. Culture methods such as *in-vitro* culture in Grace's, Novy-MacNeal-Nicolle, Schneider's, or Tobie's media, or feeding uninfected sandflies with blood from a potentially infected individual can grow amastigotes. Molecular methods such as the polymerase chain reaction can detect *Leishmania* spp.-specific DNA sequences. Serological techniques such as direct agglutination test, enzyme-linked immunosorbent assay, immunoblot, immunochromatographic test, and indirect immunofluorescence assay can recognize antibodies against *Leishmania* spp. Combined diagnostic methods improve the accuracy and reliability of the diagnosis. Direct microscopic examination and *in-vitro* culture can be conducted to diagnose CL and ML when suitable skin and mucous tissue samples can be obtained. Molecular methods must be used to identify the infecting species, which is key for selecting the proper

approach and management of the disease. Those are the most sensitive and specific tests currently available for diagnosing leishmaniasis. Serological methods can be carried out to diagnose VL when other tests are not available or have tested negative. However, they should not be used alone as they are unable to detect antibodies against *Leishmania* spp. when the parasite load is low or when the host has developed an inadequate humoral response. The Montenegro skin test has also been used. This test consists of the intradermal injection of killed amastigotes to observe whether an induration larger than 5 mm develops. However, its use is becoming anecdotic.[22, 23]

Differential diagnosis should always be conducted to rule out other causes of ulcerative lesions, such as actinomycosis, blastomycosis, Buruli ulcer, coccidioidomycosis, leprosy, sarcoidosis, syphilis, tuberculosis, Wegener's granulomatosis, and yaws, among others, as well as other causes of fever, hepatomegaly, splenomegaly, and weight loss, such as brucellosis, Chagas disease, histoplasmosis, leukemia, lymphoma, malaria, malnutrition, military tuberculosis, mononucleosis, schistosomiasis, and typhoid fever.[24]

Treatment

Treatment is mainly pharmacological and depends on the form of the disease:

- **CL.** Treatment consists of wound cleansing, documenting the evolution, and administration of leishmanicidal agents. Such agents are indicated for patients with localized CL when lesions are disfiguring or persistent (>6 months since the onset of disease) and for patients with disseminated CL. Pentavalent antimonials such as meglumine antimoniate or sodium stibogluconate are used for this purpose. The dosage regimen is 1–2 mL intralesionally every 3–7 days for 2 to 4 weeks in mild and moderate cases, or 20 mg/kg intramuscularly once a day for 10–20 days in severe cases. Miltefosine is an alternative leishmanicidal drug that has proved to be effective (2.5 mg/kg orally once a day for 28 days in children aged 2–11 years; 50 mg orally once a day for 28 days in children over 12 years and under 25 kg; 50 mg orally twice a day for 28 days in children over 12 years and over 25 kg; or 50 mg orally three times a day for 28 days in adults over 50 kg).[20, 25]

- **ML.** Treatment consists of wound cleansing, documenting the evolution, and administration of leishmanicidal agents. Such agents are indicated in all patients with ML. The first-line treatment is miltefosine (2.5 mg/kg orally once a day for 28 days in children aged 2–11 years; 50 mg orally once a day for 28 days in children over 12 years and under 25 kg; 50 mg orally twice a day for 28 days in children over 12 years and over 25 kg; and 50 mg orally three times a day for 28 days in adults over 50 kg).[20, 25]
- **VL.** Treatment consists of hydration, nutritional support, and administration of leishmanicidal agents. Such agents are indicated in all patients with VL. The first-line treatment is a pentavalent antimonial (20 mg/kg intramuscularly or intravenously once a day for 17 days) plus paromomycin (15 mg/kg intramuscularly once a day for 17 days). The second-line treatment is liposomal amphotericin B (3–5 mg/kg intravenously in infusion once a day for 6–10 days). In HIV co-infected patients, an alternative regimen is liposomal amphotericin B (3–5 mg/kg intravenously in infusion once a day for 6–10 days) plus miltefosine (2.5 mg/kg orally once a day for 28 days in children aged 2–11 years; 50 mg orally once a day for 28 days in children over 12 years and under 25 kg; 50 mg orally twice a day for 28 days in children over 12 years and over 25 kg; and 50 mg orally three times a day for 28 days in adults over 50 kg).[20, 25]

Patients with PKDL should also receive leishmanicidal treatment when lesions are disfiguring, persistent (>6 months since the onset of disease) or localized in the oral cavity and interfere with feeding in children. The first-line treatment is a pentavalent antimonial plus paromomycin as in VL. The second-line treatment is liposomal amphotericin B (2.5 mg/kg intravenously in infusion once a day for 20 days). The treatment recommended for HIV co-infected patients is miltefosine, as in VL.[20, 25]

Prevention

No vaccine to prevent leishmaniasis is currently available. The main preventive strategies include wearing protective clothing, spraying insecticide indoors and outdoors, avoiding outdoor exposure after dusk, and applying insect repellants to skin, clothes, and bed nets.[26]

Conclusion

Leishmaniasis is a parasitic disease that mainly affects people living in marginalized, neglected communities. Infected individuals can experience clinical manifestations that range from mild to severe. Epidemiological knowledge of the endemic leishmania species is essential for diagnosis, but laboratory confirmation is required. Direct microscopic examination and culture methods are widely available and affordable, being the tests most commonly employed. However, those methods are unable to identify the infecting species; this can be achieved with molecular methods, the most sensitive and specific tests currently available. The use of serological methods is limited as they are not useful for CL and ML cases, nor for immunocompromised patients. A wide range of therapeutic options is available. However, there is increasing concern about the development of resistance to leishmanicidal agents worldwide. Further commitment and funding to advance vaccine research and development are needed. Meanwhile, integrated vector control measures are essential to reduce or prevent the transmission of leishmaniasis.

References

1. Okwor I, Uzonna J. Social and Economic Burden of Human Leishmaniasis. Am J Trop Med Hyg 2016; 94 (3): 489-493.
2. Poinar Jr G. Palaeomyia burmitis (Phlebotominidae: Diptera), a new genus of Cretaceous sand flies with evidence of blood-sucking habits. Proc Entomol Soc Wash 2004; 106: 598–605.
3. Poinar Jr G, Poinar R. Paleoleishmania proterus n. gen., n. sp., (Trypanosomatidae: Kinetoplastida) from Cretaceous Burmese amber. Protist 2004; 155: 305–310.
4. Zink AR, Spigelman M, Schraut B, Greenblatt CL, Nerlich AG, Donoghue HD. Leishmaniasis in Ancient Egypt and Upper Nubia. Emerg Infect Dis 2006; 12: 1616–1617.
5. Frías L, Leles D, Araújo A. Studies on protozoa in ancient remains - a review. Mem Inst Oswaldo Cruz 2013; 108: 1–12.
6. Twining W. Observations on diseases of the spleen particularly on the vascular engorgement of that organ common in Bengal. Trans Med Phys Soc Bengal 1827; 3: 351–412.
7. Steverding D. The history of leishmaniasis. Parasit Vectors 2017; 10 (1): 82.
8. Hoare CA. Early discoveries regarding the parasites of Oriental sore. Trans R Soc Trop Med Hyg 1938; 32: 66–92.

9. World Health Organization. Leishmaniasis. [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis

10. Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. WHO Leishmaniasis Control Team Leishmaniasis worldwide and global estimates of its incidence. PLoS One 2012; 7 (5): e35671.

11. World Health Organization. Global Health Observatory Data Repository. Leishmaniasis. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDLEISH?lang=en

12. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.

13. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

14. Sunter J, Gull K. Shape, form, function and Leishmania pathogenicity: from textbook descriptions to biological understanding. Open Biol 2017; 7 (9): 1-13.

15. Centers for Disease Control and Prevention. Parasites - Leishmaniasis. Biology [Internet]. U.S. Department of Health & Human Services. [Updated: February 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/leishmaniasis/biology.html

16. Handler MZ, Patel PA, Kapila R, Al-Qubati Y, Schwartz RA. Cutaneous and mucocutaneous leishmaniasis: Clinical perspectives. J Am Acad Dermatol 2015; 73 (6): 897-908.

17. Oryan A, Akbari M. Worldwide risk factors in leishmaniasis. Asian Pac J Trop Med 2016; 9 (10): 925–932.

18. Cloots K, Burza S, Malaviya P, et al. Male predominance in reported Visceral Leishmaniasis cases: Nature or nurture? A comparison of population-based with health facility-reported data. PLoS Negl Trop Dis 2020; 14 (1): e0007995.

19. Aronson N, Weller PF, Baron EL Paragonimiasis. [Internet]. Up to date. [Updated: June 2020; Revised: January 2021]. Available at: https://www.uptodate.com/contents/cutaneous-leishmaniasis-clinical-manifestations-and-diagnosis?search=leishmaniasis&source=search_result&selectedTitle=1~108&usage_type=default&display_rank=1#H83446472

20. Médecins Sans Frontières. Leishmaniases. [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/leishmaniases-16689769.html

21. Pedrosa CM. Clinical Manifestations of Visceral Leishmaniasis (American Visceral Leishmaniasis). In: Claborn D. The Epidemiology and Ecology of Leishmaniasis. 1st edition. London, United Kingdom: IntechOpen; 2017.

22. Aronson N, Herwaldt BL, Libman M, Pearson R, López-Velez R, Weina P, et al. Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). CID 2016; 63: 1539-1557.

23. Elmahallawy EK, Sampedro-Martínez A, Rodríguez-Granger J, Hoyos-Mallecot Y, Agil A, Navarro-Mari JM, et al. Diagnosis of leishmaniasis. J Infect Dev Ctries 2014; 8 (8): 961-972.

24. Pavli A, Maltezou C. Leishmaniasis, an emerging infection in travelers. Int J Infect Dis 2010; 14: 1032-1039.

25. World Health Organization. Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases. Geneva, Switzerland: WHO 2010.

26. Centers for Disease Control and Prevention. Parasites - Leishmaniasis. Prevention & Control. [Internet]. CDC [Updated: February 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/leishmaniasis/prevent.html

Chapter 9. Leprosy

Authors

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Introduction

Leprosy, also known as Hansen's disease, is a bacterial disease caused by *Mycobacterium leprae* that primarily affects the skin, subcutaneous tissues, and nerves. Leprosy is widely distributed and, although it was declared "eliminated" as a global health issue two decades ago, it continues to be endemic to more than 140 countries.[1] The persons most affected are those living in poor, marginalized, underdeveloped, and developing communities. It causes disfiguration, impairment, disability, and social stigma; these can be prevented through integrated approaches, including early diagnosis and effective treatment.[2]

Historical Background

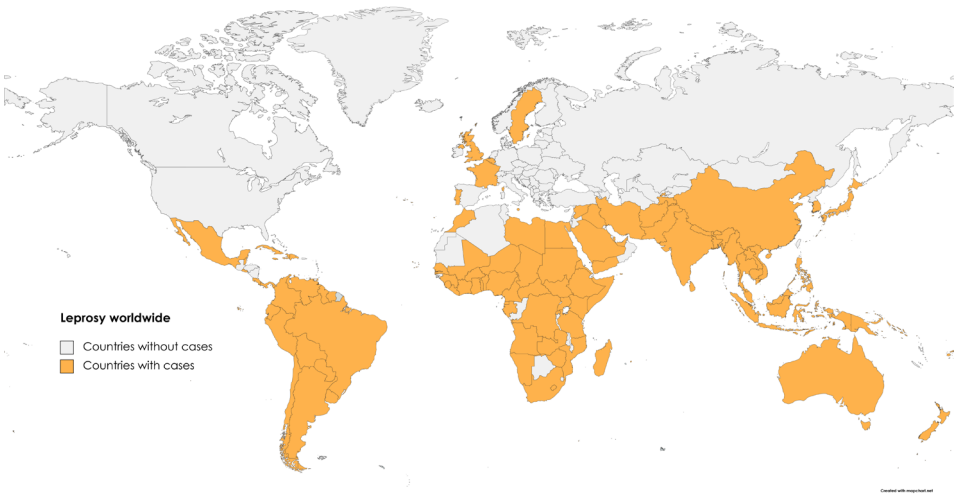
Phylogenetic studies suggest that leprosy has been on Earth for almost 100,000 years, and the earliest evidence of the disease can be traced back to a 4,000-year-old mummy. Several references to this disease have also been identified in ancient medical writings, including the *Atharvaveda* (900 BC) and the *Sushruta Samhita* (600 BC). Leprosy has been related to ancient armies that, through campaigns and crusades, spread the disease across continents. In 1873, Gerhard Hansen isolated the bacillus in unstained tissue samples in Bergen, Norway.[3]

Epidemiology

Between 10 and 12 million people are estimated to be infected,[4] but the number of people at risk of acquiring the disease and the number of deaths directly

due to leprosy are unknown. The number of cases has been decreasing steadily over the past decade: 244,796 cases were reported in 2009; 228,474 in 2010; 219,075 in 2011; 232,857 in 2012; 215,656 in 2013; 213,067 in 2014; 211,973 in 2015; 217,971 in 2016; 211,182 in 2017; 208,641 in 2018; and 202,226 in 2019. Nearly 80% of the cases reported in 2019 occurred in three countries: India (56.5% of cases), Brazil (13.7%), and Indonesia (8.6%) (Figure 1).[5] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH LEPROSY CASE REPORTS



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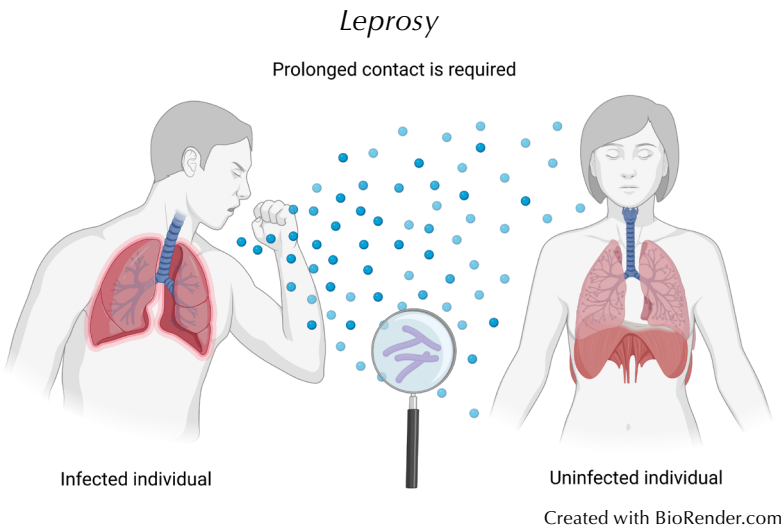
Adapted from: World Health Organization. Global Health Observatory data repository. Leprosy. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.A1638?lang=en

Etiology

Leprosy is caused by a bacteria named *Mycobacterium leprae,* which belongs to the phylum Actinobacteria, class Actinomycetia, order Corynebacteriales, family *Mycobacteriaceae*, and genus *Mycobacterium*.[6] *M. leprae* is a rod-shaped, obligate intracellular, slow-growing bacterium that cannot be cultured in artificial media. Transmission between people mainly occurs when an uninfected individual inhales the upper respiratory secretions from an infected individual (Figure 2). Transmission through abraded skin and from mother to child have al-

so been reported but are not widely akcnowledged.[1] Vectors have not been described to date, but armadillos, apes, chimps, and humans have been identified as reservoirs.[2]

FIGURE 2. MECHANISM OF TRANSMISSION FOR LEPROSY



Risk Factors

In countries where leprosy is endemic, the main risk factors for acquiring the disease include exposure to armadillos, poor hygiene, malnutrition, immunosuppression, and close contact with an infected individual. Leprosy affects men more frequently than women, but there is no significant correlation with age.[7, 8]

Clinical Manifestations

The incubation period of the disease ranges from 3 to 10 years, but infected individuals developing the disease from 2 weeks up to 30 years have been reported. Afterward, infected individuals may either remain in the indeterminate form, in which hypochromic macules with indefinite borders appear, with or without hypoesthesia and with or without increased nerve thickness. Alternatively, infected individuals may develop the determinate forms.[8]

Several classification systems have been used to classify leprosy patients for diagnostic and therapeutic purposes. The Ridley-Jopling classification[9] is the system most commonly used; it classifies the disease along a gradient between two ends based on clinical, histopathological, and immunological features to identify five determinate forms:

- **Tuberculoid form (TT).** It is characterized by erythematous or hypopigmented plaques with elevated external borders and a hypochromic center. Plaques tend to be few (up to 3) and asymmetrical. Significant hypoesthesia with increased nerve thickness can be experienced. Alopecia, anhidrosis, hyperkeratosis, and ulceration may also be present.
- **Borderline tuberculoid form (BT).** It is characterized by lesions similar to those of TT, but smaller and more numerous (up to 10). Besides, the thickening of nerves is less severe.
- **Borderline borderline form (BB).** It is characterized by erythematous plaques with fading outer borders, clear inner borders, and an hypopigmented oval center. Plaques are a mixture of TT and LL lesions of variable size and number (between 10 and 30).
- **Borderline lepromatous form (BL).** It is characterized by lesions similar to those of the LL form but of variable size, which occur in larger numbers (more than 30) and are asymmetrical. Hypoesthesia is more intense.
- **Lepromatous form (LL).** It is characterized by bright, erythematous, or hypopigmented macules with indefinite borders. Macules tend to be multiple (innumerable) and symmetrical. Edema and slight hypoesthesia without increased nerve thickness can be experienced. Macules can infiltrate the skin to form plaques and nodules (lepromas) as the disease progresses. Diffuse infiltration and loss of eyelashes (madarosis) give the face a unique appearance (leonine facies).

Two types and three groups of cases can be distinguished based on the immunological status. The TT and LL types are immunologically stable, whereas BT, BB, and LL are immunologically unstable.[2, 8, 10]

Two additional classification systems were developed by the World Health Organization (WHO) to simplify diagnosis and treatment (Table 1):

- **WHO Classification (1982).** It uses skin smears to subdivide the Ridley-Jopling's leprosy forms into two groups according to their contagiousness: TT and BT are paucibacillary (PB) forms, which are the least contagious, whereas BB, BL, and LL are multibacillary (MB) forms, which are the most contagious.[11]
- **WHO Classification (1998).** It uses clinical manifestations to subdivide the Ridley-Jopling's leprosy forms into two groups according to their contagiousness: patients with between 1 and 5 skin lesions are classified as PB, whereas patients with more than 5 skin lesions are classified as MB.[12]

Leprosy not only damages the dermal free nerve endings leading to changes in sensitivity through the determinate forms but can also invade peripheral nerve trunks and produce peripheral neuropathy. Leprosy causes sensory (hypoesthesia, anesthesia, paresis, and paralysis), motor (tendon retraction, muscle weakness, and muscle atrophy), and autonomic changes (vasomotor dysfunction, and decreased sebaceous and sweat glands secretions), and its pattern can be either a mononeuropathy or polyneuropathy. Neurological damage contributes to the emergence of lesions in the eyes, hands, and feet. These changes may lead to chronic neuropathic pain that degrades the life quality of patients.[2, 12]

TABLE 1. COMPARISON OF THE RIDLEY-JOPLING AND THE WORLD HEALTH ORGANIZATION CLASSIFICATIONS OF LEPROSY

Leprosy classification systems					
Classification	**Categories**				
Ridley-Jopling	Tuberculoid form	Borderline tuberculoid form	Mid-borderline form	Borderline lepromatous form	Lepromatous form
World Health Organization	Paucibacillary leprosy		Multibacillary leprosy		

Adapted from: Maymone MBC, Laughter M, Venkatesh S, Dacso MM, Rao PN, Stryjewska BM, et al. Leprosy: Clinical aspects and diagnostic techniques. J Am Acad Dermatol 2020; 83 (1): 1-14.

Diagnosis

The epidemiological background and clinical manifestations are sufficient to make the diagnosis in the field, but the isolation of *M. leprae* must be encour-

aged, and several laboratory tests are available for this purpose. Direct microscopic examination of slit-skin smears obtained from the nasal mucosa or the earlobe lymph and stained with the Zhiel-Nielsen technique can demonstrate the presence of acid-fast bacilli (AFB). Histopathological tests can evidence histiocytes with vacuolated cytoplasm, tuberculoid granulomas, and lymphocytic infiltration around blood vessels. Molecular methods such as the polymerase chain reaction can detect *M. leprae*-specific DNA sequences. Serological techniques can detect antigens produced by *M. leprae* or antibodies produced by the host against it. Enzyme-linked immunosorbent assay and lateral-flow assay have been used for this purpose with varying success, but none of them is sufficiently sensitive or specific to be used on its own. As per the WHO guidelines, leprosy can be diagnosed in the field when an infected individual shows at least one of the following diagnostic signs: hypoesthesia in an erythematous or hypopigmented skin patch; peripheral nerve of increased thickness; hypoesthesia or muscle weakness; or presence of AFB in a slit-skin smear.[13]

Differential diagnosis should always be conducted to rule out various other skin diseases such as annular psoriasis, cutaneous leishmaniasis, fungal infection, granuloma annulare, keloids, mycosis fungoides, and systemic lupus erythematosus, among others.[10]

Treatment

The first-line treatment against *M. leprae* is rifampicin (10 mg/kg orally once a month) plus clofazimine (100 mg orally once a month plus 50 mg twice a week) plus dapsone (2 mg/kg orally once a day) in children under 10 years of age or under 40 kg; rifampicin (450 mg orally once a month) plus clofazimine (150 mg orally once a month plus 50 mg on alternate days) plus dapsone (50 mg orally once a day) in children aged 10 to 14 years; and rifampicin (600 mg orally once a month) plus clofazimine (300 mg orally once a month plus 50 mg on alternate days) plus dapsone (100 mg orally once a day) for 6 months in case of PB or 12 months in case of MB in children over 15 years and adults (Table 2). Daily doses can be self-administered by the patient at home, but monthly doses must be administered under the supervision of a healthcare professional to increase therapeutic compliance. Second-line treatment in case of rifampicin resistance consists of the administration of at least two drugs (clarithromycin, minocycline, or

levofloxacin/moxifloxacin/ofloxacin) plus clofazimine once a day for 6 months, followed by the administration of one drug (clarithromycin, minocycline, or levofloxacin/moxifloxacin/ofloxacin) plus clofazimine once a day for 18 months.[10, 14]

TABLE 2. DOSAGE REGIMEN FOR THE FIRST-LINE TREATMENT AGAINST PAUCIBACILLARY AND MULTIBACILLARY LEPROSY

Multidrug therapy for leprosy		
Patient type	**Paucibacillary leprosy**	**Multibacillary leprosy**
First-line regimen	Rifampicin (450 mg orally once a month) + clofazimine (150 mg orally once a month plus 50 mg orally on alternate days) + dapsone (50 mg orally once a month) for 6 months	Rifampicin (450 mg orally once a month) + clofazimine (150 mg orally once a month plus 50 mg orally on alternate days) + dapsone (50 mg orally once a month) for 12 months

Adapted from: World Health Organization. Guidelines for the diagnosis, treatment, and prevention of leprosy. New Delhi, India: 2017.

Changes in the immune balance between the host and *M. leprae* during treatment produce reactional states that primarily affect the skin and nerves:

- **Type 1.** It is produced by the cellular immunological response, leading to either improvement or worsening of the disease. BB patients that have received treatment might shift towards the TT end (decreased lower bacterial load and mild clinical manifestations), whereas untreated patients might shift towards the LL end (increased bacterial burden and severe clinical manifestations). In either case, patients experience erythema, hyperesthesia, and edema that can worsen and ulcerate. Acute painful neuritis may also occur.
- **Type 2.** It is produced by the humoral immunological response, leading to worsening of the disease in patients with LL. Unspecific clinical manifestations such as fever, malaise, myalgia, arthralgia, lymph node enlargement, and edema, as well as specific clinical manifestations such as erythema nodosum leprosum or erythema multiforme can develop. Neuritis, vasculitis, and organ damage have also been reported.[2, 8]

Treatment of the reactional states consists of administration of prednisolone (0.5 to 1 mg/kg once a day for 14 days in case of type 1 or for 3 months in type 2). Follow-up every 2 weeks is recommended for up to 6 months. The prednisolone regimen should be tapered according to clinical improvement.[13, 14]

Prevention

No vaccine to prevent leprosy is currently available. The main preventive strategies include improving personal hygiene, administering preventive drug therapy (rifampicin 10 to 15 mg/kg orally in a single dose in children over 2 years and under 20 kg; 300 mg orally in a single dose in children aged 6 to 9 years and over 20 kg; 450 mg orally in a single dose in children aged 10 to 14 years; and 600 mg orally in a single dose in children over 15 years and adults administered under the supervision of a healthcare professional) after exposure, and interrupting transmission through early diagnosis and treatment of individual cases.[10, 15]

Conclusion

Leprosy is an ancient disease that has been targeted for elimination. The number of cases worldwide has remained fairly stable over the past decade, and more than 80% of them have been recorded in three endemic countries. As the incubation period may last up to decades and some patients may remain in the indeterminate form, leprosy is frequently underdiagnosed. However, determinate cases may experience mild to severe clinical manifestations that degrade their life quality and limit their productivity. New diagnostic tools that yield highly sensitive and specific results are still needed to guarantee an optimal approach in remote or poorly controlled settings. Resistance against multidrug therapy continues to be a challenge and, until new drugs are developed and approved, therapeutic compliance promoted by skillful health care professionals remains the primary resource. Social stigmatization must be eliminated first as the fight to tackle the burden of this disease progresses.

References

1. Maymone MBC, Laughter M, Venkatesh S, Dacso MM, Rao PN, Stryjewska BM, et al. Leprosy: Clinical aspects and diagnostic techniques. J Am Acad Dermatol 2020; 83 (1): 1-14.
2. Lastória JC, Abreu MA. Leprosy: review of the epidemiological, clinical, and etiopathogenic aspects - part 1. An Bras Dermatol 2014; 89 (2): 205-218.
3. Kearns SCJ, Nash JE. Leprosy - History. [Internet]. Britannica [Updated: 2018; Reviewed: January 2021]. Available at: https://www.britannica.com/science/leprosy/History
4. Ofosu AA, Bonsu G. Case control study to determine the factors associated with leprosy in the sene district, brong ahafo region of ghana. Ghana Med J 2010; 44 (3): 93-97.
5. World Health Organization. Global Health Observatory data repository. Leprosy. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.A1638?lang=en
6. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
7. Ramos JM, Martínez-Martín M, Reyes F, Lemma D, Belinchón I, Gutiérrez F. Gender differential on characteristics and outcome of leprosy patients admitted to a long-term care rural hospital in South-Eastern Ethiopia. Int J Equity Health 2012; 11: 56.
8. Bhat RM, Prakash C. Leprosy: An Overview of Pathophysiology. Interdiscip Perspect Infect Dis 2012; 2012: 181089.
9. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. Int J Leprosy Mycobacterial Dis. 1966; 34 (3): 255–273.
10. Bhandari J, Awais M, Robbins BA. StatPearls. Leprosy. [Internet]. Treasure Island. [Updated: November 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559307/
11. World Health Organization. Chemotherapy of leprosy for control programmes. World Health Organ Tech Rep Ser 1982; 675: 1-3.
12. World Health Organization. WHO Expert Committee on Leprosy. World Health Organ Tech Rep Ser 1988; 768: 1-51.
13. World Health Organization. Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi, India: 2017.
14. Médecins Sans Frontières. Clinical guidelines. Chapter 4: Skin diseases. Leprosy. [Internet]. MSF [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/leprosy-16689690.html
15. Anjum V. Leprosy: Prevention and Control. In: Anugwom EE, Awofeso N. Public Health in Developing Countries – Challenges and Opportunities. 1st edition. London, United Kingdom: IntechOpen; 2020.

Chapter 10. Lymphatic Filariasis

Authors

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Introduction

Lymphatic filariasis (LF), also known as elephantiasis, is a vector-borne parasitic disease caused by *Brugia* spp. and *Wuchereria bancrofti* that primarily affects lymphatic vessels. The persons most affected are those living in tropical and subtropical countries and continuously exposed to mosquito bites. LF causes pain, disfigurement, impairment, and disability, leading to isolation, unproductivity, and an increased socioeconomic burden for infected individuals, communities, and healthcare systems that become trapped in a vicious cycle.[1]

Historical Background

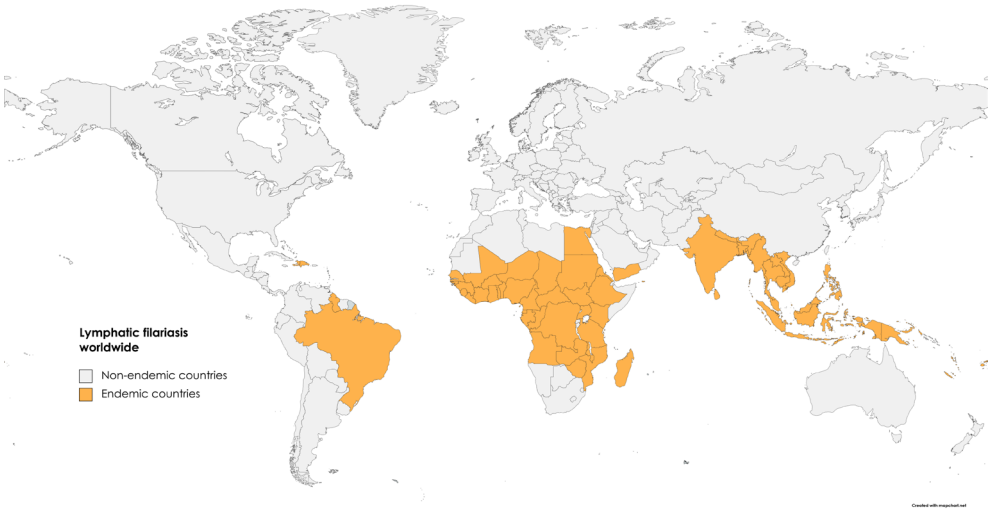
The earliest evidence of the disease can be traced back to Egypt (1500 BC), where illustrations of a prince and his wife suffering from LF can be observed in limestones. Several other paintings of people with LF have been found mainly in Africa and Asia. Jean Demarquay discovered microfilariae in a hydrocele in 1863; Otto Wucherer described the association between microfilaria and the disease in 1866; and Joseph Bancroft identified the adult form of the worm and Patrick Manson isolated microfilariae in mosquitoes in 1877.[2]

Epidemiology

About 120 million people are estimated to be infected, and almost 600 million are at risk of acquiring the disease worldwide.[1] LF is endemic to Africa (Central Africa), America (South America and The Caribbean), and Asia (South Asia and Western Pacific) (Figure 1).[3] The 2010 *Global Burden of Disease Study* estimated

that LF accounted for 2.78 million disability-adjusted life years, 2.77 years lived with disability, and 0 years of life lost.[4]

FIGURE 1. COUNTRIES WHERE LYMPHATIC FILARIASIS IS ENDEMIC



Created with MapChart.net

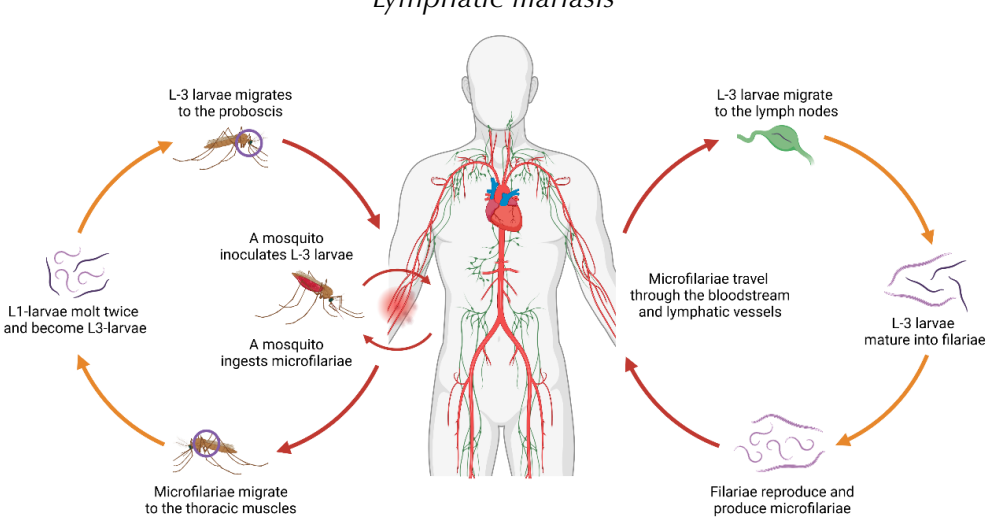
Adapted from: World Health Organization. Lymphatic filariasis. Status of Mass Drug Administration: 2020. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://apps.who.int/neglected_diseases/ntddata/lf/lf.html

Etiology

LF is caused by parasites named *Brugia malayi, Brugia timori*, and *Wuchereria bancrofti*, which belong to the phylum Nematoda, class Chromadorea, order Rhabditida, suborder Spirurina, infraorder Spiruromorpha, superfamily *Filarioidea,* family *Onchocercidae*, and genera *Brugia* and *Wuchereria*.[5] *W. bancrofti* accounts for nearly 90% of cases worldwide, whereas *B. malayi* and *B. timor* jointly account for the remaining 10%.[6] The disease is vector-borne. Transmission occurs when an infected mosquito sucks blood from an uninfected individual and introduces third-stage filarial larvae. Afterward, third-stage filarial larvae migrate towards the lymph nodes, where they mature into filariae, undergo sexual reproduction, and produce microfilariae. The microfilariae then leave the lymph nodes and travel through the bloodstream. Transmission continues when an uninfected mosquito takes a blood meal from an infected individual and ingests microfilari-

ae. Subsequently, microfilariae migrate towards the thoracic muscles, where they differentiate into first-, second-, and third-stage filarial larvae. The third-stage filarial larvae then leave the thoracic muscles and migrate towards the proboscis. The cycle is completed when an infected mosquito sucks blood from an uninfected individual and introduces third-stage filarial larvae (Figure 2).[7] Mosquitoes in the genera *Aedes, Anopheles, Culex, Mansonia,* and *Ochlerotatus* have been identified as vectors. Humans and other animals (cats, leaf monkeys, and macaques) have been identified as reservoirs for *B. malayi* and *B. timori*; humans are the only reservoir identified for *W. bancrofti*.[6, 8]

FIGURE 2. *WUCHERERIA BANCROFTI* LIFE CYCLE



Created with BioRender.com

*This is a schematization of the *W. bancrofti* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where LF is endemic, the main risk factor for acquiring the disease is occupational exposure (farming, fishing, and hunting). LF affects men and women equally and is predominantly acquired during childhood.[9]

Clinical Manifestations

The incubation period of the disease takes 8 to 26 months. Infected individuals can remain asymptomatic or may become symptomatic. Clinically, the disease develops through two distinct stages:

- **Acute episodes.** These are characterized by adenolymphangitis of the breast, genitalia, and lower extremities associated with fever, malaise, myalgia, arthralgia, nausea, vomiting, and localized pain. Epididymitis, epididymo-orchitis, and funiculitis may develop in men. Acute episodes may resolve spontaneously after days or weeks but can recur periodically during the chronic stage of the disease.
- **Chronic conditions.** These are characterized by lymphedema of the breast, genitalia, and lower extremities. The lymphedema is initially reversible but becomes chronic and severe as the disease progresses, causing hypertrophy and thickening of the skin (elephantiasis) (Table 1). Chylocele, epididymo-orchitis, hydrocele, and lymphocele may develop in men. Filarial abscesses, filarial arthritis, filarial-associated immune complex glomerulonephritis, and tropical pulmonary eosinophilia (dyspnea, chest pain, cough, wheezing, and eosinophilia) have also been reported.[6, 10]

TABLE 1. CLASSIFICATION OF FILARIAL LYMPHEDEMA

Grade	Description
I	Pitting reversible edema
II	Pitting or non-pitting, non-reversible edema
III	Non-pitting, non-reversible edema with skin thickening
IV	Non-pitting, non-reversible edema with skin thickening and nodular appearance

Adapted from: Newman TE, Juergens AL. Filariasis. In: StatPearls. Treasure Island, United States; StatPearls Publishing: 2020.

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *B. malayi, B. timori,* or *W. bancrofti* is required

for confirmation, and several laboratory tests are available for this purpose. Serological techniques can detect antigens produced by *B. malayi* and *W. bancrofti* or antibodies produced by the host against them. Antigen tests are preferred over antibody tests as the latter are unreliable for diagnosis in endemic countries. The Brugia Rapid point-of-care cassette test can detect antigens of *B. malayi*; the circulating filarial antigen test, the filariasis test strip, and the immunochromatographic card test can identify antigens of *W. bancrofti*. When these tests are not available, direct microscopic examination of smears of blood, lymph, or urine samples stained with Giemsa, hematoxylin-eosin, or Wright techniques can demonstrate the presence of microfilariae. Blood samples should be drawn between 21:00h and 03:00h because of the nocturnal habits of microfilariae. Molecular methods such as the polymerase chain reaction can detect DNA sequences specific to *B. malayi, B. timori,* or *W. bancrofti*, but they are mainly used in research.[11, 12]

Supplementary examination with imaging studies such as ultrasonography can be performed to observe microfilariae and adult worms within the lymphatic vessels and lymph nodes of the breast, thigh, scrotum, and spermatic cord.[11, 12]

Differential diagnosis should always be conducted to rule out other causes of edema, such as congenital abnormalities of lymphatic vessels, heart failure, Kaposi sarcoma, lymphoma, malnutrition, podoconiosis, and venous disease, among others.[6, 13]

Treatment

Treatment consists of the administration of antiparasitic drugs, control and prevention of inflammatory manifestations, and surgical management in advanced cases:

- **Antiparasitic drugs.** The first-line treatment against *B. malayi, B. timori,* and *W. bancrofti* is diethylcarbamazine citrate (3 mg/kg orally in a single dose for children, and 6 mg/kg orally in a single dose for adults). In tropical pulmonary eosinophilia, the course of treatment should be extended for 14 to 21 days. Doxycycline (200 mg orally once a day for 4 to 6 weeks) is an alternative antimicrobial drug. Albendazole and ivermectin should not be used to treat individual cases but are effective for massive drug administration.

- **Inflammatory manifestations.** Bed rest, cooling and elevation of the affected extremity, and administration of antipyretics in case of fever help alleviate acute episodes. Skin hygiene, cleansing of wounds, administration of antibiotics/antifungals for secondary infection, and wearing comfortable footwear help alleviate lymphangitis and lymphedema. Bandaging the affected limb during the day, elevating it during the night, and exercising/rehabilitating help alleviate lymphedema.
- **Surgical management of complications.** Indicated in cases of advanced lymphedema and hydrocele to improve lymphatic drainage, and in case of chylocele with chyluria to repair the genital structures.[1, 10, 14]

Prevention

No vaccine to prevent LF is currently available. The main preventive strategies include wearing protective clothing, applying insect repellant to the skin, prevent skin exposure with clothes, installing bed nets, spraying insecticide indoors and outdoors, and administering preventive drug therapy (MDA) in high-risk populations.[15]

Conclusion

LF is a chronic and relapsing parasitic disease that requires continued exposure of uninfected individuals to the etiological agent. LF is mainly acquired during childhood; after a variable incubation period, infected individuals may experience acute episodes and chronic complications due to the inflammatory nature of the disease. Diagnosis can be easily performed in the field, but complications require a transdisciplinary approach that can be difficult to implement in remote communities. Preventive drug therapy by MDA is making it possible to control the disease; as efforts continue to be strengthened, LF has been targeted for elimination by 2030.

References

1. World Health Organization. Lymphatic filariasis. [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/lymphatic-filariasis
2. Otsuji Y. History, epidemiology and control of filariasis. Trop Med Health 2011; 39 (2): 3-13.
3. World Health Organization. Lymphatic filariasis. Status of Mass Drug Administration: 2020. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://apps.who.int/neglected_diseases/ntddata/lf/lf.html
4. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.
5. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
6. Newman TE, Juergens AL. Filariasis. In: StatPearls. Treasure Island, United States; StatPearls Publishing: 2020.
7. Centers for Disease Control and Prevention. Parasites - Lymphatic filariasis. Life cycle of W. bancrofti. [Internet]. U.S. Department of Health & Human Services. [Updated: April 2018; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/lymphaticfilariasis/biology
8. Nutman TB, Kazura JW. Lymphatic Filariasis. In: Guerrant RL, Walker DF, Weller PF. Tropical Infectious Diseases: Principles, Pathogens and Practice. Third edition. London, United Kingdom; WB Saunders: 2011. pp. 729-734.
9. Chesnais CB, Awaca-Uvon NP, Vlaminck J, Tambwe JP, Weil GJ, Pion SD, Boussinesq M. Risk factors for lymphatic filariasis in two villages of the Democratic Republic of the Congo. Parasit Vectors 2019;12 (1): 162.
10. Médecins Sans Frontières. Lymphatic filariasis (LF). [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/lymphatic-filariasis-lf-16689898.html
11. Al-Tameemi K, Kabali R. Lymphatic filariasis: an overview. Asian J Pharmaceu Clin Research 2019; 12 (12): 1-5.
12. World Health Organization. Lymphatic filariasis. Diagnosis. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who.int/lymphatic_filariasis/epidemiology/epidemiology_diagnosis/en/

13. World Health Organization. Lymphatic filariasis. Clinical forms. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who.int/lymphatic_filariasis/epidemiology/epidemiology_clinical_forms/en/

14. Centers for Disease Control and Prevention. Parasites - Lymphatic filariasis. Guidance for Evaluation and Treatment. [Internet]. U.S. Department of Health & Human Services. [Updated: April 2018; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/lymphaticfilariasis/health_professionals/dxtx.html#:~:text=The%20main%20goal%20of%20treatment,is%20not%20affected%20by%20chemotherapy.

15. World Health Organization. Lymphatic filariasis. Treatment and prevention. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who.int/lymphatic_filariasis/epidemiology/treatment/en/

Chapter 11. Mycetoma and Chromoblastomycosis

Authors

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Mycetoma and chromoblastomycosis are bacterial and fungal infections that cause chronic, progressive, or relapsing diseases. They are endemic to tropical and subtropical environments but can occur almost anywhere in the world. Transmission occurs by direct contact between the etiological agent and skin trauma. Occupational exposure is the main risk factor for acquiring these diseases. Their incubation period is variable and clinical manifestations depend on the infecting species, but all of them can cause disability and impairment. The infected individuals frequently suffer from discrimination and stigmatization. Direct examination and *in-vitro* culture are the methods most used for diagnosis, but molecular and serological techniques can be useful when available. Imaging studies are required to assess the extent of the infection and identify underlying complications. Treatment consists of administering antibiotics or antifungals to eliminate the etiological agent and surgery to treat life-threatening complications. No prophylactic or therapeutic vaccine is currently available for these diseases.

MYCETOMA

Introduction

Mycetoma is a chronic and destructive disease caused by several bacteria and fungi species that primarily affect the skin and subcutaneous tissues. People living in tropical and subtropical regions where seasonal changes in weather favor the growth of thorny bushes are the most heavily affected, whereas people who carry out field work and tourists who explore endemic regions with no protective clothing are the most exposed. Disfigurement, impairment, discrimination, and stigmatization are common consequences.[1]

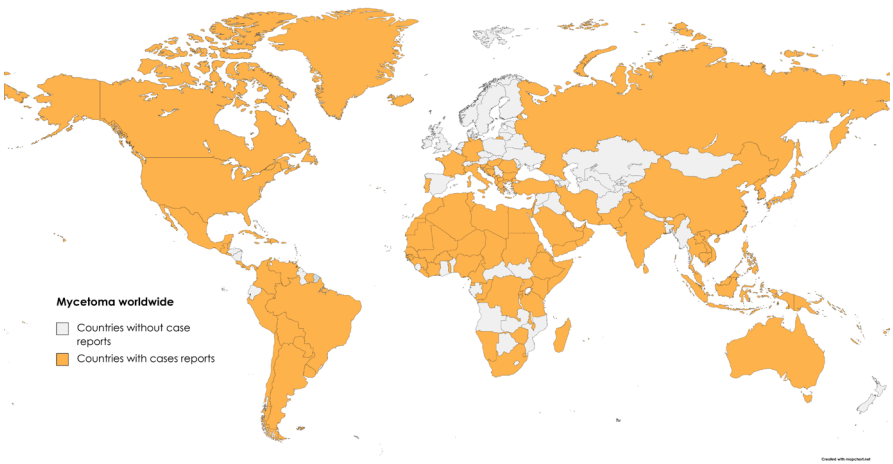
Historical Background

The earliest reports of the disease can be traced back to ancient writings such as the *Rigveda* (1,500 BC) and the *Atharva Veda* (1,200 to 1,000 BC), in which a condition that affects the feet is described.[2] Archeological and paleontological studies have identified evidence of mycetoma in skeletal remains (1,200–1,000 BC) found in Mexico.[3] However, it was until 1843 that John Gill made the first medical description of the disease[4] and until 1846 that John Godfrey documented the first cases.[5] Rubert Boyce first cultivated an etiological agent of bacterial origin in 1894[6], and Emile Brumpt first cultivated an etiological agent of fungal origin in 1906.[7]

Epidemiology

The precise prevalence and incidence of the disease are unknown. In 2020, Darcy Emery and David Denning identified that 19,494 cases were reported in 102 countries between 1876 and 2019.[8] Since this disease is not under epidemiological surveillance in most countries, substantially higher numbers can be expected. Mycetoma occurs in Africa, America, Asia, and Europe, with most cases occurring in the "Mycetoma belt" (30° North–15° South), although autochthonous mycetoma cases have also been reported elsewhere (Figure 1).[1, 9] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH CASE REPORTS OF MYCETOMA



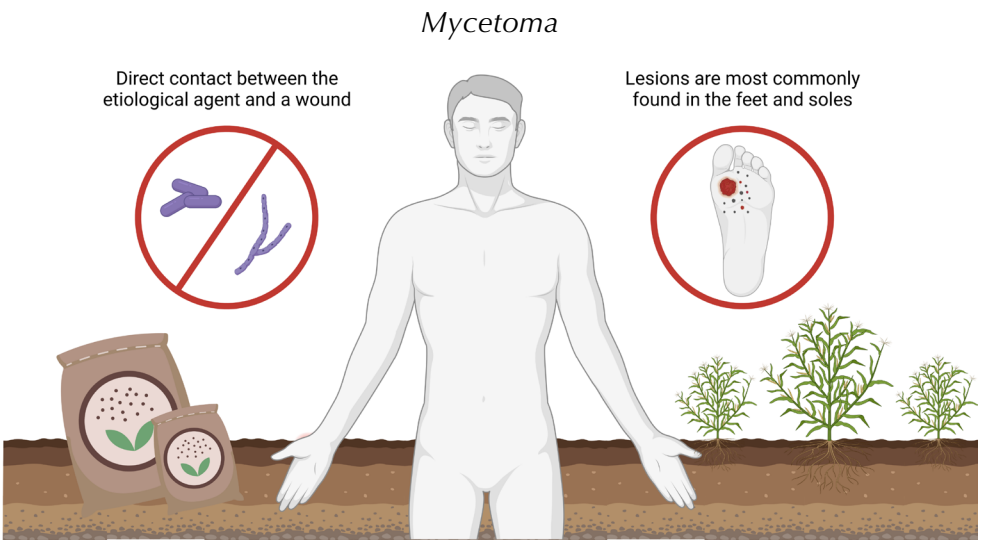
Created with MapChart.net

Adapted from: Emery D, Denning DW. The global distribution of actinomycetoma and eumycetoma. PLoS Negl Trop Dis 2020; 14 (9): e0008397.

Etiology

Mycetoma can be caused by either bacteria or fungi. Actinomycetoma is caused by aerobic bacteria, including *Actinomadura* spp. (*A. madurae* and *A. pelletieri*), *Nocardia* spp. (*N. asteroides, N. brasiliensis, N. harenae, N. otitidiscaviarum, N. takedensis,* and *N. transvalensis*), and *Streptomyces somaliensis*. Eumycetoma is caused by fungi such as *Acremonium* spp. (*A falciforme, A. kiliense,* and *A. recifei*), *Aspergillus* spp. (*A. flavus, A. fumigatus,* and *A. nidulans*), *Biatriospora mackinnonii, Clyndrocarpon* spp. (*C. destructans* and *C. nescens*), *Curvularia lunatus, Exophiala jeanselmei*, *Falciformispora senegalensis, Geotrichum candidum, Madurella* spp. (*M. grisea* and *M. mycetomatis*), *Medicopsis romeroi, Microsporum audouini, Neoscytalidium dimidiatum, Neotestudina rosatii, Phialophora verrucosa, Pyrenochaeta romeroi, Rhinocladiella atrovirens, Scedosporium* spp. (*S. apiospermum* and *S. boydii*), *Scytalidium dimidiatum,* and *Trematosphaeria grisea*, among others.[10, 11] Transmission occurs by direct contact between the etiological agent and a trauma injury in an uninfected individual (Figure 2). Vectors have not been described so far, and soil is believed to be the sole reservoir.[1, 12]

FIGURE 2. MECHANISM OF TRANSMISSION FOR MYCETOMA



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Risk Factors

In countries where mycetoma is endemic, the main risk factors for acquiring the disease include low socioeconomic status, poor hygiene, barefoot walking, and occupational exposure (farmers and livestock herders). Mycetoma affects men more frequently than women and is most common in adults than children.[13]

Clinical Manifestations

The incubation period of the disease ranges between 3 and 9 years. Infected individuals develop a small, painless nodule at the inoculation site, mostly in feet and hands. Other sites where the nodule can develop include the head, neck, shoulders, chest, back, buttocks, and upper and lower extremities. Later, the nodule softens, ulcerates, and discharges serous, serosanguinous, seropurulent, or purulent fluid that contains granules with clusters of microorganisms. Papules, pustules, nodules, and granulomas develop over time and break open to form draining sinuses. A combination of active and inactive sinuses interconnected with deep abscesses is present at any time. The skin may look shiny and smooth with areas of hypo- and hyperpigmentation; these may show increased sweating due to hyperplasia of sweat glands and increased temperature due to inflammation and vasodilatation. As the disease progresses, the surrounding tissues become swollen, indurated, distorted, and deformed. The infection may extend to adjacent tissues, such as subcutaneous tissues, adipocytes, ligaments, muscles, and bones. The infection can become over-infected with *Staphylococcus aureus* or *Streptococcus pyogenes*, among other pathogens, and may spread to other parts of the body through the bloodstream or lymphatic vessels. Actinomycetes are more aggressive than eumycetes: their lesions grow more quickly and produce more inflammation, tissue destruction, and bone involvement, causing deformity.[13, 14]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of actinomycetoma and eumycetoma spe-

cies is required for confirmation, and several laboratory tests are available for this purpose. Samples must be obtained by fine-needle aspiration of the active sinus and then split into two parts: one for direct microscopic examination and the other for culture. Direct microscopic examination can demonstrate the presence of grains characteristic of each species (Tables 1 and 2); if these are not observed, another sample must be collected by surgical biopsy. Histopathological examination can evidence the presence of a chronic granulomatous reaction and the grains characteristic of each species. Culture techniques can grow bacterial and fungal colonies (Tables 3 and 4); however, it takes up to 2 months to isolate the etiological agent. Then, specific microbiological and mycological techniques can identify the infecting species. Supplementary examination with molecular methods such as the polymerase chain reaction can detect DNA sequences specific to actinomycetoma and eumycetoma. Serological techniques such as counterimmunoelectrophoresis, enzyme-linked immunosorbent assay, indirect hemagglutination, and indirect immunofluorescence are useful for detecting antibodies against actinomycetoma and eumycetoma in biological samples.[19, 20]

TABLE 1. GRAIN FEATURES AND ESSAYS USED FOR IDENTIFYING ACTINOMYCETOMA BY DIRECT MICROSCOPIC EXAMINATION

Direct microscopic examination of actinomycetoma		
Etiological agent	**Grain features**	**Essays**
Actinomadura madurae	White to yellow. Round or oval	Growth in 0.4% gelatin (–), soluble in acetic acid (–) and 20% KOH (–)
Nocardia asteroides	White to yellow. 1 mm. Clubs and filamentous forms. Gram (+) and BAAR (+)	Casein hydrolysis (–), decomposes in tyrosine crystal (–), grows in 0.4% gelatin (–)
Nocardia brasiliensis	White to yellow. 1 mm. Clubs and filamentous forms. Gram (+) and BAAR (+)	Casein hydrolysis (+), decomposes in tyrosine crystal (+), grows in 0.4% gelatin (+)

Adapted from: Santiago-Reis CM. Mycetomas: an epidemiological, etiological, clinical, laboratory and therapeutic review. An Bras Dermatol 2018; 91 (1): 8-18.

TABLE 2. GRAIN FEATURES AND ESSAYS USED FOR IDENTIFYING EUMYCETOMA BY DIRECT MICROSCOPIC EXAMINATION

Direct microscopic examination of eumycetoma		
Etiological agent	**Grain features**	**Essays**
Madurella grisea	Black. 1 – 2 mm. Irregular or oval. Hyphae and chlamydospores	Assimilates asparagine, galactose, glucose, maltose, peptone (+), saccharose, urea (+)
Madurella mycetomatis	Black. 5 mm. Interlacing	Assimilates asparagine, galactose, glucose, lactose, maltose, peptone, urea
Scedosporium apiospermum	White. 1 – 2 mm. Hyphae and chlamydospores	Proteolytic activity in gelatin medium (+), starch hydrolysis (+)

Adapted from: Santiago-Reis CM. Mycetomas: an epidemiological, etiological, clinical, laboratory and therapeutic review. An Bras Dermatol 2018; 91 (1): 8-18.

TABLE 3. CULTURE MEDIUM, AND MACROSCOPIC AND MICROSCOPIC FEATURES FOR IDENTIFYING ACTINOMYCETOMA BY CULTURE

Culture of actinomycetoma			
Etiological agent	**Culture medium**	**Macroscopic features**	**Microscopic features**
Actinomadura madurae	Glycerol-gelatin medium, Lowenstein-Jensen medium, vegetable broth	Glabrous, serous, and ridged colony with flat border and grey folds	Long, thin, branched, and twisted filaments
Nocardia asteroides	Chocolate agar, Czapek-dox agar, Sabouraud agar	White and wrinkled on the surface and orange or yellow underneath with “wet-soil odor”	Fine filaments that fragment into bacillary structures
Nocardia brasiliensis	Chocolate agar, Czapek-dox agar, Sabouraud agar	White and wrinkled on the surface and orange or yellow underneath with “wet-soil odor”	Fine filaments that fragment into bacillary structures

Adapted from: Santiago-Reis CM. Mycetomas: an epidemiological, etiological, clinical, laboratory and therapeutic review. An Bras Dermatol 2018; 91 (1): 8-18.

TABLE 4. CULTURE MEDIUM, AND MACROSCOPIC AND MICROSCOPIC FEATURES FOR IDENTIFYING EUMYCETOMA BY CULTURE

Culture of eumycetoma			
Causal agent	**Culture medium**	**Macroscopic features**	**Microscopic features**
Madurella grisea	Potato agar, Sabouraud agar	Grey or green ridged surfaces, dark backside	Dematiaceous septate mycelium with rare chlamydospores
Madurella mycetomatis	Cornmeal agar, Czapek-dox agar, potato agar, Sabouraud agar	Brown or yellow ridged surfaces	Dematiaceous hyphae with branching conidiophores and multiple chlamydospores
Scedosporium apiospermum	Chocolate agar, Czapek-dox agar, Sabouraud agar	Fast filamentous growth with cotton-like dark-grey mycelium	Isolated annelloconidia at the apex of anellospores and pyriform aleuriospores in the apex of conidiospores

Adapted from: Santiago-Reis CM. Mycetomas: an epidemiological, etiological, clinical, laboratory and therapeutic review. An Bras Dermatol 2018; 91 (1): 8-18.

Supplementary examination with X-rays, computed tomography, magnetic resonance imaging, and ultrasonography are valuable to assess the extent of lesions, identify underlying complications, and estimate the prognosis of patients.[10]

Differential diagnosis should always be conducted to rule out other causes of skin lesions, such as actinomycosis, blastomycosis, botryomycosis, Buruli ulcer, chromomycosis, cutaneous tuberculosis, dermatophytic pseudomycetoma, Kaposi sarcoma, podoconiosis, sarcoma of the soft tissues, sporotrichosis, osteomyelitis, and yaws.[14]

Treatment

Treatment depends on the etiological agent and the progression of the disease:

- **Actinomycetoma.** It requires long-term antibacterial combination therapy. The first-line treatment is co-trimoxazole (960 mg orally twice a day) plus co-

amoxiclav (1 g orally twice a day) plus folic acid (5 g orally once a day) for at least 12 months. The second-line treatment is co-trimoxazole (trimethoprim 8 mg/kg orally once a day) plus sulfamethoxazole (40 mg/kg orally, divided into three doses for 5 weeks) plus amikacin (15 mg/kg intramuscularly or intravenously, divided into two doses for at least 3 weeks) in case of antibiotic-resistant bacteria. Other alternatives in cases of resistance include imipenem or imipenem plus amikacin. The cure rate for actinomycetoma is about 90%.

- **Eumycetoma.** It requires long-term antifungal combination therapy and surgical intervention. The first-line treatment is itraconazole (200 mg orally twice a day for up to 3 months after surgery in case of small lesions, or up to 6 months before surgery plus 6 months after surgery in mid-sized or large lesions). Itraconazole plus terbinafine before surgery can be administered in cases of antifungal-resistant fungus. Itraconazole plus antibiotics must be administered in case of secondary infection. The cure rate for eumycetoma is about 30%. Amputation is often required.[17-19]

Follow-up is recommended for up to 18 to 24 months as the recurrence rate is almost 30%.[17]

Prevention

No vaccine to prevent mycetoma is currently available. The main preventive strategies include avoiding walking barefoot on unpaved soil and using gloves when performing manual activities.[17]

Conclusion

Mycetoma is a bacterial and fungal disease that mainly affects people living in the "Mycetoma belt." Occupational exposure is the most common risk for acquiring the infection and, when acquired, infected individuals experience painless lesions that are frequently overlooked and underdiagnosed. Deformation, disfigurement, and impairment are common as the disease progresses. Prompt diagnosis and adequate treatment are not always available due to the lack of suitable healthcare services. Developing affordable, effective, and safe diagnostic tools

and treatment options is still a necessity. Mycetoma must become better detected, a robust surveillance system must be built, and global efforts must not be diminished to reduce the number of cases.

References

1. World Health Organization. Mycetoma. [Internet]. World Health Organization. Mycetoma. [Updated: June 2019; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/mycetoma
2. Hay RJ. Mycetoma – a history of the first contributions to the description of the disease and its pathogenesis. Trans R Soc Trop Med Hyg 2020; 0: 1-4.
3. Mansilla-Lory J, Contreras-López, EA. Micetoma en México prehispánico. Estudio en la colección esquelética de la cultura de Tlatilco. Rev Med Inst Mex Seguro Soc 2009; 47 (3): 237–242.
4. Gill R. Indian Army Medical Reports (1842). Cited in Godfrey J. Diseases of the foot not hereto described. Lancet 1846; 1: 593–594.
5. Godfrey J. Diseases of the foot not hitherto described. Lancet. 1846; 1: 593–594.
6. Boyce R, Surveyor NF. Upon the existence of more than one fungus in madura disease (mycetoma). Phil Trans R Soc Lond 1894; B1: 851–914.
7. Brumpt RE. Les mycetomes. Arch Parasitol 1906; 16: 489–564.
8. Emery D, Denning DW. The global distribution of actinomycetoma and eumycetoma. PLoS Negl Trop Dis 2020; 14 (9): e0008397.
9. Centers for Disease Control and Prevention. Fungal Diseases. Mycetoma. [Internet]. U.S. Department of Health & Human Services. Mycetoma. [Updated: September 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/fungal/diseases/mycetoma/index.html
10. Santiago-Reis CM. Mycetomas: an epidemiological, etiological, clinical, laboratory and therapeutic review. An Bras Dermatol 2018; 91 (1): 8-18.
11. Van de Sande WW. Global Burden of Human Mycetoma: A Systematic Review and Meta-analysis. PLoS NTDs 2013; 7 (11): e2550.
12. Van de Sande WW, Maghoub el S, Fahal AH, Goodfellow M, Welsh O, Zijlstra E. The mycetoma knowledge gap: identification of research priorities. PLoS Negl Trop Dis. 2014; 8 (3): e2667.
13. Fahal AH, Suliman SH, Hay R. Mycetoma: The Spectrum of Clinical Presentation. Trop Med Infect Dis 2018; 3 (3): 97.

14. Relhan V, Mahajan K, Agarwal P, Garg VK. Mycetoma: An Update. Indian J Dermatol. 2017; 62 (4): 332-340.

15. Fahal AH, Suliman SH, Hay R. Mycetoma: The Spectrum of Clinical Presentation. Trop Med Infect Dis 2018; 3 (3): 97.

16. Ahmed AA, van de Sande W, Fahal AH. Mycetoma laboratory diagnosis: Review article. PLoS Negl Trop Dis 2017; 11 (8): e0005638.

17. Welsh O, Vera-Cabrera L, Welsh E, Salinas MC. Actinomycetoma and advances in treatment. Clinics in Dermatology 2012; 30 (4): 372-81.

18. Scolding P, Fahal A, Yotsu RR. Drug therapy for Mycetoma. Cochrane Database Syst Rev. 2018; 2018 (7): CD013082.

19. Drugs for Neglected Diseases Initiative. Mycetoma. Symptoms, transmission, and current treatments for mycetoma [Internet]. Drugs for Neglected Diseases Initiative. [Updated: January 2020; Reviewed: January 2021]. Available at: https://dndi.org/diseases/mycetoma/facts/

CHROMOBLASTOMYCOSIS

Introduction

Chromoblastomycosis (CBM), also known as chromomycosis, is a chronic and disfiguring disease caused by several fungal species that primarily affect the skin and subcutaneous tissues. CBM is considered an occupational disease that mostly affects farmers, gardeners, and loggers. The disease progresses from a cutaneous infection to fibrotic and granulomatous reactions, formation of microabscesses, and tissue proliferation that lead to disfigurement, impairment, degraded life quality, and social stigma.[1]

Historical Background

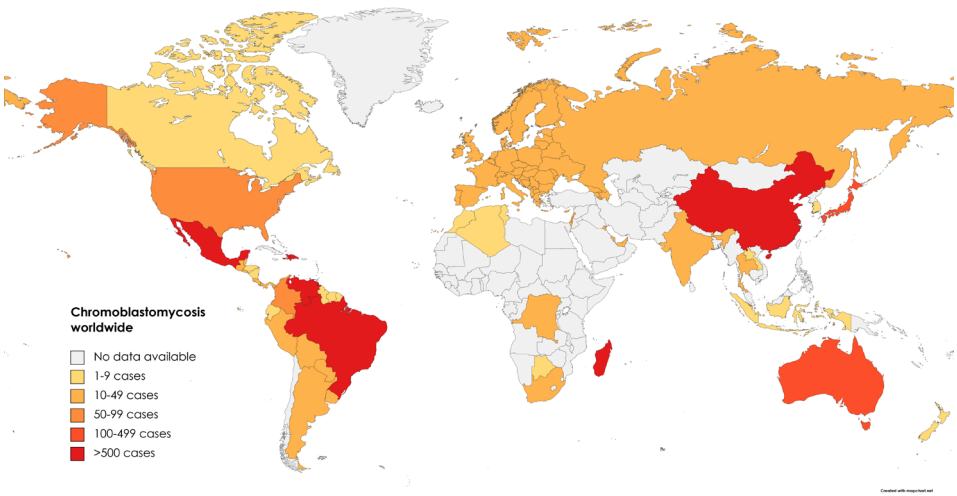
The earliest references to the disease can be traced back to 1903, when Bruas described an ailment that affected the feet but was different from mycetoma.[2] In 1911, Alexandre Pedroso and Jose Gomes reported a case series of infected individuals with "verrucous dermatitis" in which they observed muriform cells in

skin biopsies and dark fungal colonies in cultures, making it possible to isolate the etiological agent.[3] Terra coined the term "chromoblastomycosis" to differentiate the disease from "verrucous dermatitis" in 1922,[4] and Pablo Negroni formally named the genus *Fonsecaea* and the species *F. pedrosoi* in 1936.[5] Since then, several physicians and researchers have isolated new species.[6, 7]

Epidemiology

The precise prevalence and incidence of the disease are unknown, but data gathered from surveys and case series suggest that incidence ranges from 1 in 6,800 individuals in Madagascar to 1 in 8,625,000 individuals in the United States. CBM is a cosmopolitan disease, most prevalent in tropical and subtropical regions (30° North–30° South) of Africa, Asia, America, Europe, and Oceania**.** Most cases have been reported in countries where CBM is endemic, such as Australia, Brazil, China, India, Mexico, and Venezuela. However, non-endemic countries such as Canada, Czech Republic, Finland, Japan, Poland, Romania, and Russia, have also acknowledged its presence (Figure 1).[1, 7] Its global burden remains unknown.

FIGURE 1. COUNTRIES WITH CASES OF CHROMOBLASTOMYCOSIS



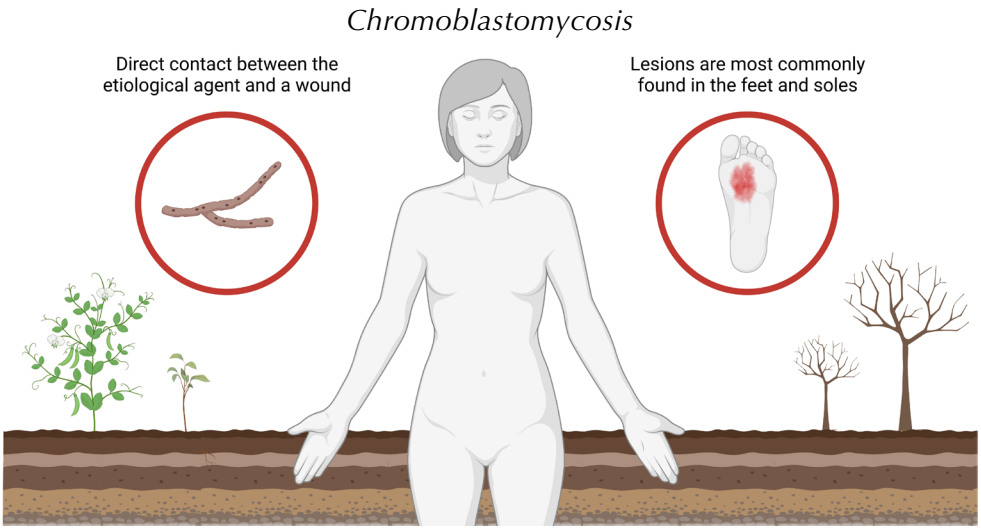
Created with MapChart.net

Adapted from: Queiroz-Telles F, de Hoog S, Santos DW, Salgado CG, Vicente VA, Bonifaz A, Roilides E, et al. Chromoblastomycosis. Clin Microbiol Rev 2017; 30 (1): 233-276.

Etiology

CBM is caused by fungi in the genera *Cladophialophora* and *Fonsecaea*, which belong to the phylum Ascomycota, subphylum Pezizomycotina, class Eurotiomycetes, subclass Chaetothyriomycetidae, order Chaetothyriales, and family *Herpotrichiellaceae*.[8] *C. carrionii* and *F. pedrosoi* are the most prevalent species; *C. carrionii* is common in semiarid climates, whereas *F. pedrosoi* is common in humid tropical climates.[9] Other causal agents include *Cladophialophora* spp. (*C. ludoviensis* and *C. samoensis*), *Exophiala* spp. (*E. jeanselmei* and *E. spinifera*), *F. monophora*, *F. nubica, F. pugnacious, Phialophora* spp. (*P. richardsiae* and *P. verrucosa*), and *Rhinocladiella* spp. (*R. aquaspersa, R. similis,* and *R. tropicalis*).[10] Transmission occurs by direct contact between the etiological agent and a trauma injury of an uninfected individual (Figure 2). Soil is believed to be the sole reservoir.[1, 7]

FIGURE 2. MECHANISM OF TRANSMISSION FOR CHROMOBLASTOMYCOSIS



Risk Factors

In countries where CBM is endemic, the main risk factors for acquiring the disease include low socioeconomic status, poor hygiene, barefoot walking, and occupational exposure (farmers, gardeners, lumberjacks, miners, and vendors of farm products). CBM affects men more frequently than women and is most common

in adults aged between 25 and 85 years. Children are rarely affected, although several cases have been reported.[1, 11]

Clinical Manifestations

The incubation period of the disease is unknown. Infected individuals develop an erythematous maculopapular lesion at the inoculation site, mostly in feet and hands. Other sites where the maculopapular lesion can develop include ears, eyelids, nose, shoulders, trunks, and buttocks. The disease is initially oligosymptomatic, causing mild to moderate pruritus and localized pain, which are frequently overlooked. If the diagnosis is not performed and treatment is not administered, the erythematous maculopapular lesion progresses to form nodules and plaques covered by crusts that eventually become extensive warty lesions with a "cauliflower"-like appearance.[1, 12] Several classification systems have been proposed to group CBM infected individuals for diagnostic and therapeutic purposes. The most used classification is that of Carrión,[1, 13] which classifies the disease along a gradient between two ends and identifies five determinate forms based on clinical, histopathological, and immunological features:

- **Nodular form (NF).** It is characterized by erythematous purple nodules with smooth, scaly, or verrucous surfaces.
- **Verrucous form (VF).** It is characterized by dry, hyperkeratotic, and warty lesions with black dots and cauliflower-like surfaces.
- **Plaque form (PF).** It is characterized by erythematous purple, circumscribed, and infiltrated plaques with black dots and sharp elevated edges.
- **Tumoral form (TF).** It is characterized by isolated or coalescent lobulated lesions with smooth or cauliflower-like surfaces.
- **Cicatricial form (CF).** It is characterized by annular, irregular, or serpiginous lesions with central atrophic-scarring areas and centrifugal growth that involve large areas of the body.[1, 7, 13]

CBM lesions can also be graded according to severity. (Table 1).[14]

Some infected individuals with advanced and severe disease can experience multiple forms of CBM. The infection may extend to compromise adjacent sub-

cutaneous tissues without affecting adipocytes, ligaments, muscles, and bones. It may spread to other parts of the body through the bloodstream or lymphatic vessels. Ankylosis, lymphedema, and malignant transformation to squamous cell carcinoma have been reported.[1, 7, 14]

TABLE 1. CLASSIFICATION OF CHROMOBLASTOMYCOSIS ACCORDING TO LESION SEVERITY

Grading system for chromoblastomycosis lesion severity	
Severity	**Description**
Mild	Solitary or multiple nodules less than 5 cm in diameter
Moderate	Solitary or multiple nodules, plaques, or verrucous lesions, covering one or more adjacent cutaneous regions, less than 15 cm in diameter
Severe	Solitary or multiple nodules, plaques, or verrucous lesions covering extensive adjacent or nonadjacent cutaneous regions larger than 15 cm in diameter

Adapted from: Queiroz-Telles F, Esterre P, Perez-Blanco M, Vitale RG, Salgado CG, Bonifaz A. Chromoblastomycosis: an overview of clinical manifestations, diagnosis, and treatment. Med Mycol 2009; 47 (1): 3-15.

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Cladophialophora* spp. and *Fonsecaea* spp. is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of skin scrapings from "cayenne pepper" lesions and prepared with potassium hydroxide can demonstrate the presence of muriform cells. Staining techniques such as calcofluor white detect fungal elements when these are scarce; if these are not observed, another sample must be collected by biopsy. The sample must be split into two portions: one for histopathological examination and the other for culture. Histopathological analysis can evidence the presence of hyperkeratosis, irregular acanthosis, pseudoepitheliomatous hyperplasia, pyogranulomatous inflammation, and the characteristic muriform cells. Culture techniques such as *in-vitro* culture in Sabouraud glucose agar can grow dark-pigmented colonies of *Cladophialophora* spp. and *Fonsecaea* spp;

however, it takes up to 2 months to isolate the etiological agent. Molecular methods such as the polymerase chain reaction can be employed to identify the infecting species but are not widely available yet. Serological techniques such as the enzyme-linked immunosorbent assay recognize antibodies against *Cladophialophora* spp. and *Fonsecaea* spp. in biological samples but are mainly used for research.[1, 15]

Differential diagnosis should always be conducted to rule out other causes of skin lesions, such as blastomycosis, botryomycosis, coccidioidomycosis, granulomatous candidiasis, granulomatous dermatophytosis, lacaziosis, leishmaniasis, leprosy, mycetoma, nocardiosis, paracoccidioidomycosis, phaeohyphomycosis, rhinosporidiosis, sarcoidosis, systemic lupus erythematosus, syphilis, and yaws.[1, 14]

Treatment

CBM is difficult to treat and is associated with low resolution and high relapse rates, posing a challenge for clinicians. Treatment requires the combination of physical methods and long-term antifungal treatment:

- **Physical methods.** They are used as adjuvant therapy and include surgery, cryotherapy, laser therapy, photodynamic therapy, and thermotherapy. Each of them has specific indications and must be performed by an experienced dermatologist.
- **Antifungal treatment.** The first-line treatment is itraconazole (200 to 400 mg orally once a day for 6 to 12 months). The second-line treatment is terbinafine (250 to 500 mg orally once a day for 6 to 12 months). The combination of itraconazole plus terbinafine is administered to patients with advanced or refractory disease. Other antifungal drugs have been administered with promising results, but further research is needed before endorsing a recommendation.[1, 15]

The cure rate after long-term antifungal therapy ranges between 15 and 80%, depending on the infecting species and severity of the disease. Therefore, strict follow-up is recommended until achieving clinical and mycological cures. Clinical cure is defined as the absence of lesions with scars; mycological cure is defined

as the absence of fungi upon direct examination and absence of fungal colonies under *in-vitro* culture.[7]

Prevention

No vaccine to prevent CBM is currently available. The main preventive strategies include avoiding walking barefoot on unpaved soil, wearing proper protective clothing, and reducing environmental traumatic transcutaneous inoculation in susceptible individuals.[1]

Conclusion

CMB is a chronic and relapsing fungal infection of global distribution, the burden of which is currently unknown. Occupational exposure is the major risk factor for acquiring the disease. Infected individuals experience a wide range of clinical manifestations. Some of them experience mild symptoms, which are frequently overlooked. When medical attention is delayed, polymorphic forms develop. Advanced cases are challenging to treat; even the combination of physical methods and long-term antifungal treatment is frequently unsuccessful. New antifungals with better efficacy and safety profile are necessary to shorten the duration of the treatment regimen, reduce the incidence of adverse effects, and lower the relapse rate.

References

1. Queiroz-Telles F, de Hoog S, Santos DW, Salgado CG, Vicente VA, Bonifaz A, Roilides E, et al. Chromoblastomycosis. Clin Microbiol Rev 2017; 30 (1): 233-276.
2. Brygoo ER. La chromoblastomycose à Madagascar. Sem Hop Paris 1957; 33: 774 -789.
3. Rippon JW. Medical mycology: the pathogenic fungi and the pathogenic actinomycetes. 3rd ed. Philadelphia; B Saunders: 1988.
4. Terra F, Torres M, Fonseca Filho O, Arêa Leão AE. Novo tipo de dermatite verrucosa; micose por Acrotheca com associação de leishmaniose. Bras Med 1922; 36: 363-368.

5. Negroni P. Estudio del primer caso Argentino de cromomicosis, Fonsecaea (Negroni) pedrosoi (Brumpt) 1921. Rev Inst Bacteriol 1936; 7: 419-426.

6. Krzyściak PM, Pindycka-Piaszczyńska M, Piaszczyński M. Chromoblastomycosis. Postepy Dermatol Alergol 2014; 31 (5): 310-321.

7. Brito AC, Bittencourt MJS. Chromoblastomycosis: an etiological, epidemiological, clinical, diagnostic, and treatment update. An Bras Dermatol 2018; 93 (4): 495-506.

8. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

9. Agarwal R, Singh G, Ghosh A, Verma KK, Pandey M, Xess I. Chromoblastomycosis in India: Review of 169 cases. PLoS Negl Trop Dis 2017; 11 (8): e0005534.

10. Vicente VA, Weiss VA, Bombassaro A, Moreno LF, Costa FF, Raittz RT, et al. Comparative Genomics of Sibling Species of Fonsecaea Associated with Human Chromoblastomycosis. Front Microbiol 2017; 8: 1924.

11. Rasamoelina T, Maubon D, Andrianarison M, Ranaivo I, Sendrasoa F, Rakotozandrindrainy N, et al. Endemic Chromoblastomycosis Caused Predominantly by Fonsecaea nubica, Madagascar. Emerging Infectious Diseases 2020; 26 (6): 1201-1211.

12. Santos DWCL, Vicente VA, Weiss VA, et al. Chromoblastomycosis in an Endemic Area of Brazil: A Clinical-Epidemiological Analysis and a Worldwide Haplotype Network. J Fungi (Basel) 2020; 6 (4): 204.

13. Carrion AL. Chromoblastomycosis. Ann N Y Acad Sci 1950; 50 (10): 1255-1282.

14. Queiroz-Telles F, Esterre P, Perez-Blanco M, Vitale RG, Salgado CG, Bonifaz A. Chromoblastomycosis: an overview of clinical manifestations, diagnosis and treatment. Med Mycol 2009; 47 (1): 3-15.

15. Queiroz-Telles F, Fahal AH, Falci DR, Caceres DH, Chiller T, Pasqualotto AC. Neglected endemic mycoses. Lancet Infect Dis 2017; 17 (11): e367-e377.

16. Queiroz-Telles F, Santos DW. Challenges in the therapy of chromoblastomycosis. Mycopathologia 2013; 175 (5-6): 477-488.

Chapter 12. Onchocerciasis

Authors

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Introduction

Onchocerciasis, also known as river blindness, is a vector-borne parasitic disease caused by *Onchocerca volvulus* that primarily affects the skin and eyes.[1] People who live near fast-flowing water bodies are the most exposed to the blackfly bites. In infected persons, the interaction between microfilariae and the immunological response of the host causes chronic inflammation that leads to disability, impairment, disfigurement, and stigmatization.[2]

Historical Background

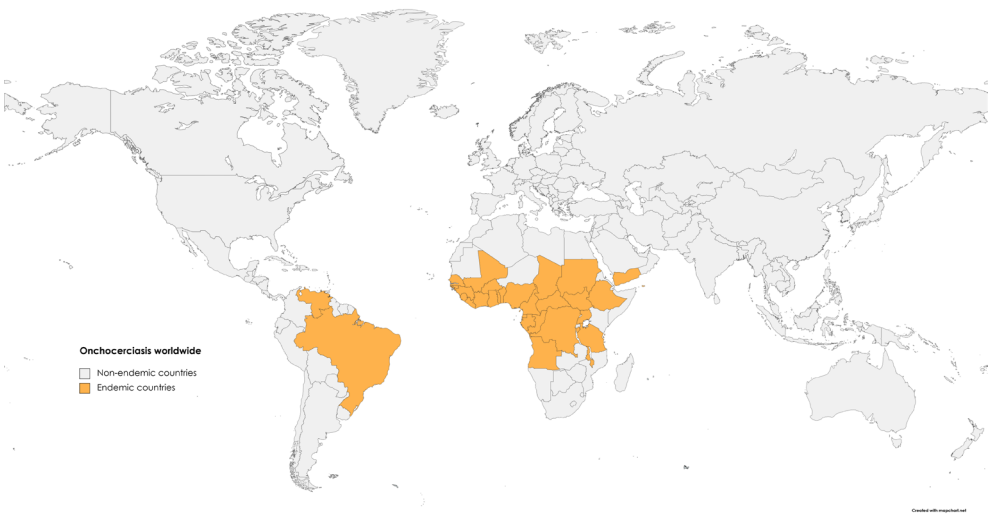
The earliest record of the disease can be traced back to the 19th century when John O'Neill described an "intractable skin disease" in Ghana in 1874; he collected samples from the papules of an infected individual and observed microfilariae on direct microscopic examination.[3] In 1890, an unknown surgeon from Ghana sent samples from nodules of an infected individual to Rudolf Leuckart, who observed male and female adult worms on direct examination. Later, Patrick Manson acknowledged this discovery and named them *Filaria volvulus*.[4] Subsequently, Raillet and Henry reassigned this species from the genus *Filaria* to the genus *Onchocerca*.[5]

Epidemiology

About 18 million people are estimated to be infected, and almost 120 million are at risk of acquiring onchocerciasis worldwide.[1] Onchocerciasis is endemic to Africa (Central and sub-Saharan Africa), America (South America), and Asia (West

Asia). As of 2019, the disease remained endemic to 30 countries, including Angola, Benin, Brazil, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, the Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Liberia, Malawi, Mali, Nigeria, Senegal, Sierra Leone, South Sudan, Sudan, Togo, Uganda, United Republic of Tanzania, Venezuela, and Yemen (Figure 1).[1, 6] The 2010 *Global Burden of Disease Study* estimated that onchocerciasis accounted for 0.49 million disability-adjusted life years, 0.49 years lived with disability, and 0 years of life lost.[7]

FIGURE 1. COUNTRIES WHERE ONCHOCERCIASIS IS ENDEMIC



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Adapted from: World Health Organization. Status of endemicity of onchocerciasis. Data by country. [Internet]. World Health Organization. [Updated: October 2019; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDONCHSTATUS?lang=en

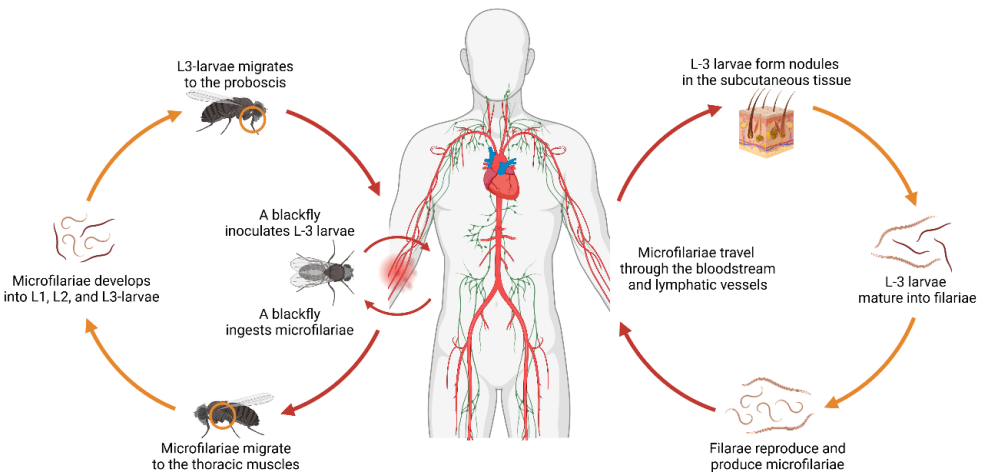
Etiology

Onchocerciasis is caused by a parasite named *Onchocerca volvulus*, which belongs to the phylum Nematoda, class Chromadorea, order Rhabditida, suborder Spirurina, infraorder Spiruromorpha, superfamily *Filarioidea*, family *Onchocercidae*, and genus *Onchocerca*.[8] Transmission is vector-borne. Transmission occurs when an infected blackfly takes a blood meal from an uninfected individual and introduces third-stage filarial larvae. Afterward, the third-stage filarial larvae pen-

etrate the cells that are allocated in the subcutaneous tissues, where they mature into filariae, undergo sexual reproduction, and produce microfilariae. The microfilariae then migrate through the bloodstream to infect new cells, mainly of the skin layers. Transmission continues when an uninfected blackfly sucks blood from an infected individual and ingests microfilariae. Subsequently, the microfilariae reach the midgut, enter the hemocoel and migrate towards the thoracic muscles, where they differentiate into first-, second-, and third-stage filarial larvae, which then migrate to the proboscis. The cycle is completed when an infected blackfly takes a blood meal from an uninfected individual and introduces third-stage filarial larvae (Figure 2).[2] Blackflies in the genus *Simulium* have been acknowledged as vectors; humans have been recognized as the only reservoir for *O. volvulus*.[9]

FIGURE 2. *ONCHOCERCA VOLVULUS* LIFE CYCLE

Onchocerciasis



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*This is a schematization of the O. *volvulus* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where onchocerciasis is endemic, the main risk factor for acquiring the disease is living in areas adjacent to fast-flowing rivers or streams. Onchocerciasis is more prevalent in men than women and in adults than children; the latter because multiple blackfly bites are needed for an individual to get infected.[10, 11]

Clinical Manifestations

The incubation period of the disease takes between 9 and 24 months. Infected individuals may experience systemic clinical manifestations such as fatigue, malaise, myalgia, arthralgia, and weight loss. If filariae form nodules in the skin, they produce dermal onchocerciasis; if filariae migrate to the eyes, they cause ocular disease:

- **Dermal onchocerciasis.** It is characterized by intense pruritus and papular rash (acute papular onchodermatitis) that lead to intense scratching, self-induced lesions, and secondary bacterial infections. Local edema and lymph node enlargement may also occur. This eventually leads to lichenification (cigarette-paper appearance) and depigmentation (leopard-like appearance) of the skin (chronic papular onchodermatitis). The shoulders, back, waist, buttocks, and lower extremities are most affected, but almost any part of the body may be involved. Chronic skin inflammation leads to atrophy; chronic inflammation of lymph nodes causes lymphatic obstruction and genital elephantiasis.
- **Ocular onchocerciasis.** It is characterized by inflammation and itching caused by microfilariae. Manifestations and complications depend on the area or structure in which microfilariae are located. Intense pruritus and punctate keratitis leading to sclerosing keratitis and corneal opacification can be experienced. Chronic anterior uveitis and secondary cataract or glaucoma that lead to blindness may also occur. The pupil might become small, deformed, and non-reactive if it adheres to the lens (posterior synechiae). Microfilariae may be observed attached to the endothelium, swimming in the aqueous humor; also, these may sink to the bottom of the anterior chamber (pseudohypopyon) or may get trapped in the vitreous. Chronic inflammation of the retina causes peripheral and central visual impairment, and chronic inflammation of the optic nerve may lead to atrophy and blindness.[9, 12]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *O. volvulus* is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic exam-

ination of at least two skin snips taken from sites where dermatitis is most evident can demonstrate the presence of microfilariae. Staining techniques such as hematoxylin and eosin can facilitate the identification of the species. Slit-lamp examination of the eyes can evidence microfilariae or damage to the cornea or anterior chamber. However, this is not useful during the acute stage of the disease.[13, 14] Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect *O. volvulus*-specific DNA sequences in skin snips and are useful to improve the sensitivity and specificity of the diagnosis when the parasite load is low or when the infection was acquired recently. However, these methods are not commercially available. Serological techniques can detect antigens produced by *O. volvulus* or antibodies produced by the host against it. Antigen detection tests are preferred over antibody detection tests as the former yield positive results only when there is an ongoing infection, while the latter cannot differentiate between previous and current infections.[12, 15] Other methods that have been used are the Mazzotti and patch tests, which consist of administering diethylcarbamazine (DEC) orally or topically to kill microfilariae and monitor the worsening of the pruritus over the next hours. The Mazzotti test can be used when other methods have tested negative, but onchocerciasis is still suspected, whereas the patch test can be used as an alternative to skin snip in areas where the disease has a low prevalence and for epidemiological surveillance.[12, 14] Supplementary examination with imaging studies such as ultrasonography can demonstrate filariae in nodules.[12]

Differential diagnosis should always be conducted to rule out other skin disease causes such as coccidioidomycosis, leprosy, lichen planus, loiasis, lymphatic filariasis, mansonelliasis, scabies, sporotrichosis, syphilis, tuberculosis, and yaws; and other ocular disease causes such as schistosomiasis, sparganosis, and taeniasis/cysticercosis, among others.[13, 16]

Treatment

Treatment consists of administering antiparasitic drugs. The first-line treatment is ivermectin (150 µg/kg orally in a single dose), which kills 99% of microfilariae but leaves filariae unaffected. To kill filariae, ivermectin should be given every 6 months for up to 10 to 15 years until the infected individual shows no signs of dermal or ocular disease.[17, 18] In areas where loiasis and onchocerciasis are en-

demic, loiasis must be resolved prior to administering ivermectin because this parasite can facilitate entry of the drug to the central nervous system. Antibiotics such as doxycycline and antiparasitic drugs such as albendazole and moxidectin have been administered as alternatives to ivermectin with promising results, but further studies are required before endorsing them as second-line treatments.[12, 13]

Prevention

No vaccine to prevent onchocerciasis is currently available. The main preventive strategies include wearing protective clothing, applying insect repellant to skin and clothes, spraying insecticide indoors and outdoors, and administering preventive drug therapy (ivermectin 150 µg/kg orally in a single dose) in high-risk populations.[1, 19]

Conclusion

Onchocerciasis is a chronic parasitic infection that mainly occurs in the African continent. Infected individuals experience chronic inflammation with dermal and ocular involvement, leading to skin atrophy and blindness. Diagnosis can be performed with simple methods, but more precise techniques are becoming available. Treatment requires ivermectin administration for up to more than a decade, and no vaccine is available for prevention. However, advances towards its control and elimination have been made in the past years. Control has been achieved in various African countries, and eradication has been successful in most Central and South American countries. Some challenges remain, including mapping transmission, suboptimal program implementation, and ivermectin resistance. The path to meeting the goals is optimistic, but efforts should be strengthened to achieve them promptly.

References

1. World Health Organization. Onchocerciasis. [Internet]. World Health Organization. Onchocerciasis. [Updated: June 2019; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/onchocerciasis

2. Centers for Disease Control and Prevention. Parasites – Onchocerciasis (also known as River Blindness). [Internet]. U.S. Department of Health & Human Services. [Updated: June 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/onchocerciasis/gen_info/faqs.html

3. O'Neil J. On the presence of a filarial in "craw craw". Lancet 1875; 1: 265-266.

4. Davidson A. Hygiene and Diseases of Warm Climates. In: Pentland YJ. Tropical Medicina. 1st edition. Edinburgh; Royal College of Physicians in Edinburgh: 1893.

5. Raillet A, Henry AC. Remarques a l'occasion de la note de M. le Dr. Antoine. Bull Soc Pathol Exot Filiales 1910; 2: 91-931.

6. World Health Organization. Status of endemicity of onchocerciasis. Data by country. [Internet]. World Health Organization. [Updated: October 2019; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDONCHSTATUS?lang=en

7. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.

8. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

9. Hopkins A, Boatin BA. Onchocerciasis. In: Selendy JMH. Water and Sanitation-Related Diseases and the Environment: Challenges, Interventions, and Preventive Measures. 1st edition. London; Wiley-Blackwell: 2011.

10. Crump A, Morel C, Omura S. The onchocerciasis chronicle: from the beginning to the end? Trends Parasitol 2012; 28 (7): 280-288.

11. Otabil KB, Gyasi SF, Awuah E, Obeng-Ofori D, Atta-Nyarko RJ, Andoh D, Conduah B, et al. Prevalence of onchocerciasis and associated clinical manifestations in selected hypoendemic communities in Ghana following long-term administration of ivermectin. BMC Infect Dis 2019; 19: 1-7.

12. Murdoch ME, Weller PF, Baron EL. Onchocerciasis [Internet]. UpToDate. Wolters Kluwer. [Updated: October 2020; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/onchocerciasis?search=onchocerciasis&source=search_result&selectedTitle=1~28&usage_type=default&display_rank=1#H5

13. Gyasi ME, Okonkwo ON, Tripathy K. StatPearls. Onchocerciasis. [Internet]. Treasure Island. [Updated: November 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559027/

14. Centers for Disease Control and Prevention. Parasites – Onchocerciasis (also known as River Blindness). Resources for Health Professionals. [Internet]. U.S. Department of

Health & Human Services. [Updated: May 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/onchocerciasis/health_professionals/index.html

15. Unnasch TR, Golden A, Cama V, Cantey PT. Diagnostics for onchocerciasis in the era of elimination. Int Health 2018; 10 (1): 20-26.

16. Smith DS, Muhammad-Shittu MI, Talavera F, King JW, Wallace MR, Lucery DR, Nettleman MD. Onchocerciasis (River Blindness) Differential Diagnoses. [Internet]. Medscape [Updated: June 2018; Reviewed: January 2021]. Available at: https://emedicine.medscape.com/article/224309-differential#1

17. Abong RA, Amambo GN, Chounna Ndongmo PW, Njouendou AJ, Manuel R, Beng A, et al. Differential susceptibility of Onchocerca volvulus microfilaria to ivermectin in two areas of contrasting history of mass drug administration in Cameroon: relevance of microscopy and molecular techniques for the monitoring of skin microfilarial repopulation within six months of direct observed treatment [published correction appears in BMC Infect Dis. 2021 Jan 18;21(1):81]. BMC Infect Dis 2020; 20 (1): 726.

18. Basáñez MG, Pion SD, Boakes E, Filipe JA, Churcher TS, Boussinesq M. Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. Lancet Infect Dis 2008; 8 (5): 310-322.

19. Centers for Disease Control and Prevention. Parasites – Onchocerciasis (also known as River Blindness). Prevention & Control. [Internet]. U.S. Department of Health & Human Services. [Updated: September 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/onchocerciasis/prevent.html

Chapter 13. Rabies

Authors

Alejandro Ortiz-Hernández, Alejandro Acuña-Macouzet, Mariana Álvarez-Sánchez, Luis-Alberto Martínez-Juárez, Diego-Abelardo Álvarez-Hernández

Introduction

Rabies is a zoonotic, life-threatening disease caused by the rabies virus (RV) that primarily affects the central nervous system (CNS). Rabies is widely distributed and mostly affects people living in rural areas together with domestic and wild animals. Although this disease is entirely preventable through vaccination and post-exposure prophylaxis (PEP), it kills tens of thousands of people every year, mainly in countries and territories lacking adequate healthcare services.[1]

Historical Background

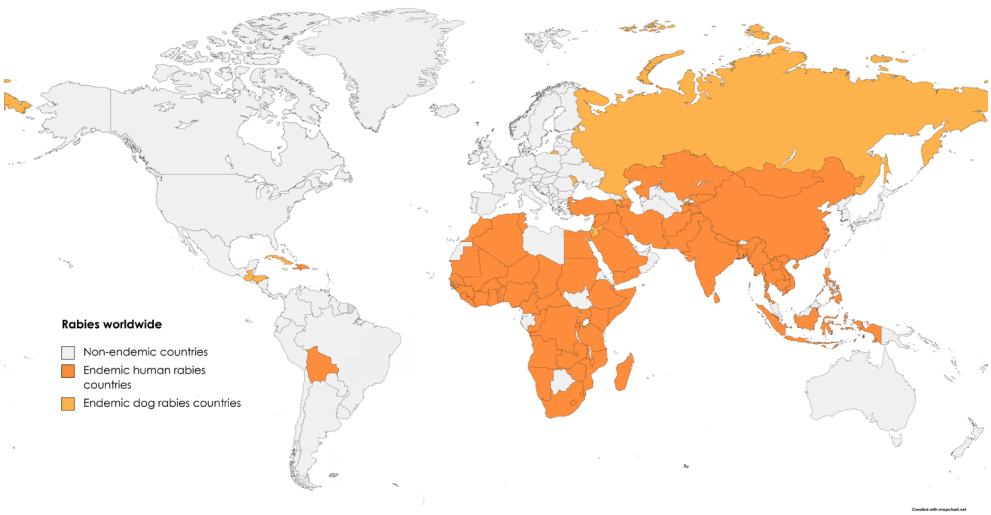
The earliest evidence of the disease can be traced back to the *Eshnunna* code (23rd century BC), which describes a "mad dog" bite linked with a human death.[2] Several historians, philosophers, and physicians have since described the clinical manifestations, put forward hypotheses about the likely transmission routes, and proposed several "preventers" and "remedies" for rabies: Homer (9th century BC), Democritus (5th century BC), Aristotle (4th century BC), Plato (4th century BC), Cicero (1st century AD), Pliny (1st century AD), and Galen (2nd century AD).[3] However, it was until 1804 that George Zinke identified the actual transmission route,[4] and until 1885 that Louis Pasteur and Émilie Roux developed the first vaccine against the virus.[5]

Epidemiology

The precise prevalence and incidence of the disease are unknown, but about 29 million people are estimated to receive a post-bite vaccination, and almost

60,000 die each year worldwide. Most deaths (99%) are dog-mediated; 95% occur in Africa and Asia, and 80% in rural communities.[6] Dog rabies is endemic to America (Cuba, Guatemala, and Honduras) and Asia (Armenia, Israel, Jordan, Moldavia, and Russia). Human rabies is endemic to Africa (Algeria, Angola, Benin, Burkina Faso, Burundi, Cambodia, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, the Democratic Republic of the Congo, Djibouti, Egypt, Eswatini, Ethiopia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mongolia, Morocco, Mozambique, Namibia, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Somalia, South Africa, Sudan, Togo, Tunisia, Turkey, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe), America (Bolivia, Dominican Republic, and Haiti), and Asia (Afghanistan, Azerbaijan, Bangladesh, China, India, Indonesia, Iran, Iraq, Kazakhstan, Kyrgyzstan, Lao People's Democratic Republic, Lebanon, Myanmar, Nepal, Pakistan, Philippines, Saudi Arabia, Sri Lanka, Syrian Arab Republic, Tajikistan, Thailand, Vietnam, and Yemen) (Figure 1).[7] The 2010 *Global Burden of Disease Study* estimated that rabies accounted for 1.46 million disability-adjusted life years, <0.01 years lived with disability, and 1.46 years of life lost.[8]

FIGURE 1. COUNTRIES WHERE RABIES IS ENDEMIC



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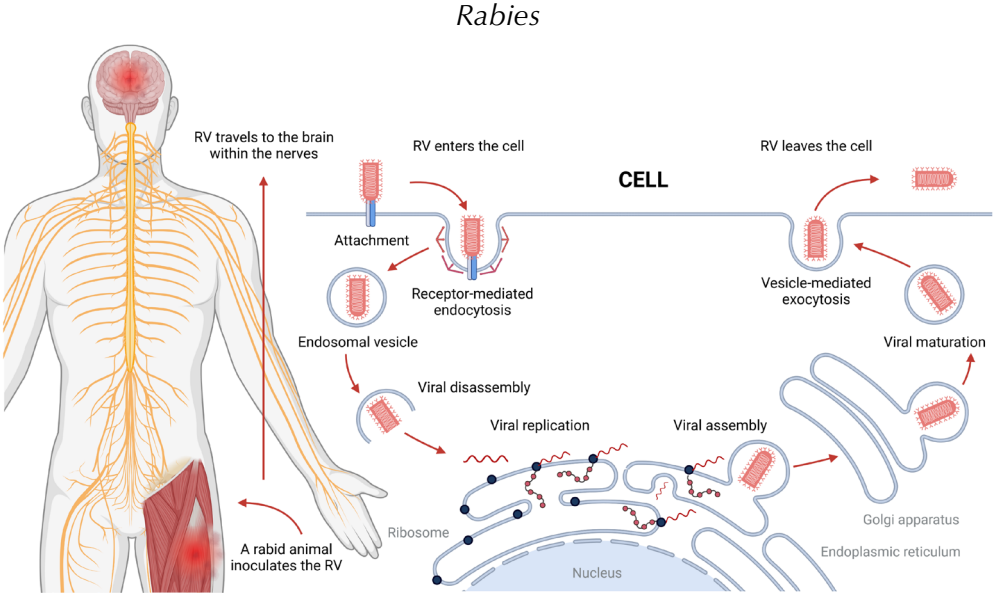
Adapted from: World Health Organization. Rabies – Presence of dog-transmitted human rabies: 2019. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/neglected_diseases/ntddata/rabies/rabies.html

Etiology

Rabies is caused by a virus named rabies virus, which belongs to the phylum Negarnaviricota, subphylum Haploviricotina, class Monjiviricetes, order Mononegavirales, family *Rhabdoviridae*, and genus *Lyssavirus*.[9] RV can be classified into two phylogroups with seven genotypes, each with a particular geographic distribution: classical RV (RV-genotype 1), Lagos bat virus (RV-genotype 2), Mokola virus (RV-genotype 3), Duvenhage virus (RV-genotype 4), European bat Lyssavirus 1 (RV-genotype 5), European bat Lyssavirus 2 (RV-genotype 6), and Australian-bat Lyssavirus (RV-genotype 7). The RV-genotype 1 is the main agent that causes disease in humans and animals worldwide; it is not viable outside the host and is inactivated by desiccation, heat, and sunlight.[10] Transmission mainly occurs when an infected animal bites an uninfected individual (Figure 2). Transmission through direct contact with saliva or brain tissue from a rabid animal, organ transplantation, and accidental exposure has also been reported. Bats, cats, coyotes, dogs, foxes, jackals, mongooses, raccoons, skunks, and wolves, among others, have been recognized as hosts.[11]

FIGURE 2. RABIES VIRUS LIFE CYCLE



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Risk Factors

In countries where rabies is endemic, the main risk factors for acquiring the disease include exposure to infected animals and close contact with saliva or brain tissue from rabid animals.[1] Rabies is more prevalent in men than women and in children than adults.[12]

Clinical Manifestations

The incubation period of the disease ranges between 1 and 3 months, but cases of infected individuals experiencing symptoms from 1 week up to 20 years after exposure have been reported. Afterward, the disease develops through two distinct stages:

- **Prodromal stage.** It is characterized by non-specific clinical manifestations such as fever, weakness, malaise, headache, and itching or prickling at the inoculation site.
- **Neurological stage.** It is characterized by specific neurological manifestations as patients undergo a unique, inevitable form:
- **Furious form.** The infected individual experiences episodes of hyperactivity with agitation, hydrophobia, and aerophobia, alternating with calm and lucid periods. Seizures, paresthesia, flaccid weakness with areflexia, hypersalivation, hyperventilation, and priapism may also be present. Death occurs 5 days after the onset of symptoms, on average.
- **Paralytic form.** It includes ascending and progressive motor weakness that involves proximal and facial muscles; coma and cardiorespiratory failure are experienced. This form of the disease is frequently mis- or undiagnosed. Death occurs 13 days after the onset of symptoms, on average.[13, 14]

Diagnosis

The epidemiological background and clinical manifestations (acute neurological syndrome dominated by hyperactivity or paralytic syndromes, which progress to coma and death 7 to 10 days after the onset of symptoms) are sufficient to make the diagnosis in the field. However, the detection of RV is required for

confirmation, and several laboratory tests are available for this purpose.[15] Electron microscopic examination of infected tissues can demonstrate the presence of bullet-shaped particles.[16] Culture techniques such as *in-vitro* cell culture in baby hamster kidney cells or mouse neuroblastoma cells can grow the RV. Molecular methods such as the polymerase chain reaction can detect RV-specific RNA sequences.[17] Serological techniques such as the fluorescent antibody test and direct rapid immunohistochemistry test can recognize antibodies against RV in biological samples.[18] Combining diagnostic methods improves the accuracy and reliability of the diagnosis but are time-consuming. As infected individuals deteriorate quickly, diagnostic methods should not delay the management of suspected cases.[19] When suitable, biological samples such as saliva, serum, spinal fluid, and skin biopsy samples of hair follicles from the base of the neck should be collected under rigorously controlled conditions to prevent accidental exposure. The preferred screening approaches include *in-vitro* culture and molecular methods for saliva samples, molecular methods and serological techniques for skin biopsies, and serological techniques for serum and spinal fluid.[20]

Differential diagnosis should always be conducted to rule out other causes of encephalitides, such as bacterial meningitis, cerebral malaria, rickettsial disease, tetanus, typhoid fever, and viral encephalitis, as well as other causes of paralysis, such as botulism, Guillain-Barre syndrome, poliomyelitis, and simian herpes type B encephalitis, among others.[21]

Treatment

Rabies is a non-treatable disease; no authorized or effective treatment is currently available after the onset of clinical manifestations. Therefore, efforts must be focused on the PEP of the suspected cases to prevent the virus from entering the CNS of the patient.[22] PEP may vary according to the severity of the contact with the suspected rabid animal (Table 1). The exposed or wounded area must be thoroughly washed for a minimum of 15 minutes with soap, water, and 10% povidone-iodine solution. The selection of a vaccine against RV should be based on its efficacy and safety profile as per the WHO standards. The administration of rabies immunoglobulin must be guided by the available resources and the dosage (20 IU/kg of human rabies immunoglobulin or 40 IU/kg of highly purified rabies immunoglobulin Fab2 fragments), and the dosing regimen should be ad-

justed as appropriate. PEP may be discontinued if the suspected rabid animal is proven to be free of rabies.[1, 23]

TABLE 1. DESCRIPTION AND MEASURES TO BE TAKEN ACCORDING TO THE RISK OF EXPOSURE TO RABIES

Categories of rabies post-exposure prophylaxis		
Category	**Description**	**Measures**
I	• Feeding or touching animals	• Washing the exposed area
II	• Nibbling of uncovered skin • Minor non-bleeding abrasions or scratches	• Washing the wounded area • Immediate vaccination
III	• Transdermal bites or scratches • Contamination of membranes or wounds with saliva from a suspect animal • Direct contact with bats	• Washing the wounded area • Immediate vaccination • Administration of rabies immunoglobulin

Adapted from: World Health Organization. Rabies. [Internet]. World Health Organization. [Updated: April 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis

Prevention

The main preventive strategies include increasing disease awareness, vaccinating animals, and administering pre-exposure immunization to people who have high-risk occupations (animal handlers, laboratory workers, and veterinarians) or who travel to highly endemic regions.[1]

Conclusion

Rabies is a disease that can be prevented through vaccination. However, the lack of adequate healthcare facilities in several communities continues to be a serious problem that unnecessarily exposes people to risk. When a case is suspected, the epidemiological background is essential to identify the root cause of the clinical manifestations as this disease can easily be misdiagnosed other other causes

of encephalitides and paralysis. Diagnosis confirmation through laboratory examination cannot always be performed due to the fast and inevitable course of the disease; confirmation is often performed post-mortem. Prompt diagnosis is essential to increase the probability of survival, as there is no effective treatment and PEP must be administered immediately. Research and development of new drugs to improve the odds of patients are required.

References

1. World Health Organization. Rabies. [Internet]. World Health Organization. [Updated: April 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/rabies
2. Théodorides J. Histoire de la rage. Med History 1987; 31 (1): 108-109.
3. Baer GM. The History of Rabies. In Jackson AC, Wunner WH. Rabies. Madrid, Spain: Elsevier; 2007.
4. Zinke G. Neue Ansichten der Hundswut, ihre Ursachen und Folgen, nebst einer sicheren Behandlungsart der von tollen Tieren gebissenen Menschen. Jena Review 1804; 16: 212-218.
5. Pasteur L. Méthode pour prévenir la rage après morsure. Compte Rendue Académie Science (Paris) 1885; 101: 765-773.
6. World Health Organization. Rabies. Epidemiology and burden of disease. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who.int/rabies/epidemiology/en/
7. World Health Organization. Rabies – Presence of dog-transmitted human rabies: 2019. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/neglected_diseases/ntddata/rabies/rabies.html
8. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.
9. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
10. Singh R, Singh KP, Cherian S, Saminathan M, Kapoor S, Manjunatha Reddy GB, Panda S, Dhama K. Rabies - epidemiology, pathogenesis, public health concerns and advances in diagnosis and control: a comprehensive review. Vet Q 2017; 37 (1): 212-251.

11. Freuling C, Vos A, Johnson N, Mühle RU, Müller T. Rabies. Animal Reservoirs of an Ancient Disease. In: Johnson N. The Role of Animals in Emerging Viral Diseases. 1st edition. London, United Kingdom: Academic Press; 2014. pp 63-87.

12. Tenzin, Dhand NK, Gyeltshen T, et al. Dog bites in humans and estimating human rabies mortality in rabies endemic areas of Bhutan. PLoS Negl Trop Dis 2011; 5 (11): e1391.

13. Médecins Sans Frontières. Clinical guidelines. Chapter 8: Viral disease. Rabies. [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/rabies-16689982.html

14. Hemachudha T, Ugolini G, Wacharapluesadee S, Sungkarat W, Shuangshoti S, Laothamatas J. Human rabies: neuropathogenesis, diagnosis, and management. Lancet Neurol 2013; 12 (5): 498-513.

15. World Health Organization. Rabies. Diagnosis. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who.int/rabies/about/home_diagnosis/en/

16. Centers for Disease Control and Prevention. Rabies. Electron microscopy. [Internet]. U.S. Department of Health & Human Services. [Updated: April 2011; Reviewed: January 2021]. Available at: https://www.cdc.gov/rabies/diagnosis/electron_microscopy.html

17. Centers for Disease Control and Prevention. Rabies. Amplification methods. [Internet]. U.S. Department of Health & Human Services. [Updated: April 2011; Reviewed: January 2021]. Available at: https://www.cdc.gov/rabies/diagnosis/amplification_methods.html

18. World Health Organization. Diagnosis of rabies [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.who-rabies-bulletin.org/site-page/diagnosis-rabies

19. DeMaria A, Brown C, Hirsch MS, Mitty J. Clinical manifestations and diagnosis of rabies. [Internet]. UpToDate. Wolters Kluwer. [Updated: October 2020; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-rabies?search=rabies&source=search_result&selectedTitle=3~90&usage_type=default&display_rank=3#H11

20. Centers for Disease Control and Prevention. Rabies. Diagnosis in animals and humans. [Internet]. U.S. Department of Health & Human Services. [Updated: September 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/rabies/diagnosis/animals-humans.html

21. Rupprecht CE. Rhabdoviruses: Rabies Virus. In: Baron S. Medical Microbiology. 4th edition. Galveston, United States of America: University of Texas Medical Branch at Galveston; 1996.

22. Weant KA, Baker SN. Review of human rabies prophylaxis and treatment. Crit Care Nurs Clin North Am. 2013 Jun; 25 (2): 225-42.

23. Zhu S, Guo C. Rabies Control and Treatment: From Prophylaxis to Strategies with Curative Potential. Viruses. 2016 Oct 28; 8 (11): 279.

Chapter 14. Scabies

Authors

Alejandro Acuña-Macouzet, Diego-Abelardo Álvarez-Hernández, Isabel Martín del Campo-Rota, Alejandro Ortiz-Hernández, Larissa-Margarita Zárate-Flores

Introduction

Scabies is a parasitic disease caused by *Sarcoptes scabiei* var. *hominis* that primarily affects the skin. It is a common dermatological condition in developing countries, but it also causes outbreaks in vulnerable communities of developed countries. Scabies can become a recurrent infection that causes stigmatization of people, impairment of health systems, and significant economic burden to all.[1]

Historical Background

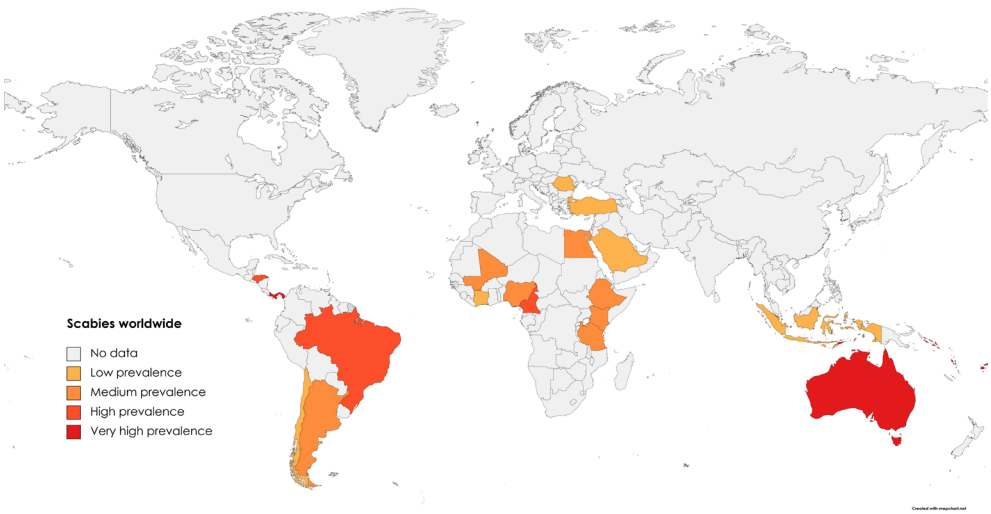
The earliest evidence of the disease can be traced back to the *Leviticus* in the Bible (1200 BC). Several philosophers and practitioners, including Aristotle, Galen, Celsus, Avenzoar, and Hauptman, commented on the characteristics of scabies. However, it was not until the 17th century when the etiological agent was first described and until the 19th century that its transmission mechanism became known.[2] In 1687, Giovanni Bonomo and Diacinto Cestoni elucidated the causal relationship between the etiological agent and the development of the disease; in 1844, Ferdinand Ritter described the life cycle of the mite and the infection stages; and in 1943, Kenneth Mellanby identified the route of transmission and demonstrated the immune response of the host.[3]

Epidemiology

About 200 million people are estimated to be infected worldwide. However, the precise prevalence is uncertain, as estimates range from 0 to 70%, depending on the study.[1] Scabies occurs in almost any country, but data are scarce due to un-

derreporting. In 2020, Daniel Engelman et al estimated that scabies is very highly prevalent (>20%) in children and adolescents under 19 years in Australia, Fiji, Panama, Solomon Islands, Timor-Leste, and Vanuatu; highly prevalent (10-19%) in Brazil, Cameroon, and Honduras; moderately prevalent (3-9%) in Argentina, Egypt, Ethiopia, Kenya, Mali, Nigeria, and Tanzania; and marginally prevalent (0-2%) in Chile, Côte d'Ivoire, Indonesia, Romania, Saudi Arabia, and Turkey. (Figure 1).[4] The 2016 *Global Burden of Disease Study* estimated that scabies accounted for 3.8 million disability-adjusted life years.[5]

FIGURE 1. PREVALENCE OF SCABIES IN CHILDREN AND ADOLESCENTS UNDER 19 YEARS WORLDWIDE



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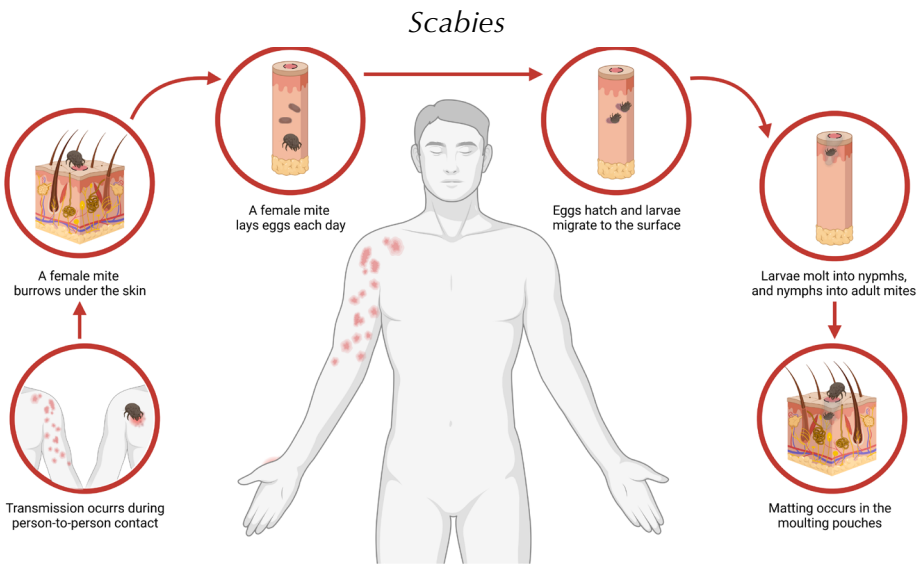
Adapted from: Engelman D, Cantey PT, Marks M, Solomon AW, Chang AY, Chosidow O, Enbiale W, et al. The public health control of scabies: priorities for research and action. Lancet 2019; 394 (10192): 81-92.

Etiology

Scabies is caused by a parasite named *Sarcoptes scabiei* var. *hominis,* which belongs to the phylum Arthropoda, subphylum Chelicerata, class Arachnida, subclass Acari, superorder Acariformes, order Sarcoptiformes, suborder Astigmata, parvorder Psoroptidae, superfamily *Sarcoptoidae*, family *Sarcoptidae,* subfamily *Sarcoptinae*, and genus *Sarcoptes*.[6] Other species can cause self-limit-

ing infestations in humans but only reproduce in other mammals. Transmission mainly occurs when an infected individual comes in direct skin-to-skin contact with an uninfected person, but transmission through fomites (bedding or clothing) has also been reported. Transmission occurs when a female mite contacts the skin of a human host, burrows under the skin, and lays her eggs. Afterward, the eggs hatch and larvae emerge to migrate towards the skin surface, where they build molting pouches. The larvae then molt and produce nymphs. Subsequently, nymphs emerge to molt again and become adult mites that undergo sexual reproduction. The adult pregnant female mites then leave their molting pouches to wander on the skin surface until they find a suitable place to burrow and lay their eggs for the rest of their lifetime (Figure 2). There is no vector, and humans are the only known reservoir for *S. scabiei* var. *hominis*.[7, 8]

FIGURE 2. *SARCOPTES SCABIEI* VAR. *HOMINIS* LIFE CYCLE



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*This is a schematization of the *Sarcoptes scabiei* var. *hominis* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where scabies is endemic, the main risk factors for acquiring the disease include crowded conditions and close contact with infected individu-

als. Scabies affects men and women equally, and there is no significant correlation with age.[9]

Clinical Manifestations

The incubation period of the disease ranges between 4 and 6 weeks in primary infection cases and between 24 and 48 hours in reinfections. Afterward, depending on the severity of the inflammatory response of the host, infected individuals may develop one of the following forms:

- **Classical or typical scabies.** This form is characterized by pruritus, which is more intense at night, and comma-like or irregular tracks with a serpiginous path, mainly on the upper (arms, armpits, elbows, wrists, fingers) and lower extremities (groins, tights, knee pits, legs, ankles, feet), genitalia, and buttocks. Lesions in the head, face, neck, hand palms, and feet soles may be observed in infants. Vesicles, pustules, and nodules can occur in children and elderly adults. Severe pruritus and "scabies nodules" can be seen in the breasts and male genitalia after reinfestation.
- **Norwegian or crusted scabies.** This form is characterized by pruritus, which is less intense than the one produced by classical scabies, with widespread crusts and scales. This uncommon form of scabies usually occurs in disabled or immunocompromised individuals and is accompanied by an overwhelming number of mites on the skin.

Pruritus caused by mites leads to continuous scratching of the skin and inoculation of resident bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*). Impetigo, abscesses, sepsis, chronic kidney damage, and rheumatic heart disease may develop if scabies is either misdiagnosed or left untreated.[10, 11]

Diagnosis

The epidemiological background and clinical manifestations are sufficient to make the diagnosis in the field, but detection of *S. scabiei* var. *hominis* is required for confirmation, and several laboratory tests are available for this purpose. Direct

methods such as dermoscopy, video dermoscopy, or microscopic examination of skin scrapings can demonstrate the presence of mites or their eggs.[12] Bedside tests such as the adhesive tape test and the burrow ink test facilitate observation of the parasite. Molecular methods like the polymerase chain reaction can detect DNA sequences specific to *S. scabiei* var. *hominis*. Serological techniques such as enzyme-linked immunosorbent assay can recognize antibodies against *S. scabiei* var. *hominis* in biological samples.[13] Combining clinical manifestations with the microorganism features observed by direct examination is the preferred approach for diagnosing scabies. The International Alliance for the Control of Scabies (IACS) criteria can be applied to determine the likelihood of having scabies (Table 1).[14] Molecular methods and serological techniques are expensive, impractical, and not fully validated because of their variable sensitivity and specificity. They should be performed only when available and in case of doubt.[13]

Differential diagnosis should always be conducted to rule out other causes of pruriginous disease, such as atopic dermatitis, contact dermatitis, dermatitis herpetiformis, folliculitis, insect bites, papular urticaria, and prurigo nodularis, among others.[13]

TABLE 1. CONDITION AND DESCRIPTION OF SCABIES LESIONS REQUIRED FOR EACH TYPE OF DIAGNOSIS

IACS diagnostic criteria for scabies		
Diagnosis	**Condition**	**Description**
Confirmed case	At least one of:	A1: Mites, eggs, or feces observed in skin samples under light microscopy
		A2: Mites, eggs, or feces observed on the skin of an individual using videoscopy
		A3: Mites observed on the skin of an individual using dermoscopy
Clinical case	At least one of:	B1: Scabies burrows
		B2: Typical lesions in male genitalia
		B3: Typical lesions in the typical location and two previous clinical features

IACS diagnostic criteria for scabies		
Diagnosis	**Condition**	**Description**
Suspected case	At least one of:	C1: Typical lesions in the typical location and one previous clinical feature
		C2: Atypical lesions or atypical location and two previous clinical features
History features	Considered as:	H1: Pruritus
		H2: Close contact with an individual with pruritus or typical lesions in the typical location

*IACS: International Alliance for the Control of Scabies. Clinical and suspected cases diagnosis of scabies should only be made if other differential diagnoses are unlikely.

Adapted from: Engelman D, Fuller LC, Steer AC. Consensus criteria for the diagnosis of scabies: a Delphi study of international experts. PLoS Negl Trop Dis 2018; 12: e0006549.

Treatment

Treatment consists of administering scabicides, change bedding and clothing after each treatment, and close contact management. The dosage regimen and special measures depend on the form of scabies:

- **Classical or typical scabies.** The first-line treatment is 5% permethrin cream applied onto the entire body once a week for 2 weeks. At least 8 hours of contact are required before rinsing in infants over 2 months of age and adults. The second-line treatment is 25% benzyl benzoate lotion applied once or twice according to the age of the patient. Information on the dosage, contact time, and the number of applications can be found in Table 2. Ivermectin (200 µg/kg orally in a single dose) is a highly effective alternative treatment that is more practical than topical creams and lotions. However, its use is limited by availability, is contraindicated in patients with loiasis, and is not recommended for pregnant women or children under 10 years of age or weighing under 15 kg. As ivermectin does not kill the eggs of *S. scabiei* var. *hominis*, a second dose should be administered 1 week later to reduce the risk of treatment failure.

TABLE 2. DILUTION, CONTACT TIME, AND NUMBER OF APPLICATIONS FOR 25% BENZYL BENZOATE BY AGE

Features	Treatment with 25% benzyl benzoate			
	Children under 2 years	Children 2–12 years	Children over 12 years	Pregnant women
Dilution	1 part of lotion 3 parts of water	1 part of lotion 1 part of water	Undiluted	Undiluted
Contact time	6 hours if <6 months of age 12 hours if >6 months of age	24 hours	24 hours	12 hours
Number of applications	One	Two*	Two*	One

*Two applications separated by 24 hours and with a rinse in between.

Adapted from: Médecins Sans Frontières. Scabies. [Internet]. MSF [Updated: 2018; Consulted: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/scabies-16689646.html

- **Norwegian or crusted scabies.** The treatment of this form is more laborious, as crusts must first be softened and removed, and scales should be exfoliated prior to the application of topical drugs. Healthcare professionals must wear personal protective equipment, patients must be isolated during treatment, and the environment must be decontaminated after treatment to avoid further contagions. The treatment regimen consists of administering 5% permethrin cream or 25% benzyl benzoate lotion combined with ivermectin at regular intervals for up to 2 to 4 weeks, depending on the clinical response of the patient.[14, 15]

Bedding and clothing must be washed with hot water (60 °C) and sun-dried for up to 3 days for both forms of the disease. If washing and drying cannot be performed, the potentially contaminated garments should be stored and sealed in a plastic bag for several days. All close contacts and household members should be treated simultaneously, regardless of their symptoms, to avoid outbreaks.[16]

Prevention

No vaccine to prevent scabies is currently available. The main preventive strategies include avoiding direct contact with infected individuals and their bedding and clothing.[16]

Conclusion

Scabies is one of the most common dermatological conditions that affect people living in developing countries but can also cause outbreaks in developed areas. Transmission of the disease during the asymptomatic period and delay in seeking medical attention during the symptomatic period are two everyday situations that can be managed through community awareness and education campaigns. The diagnosis is relatively simple, and treatment options are broadly available. However, there is an increasing concern about resistance against scabicides. With new promising drugs under investigation, healthcare professionals should find ways to increase the compliance of patients with the treatment to extend their lifetime. Individuals, institutions, and governments should strengthen their commitment to achieving full control of this disease in the next decade.

References

1. World Health Organization. Scabies. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/scabies
2. Currier RW, Walton SF, Currie BJ. Scabies in animals and humans: history, evolutionary perspectives, and modern clinical management. Ann N Y Acad Sci 201; 1230: 50-60.
3. Arilian LG, Morgan MS. A review of Sarcoptes scabiei: past, present and future. Parasites Vectors 2017; 10 (1): 297.
4. Engelman D, Cantey PT, Marks M, Solomon AW, Chang AY, Chosidow O, Enbiale W, et al. The public health control of scabies: priorities for research and action. Lancet 2019 ;394 (10192): 81-92.
5. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1260–344.

6. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

7. Centers for Disease Control and Prevention. Parasites - Scabies. Biology [Internet]. U.S. Department of Health & Human Services. [Updated: November 2010; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/scabies/biology

8. Gilson RL, Crane JS. Scabies. In: StatPearls. Treasure Island, United States; StatPearls Publishing: 2020.

9. Centers for Disease Control and Prevention. Parasites - Scabies. Epidemiology & Risk Factors. [Internet]. U.S. Department of Health & Human Services. [Updated: November 2010; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/scabies/epi.html

10. Korycinska J, Dzika E, Lepczynska M, Kubiak K. Scabies: Clinical manifestations and diagnosis. Polish Ann Med 2015; 22: 63-66.

11. Goldstein BG, Goldstein AO. Scabies: Epidemiology, clinical features, and diagnosis. [Internet]. UpToDate. Wolters Kluwer. [Updated: August 2019; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/scabies-epidemiology-clinical-features-and-diagnosis?search=scabies&source=search_result&selectedTitle=1~91&usage_type=default&display_rank=1#H5

12. World Health Organization. Scabies and other ectoparasites. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: World Health Organization. Scabies. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/scabies

13. Micali G, Lacarrubba F, Verzì AE, Chosidow O, Schwartz RA. Scabies: Advances in Noninvasive Diagnosis. PLoS Negl Trop Dis 2016; 10 (6): e0004691.

14. Engelman D, Fuller LC, Steer AC. Consensus criteria for the diagnosis of scabies: a Delphi study of international experts. PLoS Negl Trop Dis 2018; 12: e0006549.

15. Médecins Sans Frontières. Scabies. [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/scabies-16689646.html

16. Chandler DJ, Fuller LC. A Review of Scabies: An Infestation More than Skin Deep. Dermatol 2019; 235: 79-90.

17. Centers for Disease Control and Prevention. Parasites - Scabies. Prevention & Control. [Internet]. U.S. Department of Health & Human Services. [Updated: November 2010; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/scabies/prevent.html

Chapter 15. Schistosomiasis

Authors

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Introduction

Schistosomiasis, also known as bilharziasis, is an acute and chronic parasitic disease caused by *Schistosoma* spp. that primarily affects the intestinal and urogenital tracts.[1] It has been acknowledged as a public health issue in Africa, America, and Asia, where prevention and control efforts have been insufficient to reduce the burden of the disease. Besides, it has been identified as a hidden epidemic in Europe due to cases imported by migrants and travelers.[2]

Historical Background

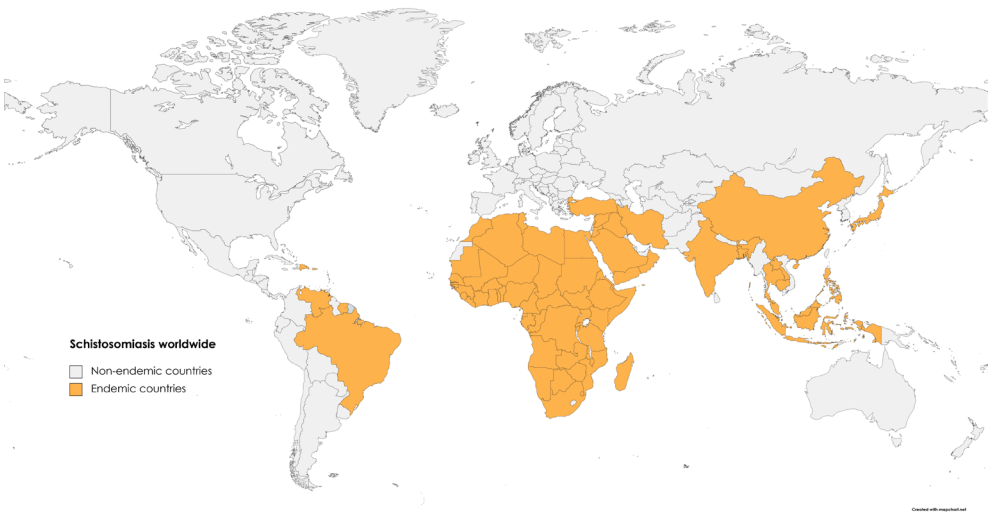
The earliest evidence of the disease can be traced back to mummies from 1250-1000 BC.[3] Several emperors and kings, including Alexander the Great and Herod the Great, have been associated with the disease. However, it was not until 1851 that Theodor Bilharz isolated the parasite from the bladder and portal system of infected individuals in Egypt. In 1847, Yoshinao Fuji described the clinical manifestations of the disease in Japan, and in 1904, Fujiro Katsurada identified that several different species can cause the disease.[4]

Epidemiology

About 200 million people are estimated to be infected, almost 780 million are at risk of acquiring the disease, and nearly 12,000 deaths are caused by schistosomiasis each year worldwide.[5] Schistosomiasis is endemic to Africa (Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, the Democratic Republic of the Congo,

Djibouti, Egypt, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Libya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Rwanda, Togo, Tunisia, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe), America (Antigua and Barbuda, Brazil, Dominican Republic, Guadeloupe, Martinique, Montserrat, Puerto Rico, Saint Lucia, Sao Tome and Principe, Suriname, and Venezuela), and Asia (Cambodia, China, India, Indonesia, Iran, Iraq, Japan, Jordan, Lao People's Democratic Republic, Lebanon, Malaysia, Oman, Philippines, Saudi Arabia, Senegal, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Syrian Arab Republic, Thailand, Turkey, and Yemen) (Figure 1).[6] The 2010 *Global Burden of Disease Study* estimated that schistosomiasis accounted for 3.31 million disability-adjusted life years, 2.99 years lived with disability, and 0.32 years of life lost.[7]

FIGURE 1. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR SCHISTOSOMIASIS



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Adapted from: World Health Organization. Neglected tropical diseases: Schistosomiasis. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://www.who.int/data/gho/data/themes/neglected-tropical-diseases/neglected-tropical-diseases-schistosomiasis

Etiology

Schistosomiasis is caused by parasites from the *Shistosoma* spp., which belong to the phylum Platyhelminthes, class Trematoda, subclass Digenea, order Strigeidida, superfamily *Schistosomatoidea*, family *Schistosomatidae*, and genus *Schistosoma*.[8] Five *Schistosoma* spp. cause disease in humans (Table 1).[1] Transmission occurs when immature *Schistoma* spp. eggs are excreted with feces or urine into water, where they hatch and release miracidia, which swim and penetrate the tegmentum of freshwater snails. Upon reaching the gastrointestinal tract, they penetrate the intestinal wall. The miracidia then differentiate into two-stage sporocysts and cercariae, which are shed into the water, where they swim and penetrate the skin of an uninfected individual. Upon reaching the subcutaneous tissues, the cercariae differentiate into schistosomula and migrate through the venous circulation to the lungs, heart, and liver, where they mature into schistosomes, undergo sexual reproduction, and produce immature eggs. Those eggs may remain in the body and cause immune reactions and organ damage or may be shed with feces or urine, depending on the infecting species. The cycle is completed when immature *Schistoma* spp. eggs are excreted with feces or urine into water (Figure 2).[9] Freshwater snails act as intermediate hosts harboring the larval stage of the parasite. Several mammalian species, including humans, cattle, cats, dogs, goats, horses, pigs, other primates, and rodents act as definitive hosts harboring the adult stage of the parasite.[10]

FIGURE 2. *SCHISTOSOMA MANSONI* LIFE CYCLE

Schistosomiasis

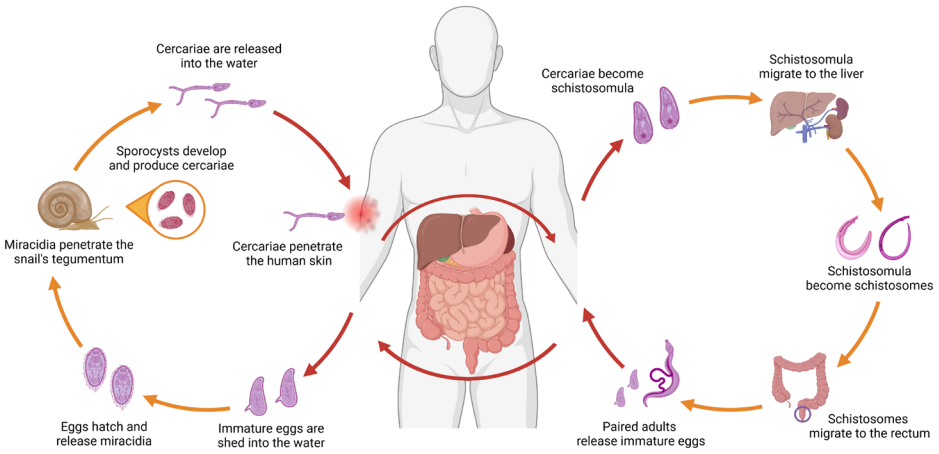

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TABLE 1. DISEASE, SPECIES, AND GEOGRAPHIC DISTRIBUTION OF THE ETIOLOGICAL AGENTS OF SCHISTOSOMIASIS

Etiological agents of schistosomiasis		
Disease	**Species**	**Distribution**
Intestinal	*S. guineensis*/ *S. intercalatum*	Central Africa
	S. japonicum	South and East Asia (China, Indonesia, and Philippines)
	S. mansoni	Africa, the Caribbean, the Middle East, and South America (Brazil, Suriname, and Venezuela)
	S. mekongi	South and East Asia (Cambodia and Lao People's Democratic Republic)
Urogenital	*S. haematobium*	Africa and the Middle East

Adapted from: World Health Organization. Schistosomiasis. [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/schistosomiasis

Risk Factors

In countries where schistosomiasis is endemic, the main risk factors for acquiring the disease include low socioeconomic status, inadequate sanitation, poor hygiene, and direct contact with unprotected water sources. Schistosomiasis affects men and women equally and is most common in children than adults.[11]

Clinical Manifestations

The incubation period of the disease ranges between 14 and 84 days. Infected individuals can remain asymptomatic or may become symptomatic. Clinically, the disease develops through two distinct stages:

- **Acute stage.** It is characterized by a systemic hypersensitivity reaction against the eggs of *Schistosoma* spp. Fever, fatigue, malaise, myalgia, headache, dry cough, pruritus, and rash are common; this syndrome is known

as Katayama fever. Gastrointestinal manifestations can be experienced after about two weeks, and neurological manifestations have also been reported. Infected individuals may recover spontaneously or may enter the chronic stage. This stage lasts between 2 and 10 weeks.

- **Chronic stage.** It is characterized by the presence of intestinal or urogenital disease, depending on the infecting species:
  - ◊ **Intestinal schistosomiasis.** Hyporexia, abdominal pain, diarrhea, tenesmus, and hematochezia are common. Weight loss, hepatomegaly, splenomegaly, hepatic fibrosis, portal hypertension, cirrhosis, and gastrointestinal bleeding have been reported in advanced cases.
  - ◊ **Urogenital schistosomiasis.** Dysuria, polyuria, and hematuria are common. Men can experience hematospermia, seminal vesiculitis, and prostatitis; women can experience genital lesions, vaginal bleeding, vaginal discharge, and dyspareunia. Infertility may occur in both. Bladder and ureter fibrosis, kidney damage, hepatocellular carcinoma, and squamous cell carcinoma of the bladder have been reported in advanced cases.

Schistosomes can be embolized to the lungs and central nervous system. If they reach the lungs, they can cause pulmonary hypertension, cor pulmonale, and cardiac enlargement. If they reach the brain, they can cause intracerebral lesions and multifocal encephalopathy; if they reach the spinal cord, they can cause transverse myelitis.[12, 13]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Schistosoma* spp. is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of stool or urine can demonstrate the presence of *Schistosoma* eggs. Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low; flotation techniques such as the FLOTAC technique may be performed to separate the eggs from stool; and quantitative techniques such as the Kato-Katz technique (KKT) can be used to estimate the infection intensity (Table 2). Direct microscopic examination com-

bined with FECT, FLOTAC, or KKT is the preferred approach for detection, but they are not useful during the acute stage of the disease. Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect *Schistosoma* spp.-specific DNA sequences in stool, urine, blood, and cerebrospinal fluid. These methods are highly sensitive and specific and can be applied during the acute stage of the disease. However, they are mainly used for research. Serological techniques can detect antigens produced by *Schistosoma* spp. or antibodies produced by the host against it. Antigen detection tests can be performed to estimate the disease intensity and assess treatment efficacy; antibody detection tests can be used during the subacute stage of the disease before the parasite eggs become detectable.[14-16]

TABLE 2. SCHISTOSOMIASIS SEVERITY GRADING BASED ON PARASITE LOAD

Grading system for schistosomiasis burden severity		
Severity	**Intestinal**	**Urogenital**
Mild	<100 eggs per gram of feces	50 eggs per 10 mL of urine
Moderate	100 – 400 eggs per gram of feces	
Severe	>400 eggs per gram of feces	>50 eggs per 10 mL

Adapted from: Clerinx J, Soentjens P, Weller PF, Baron EL. Schistosomiasis: Epidemiology and clinical manifestations. [Internet]. UpToDate. Wolters Kluwer. [Updated: December 2019; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/schistosomiasis-epidemiology-and-clinical-manifestations?sectionName=Neuroschistosomiasis&search=schistosomiasis&topicRef=5682&anchor=H3347989&source=see_link#H3347989

Supplementary examination with imaging studies such as X-rays, CT scans, magnetic resonance imaging, and ultrasonography may show the presence of underlying complications.[13]

Differential diagnosis should always be conducted to rule out other causes of gastrointestinal disease such as brucellosis, clonorchiasis, giardiasis, leptospirosis, salmonellosis, and typhoid fever, as well as other causes of urogenital disease such as acute nephritis, urogenital cancer, renal tuberculosis, and urinary tract infections, among others.[12, 13]

Treatment

Treatment consists of administering antischistosomal drugs. Praziquantel is the antischistosomal drug of choice for treating all forms of schistosomiasis. The dosage regimen is 40 mg/kg orally in a single dose (it may be divided into two doses of 20 mg/kg administered 4 hours apart) for children over 4 years of age and adults infected with *S. mansoni*, *S. intercalatum*, or *S. haematobium*; or 60 mg/kg orally in a single dose (it may be divided into three doses of 20 mg/kg administered 4 hours apart) for children over 4 years of age and adults infected by *S. japonicum* and *S. mekongi*. Administration of praziquantel in children under 4 years and pregnant women is still controversial. As praziquantel does not kill immature worms, it is recommended to repeat the dose after 2 to 4 weeks to improve the efficacy of the treatment.[17, 18] A combination of artemisinin and praziquantel has been used as an alternative to improve the efficacy of the treatment, but further studies are needed to endorse it.[19]

Follow-up should be done after 1 to 2 months to confirm the clearance of the infection.[18]

Prevention

No vaccine to prevent schistosomiasis is currently available. The main preventive strategies include avoiding swimming or wading in freshwater bodies in countries where schistosomiasis is endemic, heating water to 50 °C for 5 minutes if used for bathing or washing, implementing integrated vector management control, and administering preventive drug therapy in high-risk populations.[1, 19]

Conclusion

Schistosomiasis is one of the most prevalent parasitic infections that affect humans. Most cases have occurred in Africa, but migration and globalization have spread the disease to non-endemic countries, becoming an increasing public health issue worldwide. As many cases remain asymptomatic, epidemiological surveillance has significant relevance to identifying suspected cases of schistosomiasis. The use of accessible, low-cost, reliable screening and diagnostic tools is crucial to treat patients before complications develop. Prophylactic vaccines may

improve the control, elimination, and eradication of schistosomiasis; however, they still are in the preclinical trial stage. Integrated approaches that include the administration of preventive drug therapy are the main options currently available to fight the burden of this disease.

References

1. World Health Organization. Schistosomiasis. [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/schistosomiasis
2. Beltrame A, Buonfrate D, Gobbi F, Angheben A, Marchese V, Monteiro GB, et al. The hidden epidemic of schistosomiasis in recent African immigrants and asylum seekers to Italy. Eur J Epidemiol 2017; 32 (8): 733-735.
3. Ruffer MA. Note on the presence of "Bilharzia haematobia" in Egyptian mummies of the twentieth dynasty. Br. Med. J 1910; 1:16.
4. Coon DR. Schistosomiasis: Overview of the History, Biology, Clinicopathology, and Laboratory Diagnosis. Clin Microbiol News 2005; 27 (21): 163-169.
5. Pan American Health Organization. Schistosomiasis. [Internet]. Pan American Health Organization. [Updated: 2018; Reviewed: January 2021]. Available at: https://www.paho.org/hq/index.php?option=com_content&view=article&id=9474:schistosomiasis-factsheet&Itemid=40721&lang=en
6. World Health Organization. Neglected tropical diseases: Schistosomiasis. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://www.who.int/data/gho/data/themes/neglected-tropical-diseases/neglected-tropical-diseases-schistosomiasis
7. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.
8. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
9. Centers for Disease Control and Prevention. Parasites - Biology. [Internet]. U.S. Department of Health & Human Services. [Updated: August 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/schistosomiasis/epi.html
10. Ciddio M, Mari L, Sokolow SH, De Leo GA, Casagrandi R, Gatto M. The spatial spread of schistosomiasis: A multidimensional network model applied to Saint-Louis region, Senegal. Adv Water Resour 2017; 108: 406-415.

11. Centers for Disease Control and Prevention. Parasites - Schistosomiasis. Epidemiology & Risk Factors. [Internet]. U.S. Department of Health & Human Services. [Updated: June 2018; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/schistosomiasis/epi.html

12. Lackey EK, Horrall S. Schistosomiasis. In: StatPearls. Treasure Island, United States; StatPearls Publishing: 2020.

13. Clerinx J, Soentjens P, Weller PF, Baron EL. Schistosomiasis: Epidemiology and clinical manifestations. [Internet]. UpToDate. Wolters Kluwer. [Updated: December 2019; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/schistosomiasis-epidemiology-and-clinical-manifestations?sectionName=Neuroschistosomiasis&search=schistosomiasis&topicRef=5682&anchor=H3347989&source=see_link#H3347989

14. Weerakoon KG, Gobert GN, Cai P, McManus DP. Advances in the Diagnosis of Human Schistosomiasis. Clin Microbiol Rev 2015; 28 (4): 939-967.

15. Nelwan ML. Schistosomiasis: Life Cycle, Diagnosis, and Control. Curr Ther Res Clin Exp 2019; 91: 5-9.

16. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Public Health Concern. Schistosomiasis. [Internet]. U.S. Department of Health & Human Services. [Updated: August 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/dpdx/schistosomiasis/index.html

17. Médecins Sans Frontières. Clinical guidelines / Chapter 6. Parasitic disease. Schistosomiasis. [Internet]. Médecins Sans Frontières. [Updated: May 2020; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/schistosomiases-16689787.html

18. Centers for Disease Control and Prevention. Parasites - Schistosomiasis. Resources for Health Professionals. [Internet]. U.S. Department of Health & Human Services. [Updated: October 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/schistosomiasis/health_professionals/index.html#tx

19. Ross AG, Vickers D, Olds GR, Shah SM, McManus DP. Katayama syndrome. Lancet Infect Dis 2007; 7: 218-224.

Chapter 16. Sleeping Sickness

Authors

Alejandro Ortiz-Hernández, Diego-Abelardo Álvarez-Hernández, Mariana Álvarez-Sánchez, Rodolfo García-Rodríguez-Arana, Luis-Alberto Martínez-Juárez

Introduction

Sleeping sickness (SS), also known as African trypanosomiasis, is a parasitic disease caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* that primarily affects the central nervous system (CNS). It is endemic to African countries, where it mostly infects people living in poor, neglected communities where tsetse flies are common.[1] SS is considered a significant public health issue due to its presence in populations with inadequate healthcare services, making it difficult to diagnose, treat, and monitor.[2]

Historical Background

Phylogenetic studies suggest that salivarian trypanosomes have thrived on Earth for almost 300 million years and tsetse flies for nearly 35 million years.[3] The earliest description of the disease in animals can be traced back to the *Veterinary Papyrus* of the *Kahun Papyri* (20th century BC)[4], and the disease in humans was first described in a case report by Ibn Khaldun in the Middle Ages (14th century AD).[5] Afterward, the disease was related to slavery trading, and several doctors and physicians, including John Atkins and Thomas Winterbottom, described infected individuals with disease-related symptoms.[6] However, it was until 1895 that David Bruce first isolated the parasite from cattle,[7] and until 1901 that Robert Forde isolated the parasite from humans.[8]

Epidemiology

Almost 20,000 people are estimated to be infected, and more than 36 million are at risk of acquiring the disease worldwide. SS due to *T. brucei gambiense* ac-

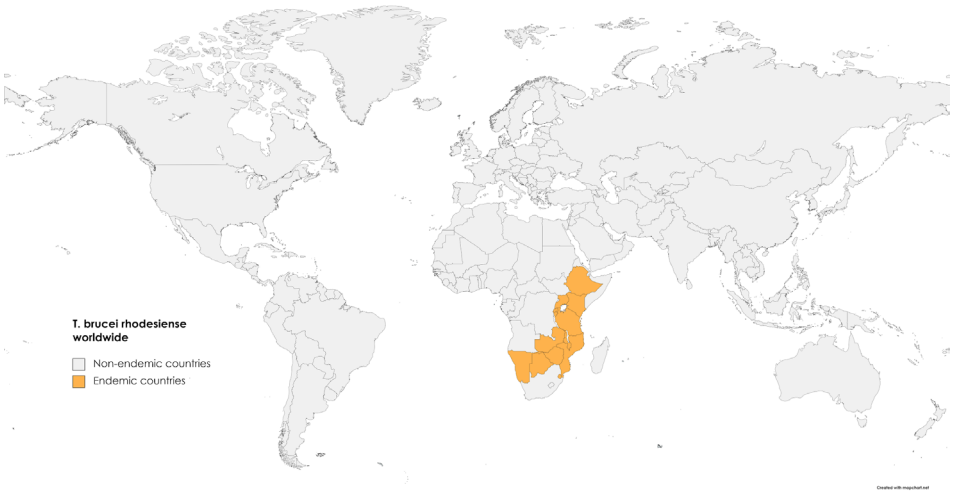
counts for 98% of the reported cases and is endemic to 24 countries in Central and West Africa (Figure 1). SS due to *T. brucei rhodesiense* accounts for 2% of the reported cases and is endemic to 13 countries in Eastern and Southern Africa (Figure 2).[9] The precise prevalence of the disease is unknown. While more than 10,000 cases were reported in 2009, the number of new cases has been declining since then: a total of 2,729 cases of SS caused by *T. brucei gambiense* were reported in 2015; 2,110 in 2016; 1,409 in 2017; 874 in 2018; and 876 in 2019. The cases reported in 2019 occurred in 12 countries: The Democratic Republic of the Congo (613 cases), Central African Republic (86 cases), Guinea (69 cases), Angola (30 cases), Cameroon (20 cases), Congo (17 cases), Chad (16 cases), South Sudan (11 cases), Gabon (8 cases), Equatorial Guinea (3 cases), Uganda (2 cases), and Côte d'Ivoire (1 case). On the other hand, 72 cases of SS caused by *T. brucei rhodesiense* were reported in 2015; 54 in 2016; 27 in 2017; 24 in 2018; and 116 in 2019. The cases reported in 2019 occurred in 5 countries: Malawi (91 cases), Zambia (15 cases), Uganda (5 cases), United Republic of Tanzania (3 cases), and Zimbabwe (2 cases).[10] The 2010 *Global Burden of Disease Study* estimated that SS accounted for 0.56 million disability-adjusted life years, 0.08 years lived with disability, and 0.55 years of life lost.[11]

FIGURE 1. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR T. *BRUCEI GAMBIENSE*

Created with MapChart.net

Adapted from: World Health Organization. Global Health Observatory Data Repository. Human African trypanosomiasis. [Internet]. World Health Organization [Updated: November 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.A1635

FIGURE 2. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR T. *BRUCEI RHODESIENSE*



Created with MapChart.net

Adapted from: World Health Organization. Global Health Observatory Data Repository. Human African trypanosomiasis. [Internet]. World Health Organization [Updated: November 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.A1635

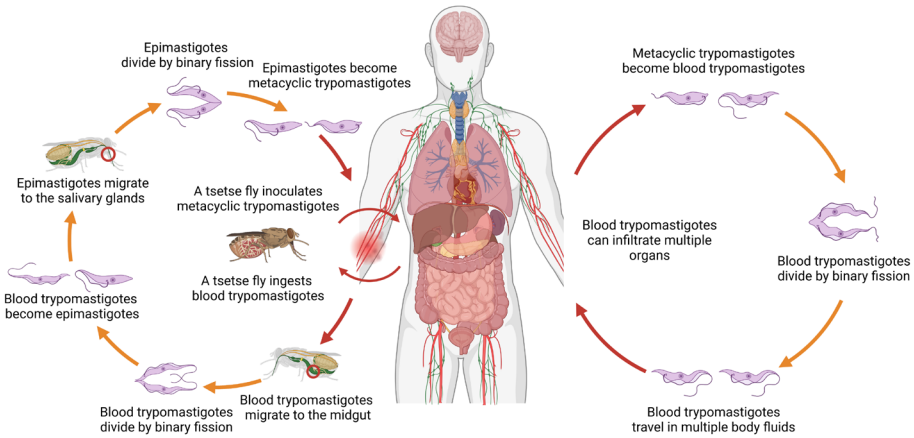
Etiology

SS is caused by parasites named *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, which belong to the phylum Euglenozoa, class Kinetoplastea, subclass Metakinetoplastina, order Trypanosomatida, family *Trypanosomatidae*, genus *Trypanosoma*, and species *Trypanosoma brucei*.[12] *T. brucei* is an obligate extracellular protozoan; it comprises one subspecies (*T. brucei brucei*) that causes disease in animals and two subspecies that cause disease in humans (*T. brucei gambiense* and *T. brucei rhodesiense*).[13] The disease is mainly vector-borne. Transmission occurs when an infected tsetse fly sucks blood from an uninfected individual and introduces metacyclic trypomastigotes. Afterward, metacyclic trypomastigotes enter the lymphatic system, pass into the bloodstream, differentiate into blood trypomastigotes, and replicate by binary fission. The blood trypomastigotes then infiltrate the interstitial space and reach several organs and tissues, including the skin, heart, testes, and adipose tissue.

Transmission continues when an uninfected tsetse fly takes a blood meal from an infected individual and ingests blood trypomastigotes. Subsequently, blood trypomastigotes migrate to the midgut, differentiate into procyclic trypomastigotes, and replicate by binary fission. The procyclic trypomastigotes then leave the midgut, transform into epimastigotes, migrate towards the salivary glands, replicate by binary fission, and differentiate into metacyclic trypomastigotes. The cycle is completed when the infected tsetse fly sucks blood from an uninfected individual and introduces metacyclic trypomastigotes (Figure 3).[14] Only flies in the genus *Glossina* (*G. palpalis* spp. and *G. fuscipes* spp.) have been identified as vectors; humans are the main reservoir for *T. brucei gambiense*, and cattle for *T. brucei rhodesiense*. Transmission through blood transfusion or organ transplantation, from mother to child, through sexual intercourse, and by accidental exposure has also been reported.[15]

FIGURE 3. *T. BRUCEI GAMBIENSE* AND *T. BRUCEI RHODESIENSE* LIFE CYCLE

Sleeping sickness



Created with BioRender.com

Risk Factors

In countries where SS is endemic, particularly in areas adjacent to lakes or ponds, the main risk factors for acquiring the disease include having domestic animals, fishing, raising livestock, and being bitten by tsetse flies. SS is more prevalent in men than women and in adults than children[16]

Clinical Manifestations

The incubation period of the disease caused by *T. brucei gambiense* ranges from weeks to months, and in the disease caused by *T. brucei rhodesiense*, between 1 and 3 weeks. Afterward, a trypanosomal chancre may develop at the inoculation site. Clinically, SS develops through two distinct stages:

- **Primary stage.** It is known as the hemolymphatic stage, characterized by the dissemination of trypanosomes through the bloodstream and lymphatic vessels. Non-specific clinical manifestations such as fever (intermittent and relapsing), fatigue, malaise, weakness, myalgia, arthralgia, headache, facial edema, lymph node enlargement (submandibular, cervical, subclavicular, axillar, inguinal or epitrochlear regions), hepatomegaly, splenomegaly, and weight loss can be experienced. Cardiac involvement has been reported. This stage lasts 526 days for *T. brucei gambiense* and 40 days for *T. brucei rhodesiense*, on average.
- **Secondary stage.** It is known as the meningoencephalitis stage, characterized by the penetration of trypanosomes into the CNS. Specific clinical manifestations such as psychiatric disorders (agitation, aggression, anxiety, apathy, attention deficit, confusion, and emotional lability), disturbance of the sleep cycle (daytime somnolence and nighttime insomnia), sensory disturbances (anesthesia, hyperesthesia, paresthesia, and visual impairment), motor disturbances (abnormal tone, aphasia, ataxia, gait disturbance, motor weakness, tremors, and seizures), and neuroendocrine disorders (amenorrhea or impotence) may be experienced.[17, 18]

The above stages are similar for both species. The main difference between them is that the disease caused by *T. brucei gambiense* progresses more slowly and with less severe clinical manifestations (infected individuals may experience coma and die if untreated) than the disease caused by *T. brucei rhodesiense* (infected individuals may experience myocarditis and die without developing the secondary stage).[17, 18]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *T. brucei* spp. is required for confirmation, and

several laboratory tests are available for this purpose. Serological techniques that detect antigens produced by *T. brucei* spp. or antibodies produced by the host against it are the preferred approach for screening. Rapid diagnostic tests such as the card agglutination test and the rapid lateral-flow test can be performed to detect antibodies against *T. brucei gambiense* in remote settings. The enzyme-linked immunosorbent assay and the indirect immunofluorescent assay can be performed to detect antibodies against *T. brucei gambiense* and *T. brucei rhodesiense* in clinical settings; if these assays test positive, confirmation must be done by direct microscopic examination, culture techniques, or molecular methods. Samples must be taken from body fluids, chancres, or lymph nodes. Then, direct microscopic examination of a blood smear or wet mount preparations or Giemsa-stained smears can demonstrate the presence of trypomastigotes. Concentration techniques such as microhematocrit centrifugation (mHCT) or mini anion-exchange centrifugation (mAECT) may be necessary when the parasite load is low. If trypanosomes are detected, the epidemiological background will help identify the infecting species, as both species have identical morphology. Culture techniques such as fluid culture in HMI-11 or TbM50 media or feeding uninfected tsetse flies with blood from a presumably infected individual can grow epimastigotes and trypomastigotes. However, these methods are time-consuming and are mainly used for research. Molecular methods such as the loop-mediated isothermal amplification and polymerase chain reaction can detect DNA sequences specific to *T. brucei* and may be used to identify the infecting species when available.[19, 20]

Once the disease has been confirmed, staging is required. Clinical examination is carried out to assess whether infected individuals are in the primary or secondary stage and suffer a mild, moderate, or severe disease (confusion, anxiety, aphasia, ataxia, gait disturbance, motor weakness, or tremors). If secondary stage with severe disease is suspected, a lumbar puncture must be performed to count white blood cells (WBC) in cerebrospinal fluid (CSF) (Table 1). Infected individuals with fewer than 100 WBC/mm^3 are in the secondary stage and present with a mild to moderate disease; individuals with more than 100 WBC/mm^3 are in the secondary stage and present with severe disease.[21]

Supplementary examination with imaging studies such as X-rays, computerized tomography, and magnetic resonance may demonstrate lesions in the brain.[18]

Differential diagnosis should always be conducted to rule out other causes of intermittent and relapsing fever, such as babesiosis, brucellosis, cryptococ-

cosis, dengue, ehrlichiosis, malaria, toxoplasmosis, tuberculosis, typhoid fever, and yellow fever.[22]

TABLE 1. STEPS FOR DIAGNOSING SS CAUSED BY *T. BRUCEI GAMBIENSE* AND *T. BRUCEI RHODESIENSE*

Diagnosis of sleeping sickness		
Species	***T. brucei gambiense***	***T. brucei rhodesiense***
Steps for diagnosis	1. Screening testing with serological methods: card-agglutination trypanosomiasis test 2. Diagnosis with direct parasitological methods: aspirates of lymph nodes from the cervical region 3. Staging with clinical examination: lumbar puncture if secondary stage with severe disease* is suspected	Diagnosis with direct parasitological methods: Giemsa-stained concentrated blood smears Staging with clinical examination: lumbar puncture if secondary stage with severe disease* is suspected

*Severe disease: confusion, anxiety, aphasia, ataxia, gait disturbance, motor weakness, or tremors.

Adapted from: World Health Organization. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva, Switzerland: WHO 2019.

Treatment

Treatment depends on the disease stage and the infecting species (Table 2):

- **Primary stage.** Treatment consists of hydration, nutritional support, and administration of organic sulfonate salts, inhibitors of DNA synthesis, or polysulphonated napthylureas.
- **Secondary stage.** Treatment consists of hydration, nutritional support, and administration of trypanocidal agents.[21, 23]

Follow-up for up to 24 months is recommended, in which clinical assessment and laboratory examination of blood samples, lymph node aspirates, and CSF should be performed, as needed.[1]

TABLE 2. TREATMENT OF SS CAUSED BY *T. BRUCEI GAMBIENSE* AND *T. BRUCEI RHODESIENSE*

Treatment of sleeping sickness			
Stage	**Patient condition**	***T. brucei gambiense***	***T. brucei rhodesiense***
Primary	<6 years or <20 kg	Pentamidine isethionate (4 mg/kg intramuscularly every 24 hours for 7–10 days)	Suramin (4–5 mg/kg intravenously as on day 1 to test for anaphylaxis, followed by 20 mg/kg intravenously in a single dose on days 3, 10, 17, 24, and 31)
	>6 years and >20 kg	Fexinidazole (1,200 mg orally every 24 hours for 4 days followed by 600 mg orally every 24 hours for 6 days if body weight is 20–34 kg, or 1,800 mg orally every 24 hours for 4 days followed by 1,200 mg orally every 24 hours for 6 days if body weight is over 34 kg)	
Secondary	<6 years or <20 kg with mild to moderate disease	Nifurtimox (15 mg/kg orally divided into three doses every 24 hours for 10 days) + eflornithine (200 mg/kg intravenously in infusion every 12 hours for 14 days)	Melarsoprol (2.2 mg/kg intravenously every 24 hours for 10 days) + prednisolone (1 mg/kg orally every 24 hours for 10 days)
	>6 years and >20 kg with non-severe disease	Fexinidazole (1,200 mg orally every 24 hours for 4 days followed by 600 mg orally every 24 hours for 6 days if body weight is 20–34 kg, or 1,800 mg orally every 24 hours for 4 days followed by 1,200 mg orally every 24 hours for 6 days if body weight is over 34 kg)	
	Severe disease	Nifurtimox (15 mg/kg orally divided in three doses every 24 hours for 10 days) + eflornithine (200 mg/kg intravenously in infusion every 12 hours a day for 14 days)	

Adapted from: World Health Organization. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva, Switzerland: WHO 2019.

Prevention

No vaccine to prevent SS is currently available. The main preventive strategies include avoiding areas infested with tsetse flies, avoiding bushes during the hottest hours of the day, wearing protective clothing, applying insect repellant to skin and clothes, sleeping inside insecticide-treated bed nets, and spraying insecticide in living/sleeping areas.[24]

Conclusion

SS is a significant public health issue in African countries. However, as the number of reported cases has been declining over the past decade, the interruption of transmission of the disease caused by *T. brucei gambiense* and elimination of the disease caused by *T. brucei rhodesiense* as a public health problem have been set as achievable goals for 2030. Diagnosis for *T. brucei gambiense* has been simplified and can now be performed in the field with accessible, low-cost, and reliable diagnostic tools. However, similar screening tools for *T. brucei rhodesiense* still need to be developed. Moreover, fexinidazole has emerged as an effective, non-invasive treatment for the primary and secondary stages of mild to moderate disease caused by a *T. brucei gambiense* infection. An optimal drug with a similar profile for *T. brucei rhodesiense* is still required. Integrated vector-control measures must be strengthened to meet the targets set.

References

1. World Health Organization. Trypanosomiasis, human African (sleeping sickness). [Internet]. World Health Organization. [Updated: February 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)
2. World Health Organization. Ending the Neglect to Attain the Sustainable Development Goals. A Road Map for Neglected Tropical Diseases 2021-2030. Geneva, Switzerland: World Health Organization; 2020.
3. Lambrecht FL. Trypanosomes and hominid evolution. Bioscience 1985; 35: 640-646.
4. Ebbell B. The papyrus Ebers The greatest Egyptian medical document. 1st edition. Copenhagen; Levin & Munksgaard: 1937.

5. Williams BI. African trypanosomiasis. In: Cox FEG. The Wellcome Trust Illustrated History of Tropical Diseases. 1st edition. London; The Wellcome Trust: 1996.

6. Steverding D. The history of African trypanosomiasis. Parasit Vectors 2008; 1 (1): 3.

7. Bruce D. Preliminary report on the tsetse fly disease or nagana in Zululand. 1st edition. Durban; Bennett and Davis: 1895.

8. Forde RM. Some clinical notes on a European patient in whose blood a trypanosome was observed. J Trop Med 1902; **5**: 261–263.

9. World Health Organization. Human African trypanosomiasis (sleeping sickness). [Internet]. World Health Organization. [Updated: November 2020; Reviewed: January 2021]. Available at: https://www.who.int/health-topics/human-african-trypanosomiasis#tab=tab_1

10. World Health Organization. Global Health Observatory Data Repository. Human African trypanosomiasis. [Internet]. World Health Organization [Updated: November 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.A1635

11. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.

12. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

13. Rijo-Ferreira F, Takahashi JS. Sleeping Sickness: A Tale of Two Clocks. Front Cell Infect Microbiol 2020; 10: 525097.

14. Centers for Disease Control and Prevention. Parasites - African trypanosomiasis (also known as Sleeping Sickness). Biology. [Internet]. U.S. Department of Health & Human Services. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/sleepingsickness/biology.html

15. Franco JR, Simarro PP, Diarra A, Jannin JG. Epidemiology of human African trypanosomiasis. Clin Epidemiol. 2014; 6: 257-275.

16. Uba BV, Aliyu A, Abubakar A, Uba SA, Gidado S, Edukugho A, et al. Knowledge and prevalence of Human African Trypanosomiasis among residents of Kachia grazing reserve, Kachia local government area, Kaduna state, Nigeria 2012. Pan Afr Med J 2016; 23: 89.

17. Dunn N, Wang S, Adigun R. African Trypanosomiasis. In: StatPearls. Treasure Island, United States; StatPearls Publishing: 2020.

18. Krishna S, Lindner A, Lejon V, Weller PF, Baron EL. Schistosomiasis: Epidemiology and clinical manifestations. [Internet]. UpToDate. Wolters Kluwer. [Up-

dated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/human-african-trypanosomiasis-epidemiology-clinical-manifestations-and-diagnosis?search=sleeping%20sickness&source=search_result&selectedTitle=1~96&usage_type=default&display_rank=1#H2969922244

19. Centers for Disease Control and Prevention. Parasites - African trypanosomiasis (also known as Sleeping Sickness). Resources for Health Professionals. Diagnosis. [Internet]. U.S. Department of Health & Human Services. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/sleepingsickness/disease.html

20. Bonnet J, Boudot C, Courtioux B. Overview of the Diagnostic Methods Used in the Field for Human African Trypanosomiasis: What Could Change in the Next Years? BioMed Research International 2015; 1: 1-10.

21. World Health Organization. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva, Switzerland: WHO 2019.

22. Maxfield L, Bermudez R. StatPearls. Trypanosomiasis. [Internet]. StatPearls Publishing; [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK535413/

23. Médecins Sans Frontières. Human African trypanosomiasis (sleeping sickness). [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/human-african-trypanosomiasis-sleeping-sickness-16689763.html

24. Centers for Disease Control and Prevention. Parasites - African trypanosomiasis (also known as Sleeping Sickness). Prevention & Control. [Internet]. U.S. Department of Health & Human Services. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/sleepingsickness/prevent.html

Chapter 17. Soil-Transmitted Helminthiasis

Authors

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Soil-transmitted helminthiasis includes the parasitic diseases ancylostomiasis, ascariasis, and trichuriasis. They occur mainly in Africa, America, and Asia, where they are highly prevalent. Transmission occurs when an uninfected individual ingests soil, raw vegetables, or water contaminated with hookworms, roundworms, or whipworms. Hookworms can also be transmitted by direct contact when an uninfected individual walks barefoot on soil that contains filariform larvae. The incubation period is variable. Clinical manifestations depend on the parasite burden and the stage of the disease. Some infected individuals experience a pulmonary stage, but all undergo a gastrointestinal stage in which malnutrition and its consequences are expected. Diagnosis requires considering the epidemiological background and clinical manifestations, but confirmation can only be done by direct microscopic examination. Molecular methods can be used for the identification of species, and serological methods are under development. Imaging studies are useful to identify the presence of parasites. Anthelmintic drugs such as albendazole and mebendazole are highly effective against helminthiasis, but recurrence is common. No prophylactic or therapeutic vaccines are currently available for any of these diseases.

ANCYLOSTOMIASIS

Introduction

Ancylostomiasis, also known as hookworm disease, is a parasitic soil-borne disease caused by *Ancylostoma* spp. and *Necator americanus* that primarily affects the respiratory and gastrointestinal tracts. The persons most at risk of ac-

quiring the disease are those living in remote areas where inadequate sanitation and poor hygiene habits prevail. Infected individuals experience severe morbidity that degrades their life quality: children development is impaired, and adults reduce their economic productivity, becoming a burden for families and communities.[1]

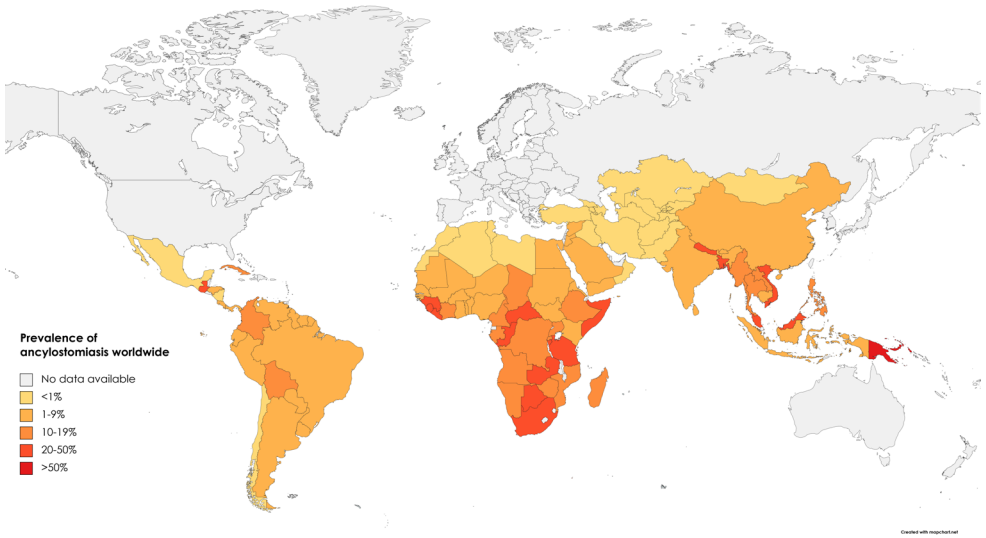
Historical Background

The earliest reports of the disease can be traced back to the *Corpus hippocraticum* (450–350 BC), in which eating dirt was associated with developing yellowish skin and intestinal distress. In 1813, Angelo Dubini isolated hookworms from the intestinal tract of an infected individual while performing an autopsy; he named them *Ancylostoma duodenale*. In 1898, Arthur Loss described the route of transmission; and in 1902, Charles Stiles isolated a different hookworm species from the intestinal tract of infected agricultural workers; he named it *Necator americanus*.[2]

Epidemiology

About 500 million people are estimated to be infected, and almost 5 billion are at risk of acquiring the disease.[3] Ancylostomiasis has a worldwide distribution but is endemic to Africa, America, and Asia. Among the species that can infect humans, *N. americanus* accounts for most of the cases.[4] In 2010, Rachel Pullan et al. estimated its prevalence (Figure 1); of the regions studied, the highest prevalence was found in Asia (281.8 million cases), followed by sub-Saharan Africa (117.7 million cases), Latin America and the Caribbean (30.3 million cases), North Africa, the Middle East (4.6 million cases), and Oceania (4.6 million cases).[5] The 2010 *Global Burden of Disease Study* estimated that the hookworm disease accounted for 3.23 million disability-adjusted life years, 3.23 years lived with disability, and 0 years of life lost.[6]

FIGURE 1. PREVALENCE OF ANCYLOSTOMIASIS WORLDWIDE



Created with MapChart.net

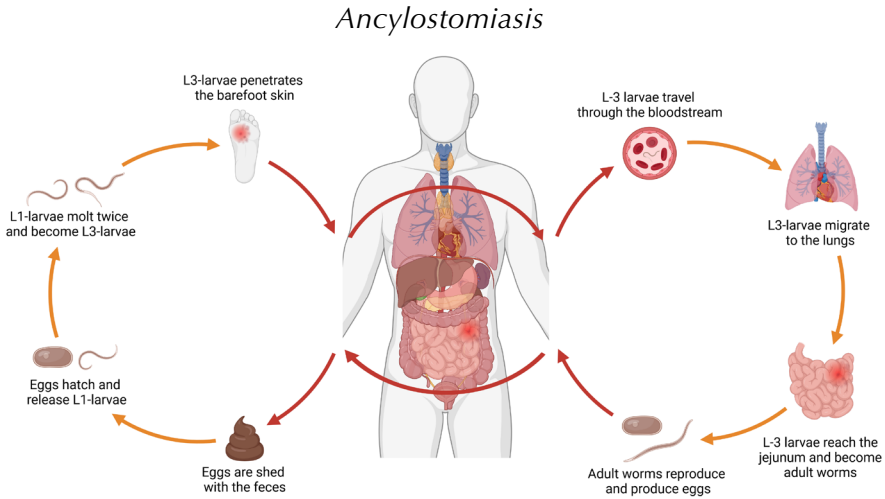
Adapted from: Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014; 7 (37): 1-19.

Etiology

Ancylostomiasis is caused by parasites named *Ancylostoma ceylanicum, Acylostoma duodenale*, and *Necator americanus*, which belong to the phylum Nematoda, class Chromadorea, order Strongylida, superfamily *Ancylostomatoidea*, family *Ancylostomatidae*, subfamilies *Ancylostomatinae* and *Bunostominae*, and genera *Ancylostoma* and *Necator*, respectively.[7] The disease is soil-borne. Transmission occurs by direct contact when an uninfected individual walks barefoot on soil that contains filariform larvae. Afterward, they penetrate the skin and travel through the bloodstream to reach the heart and lungs. Upon reaching the lungs, the filariform larvae penetrate the alveoli and ascend through the tracheobronchial tree to reach the oropharynx, where they get swallowed. Upon reaching the jejunum, they mature into adult worms, which attach to the intestinal wall, and undergo sexual reproduction to produce embryonated eggs that are excreted with the feces onto the soil. Subsequently, the eggs hatch and release rhabditiform larvae, which molt twice to become filariform larvae. The cycle is completed when an uninfected individual walks barefoot on soil that contains filariform

larvae (Figure 2). Oral infection also occurs after ingesting contaminated soil or unwashed, unpeeled, or raw vegetables; or from drinking untreated water that contains filariform larvae. Humans are the main reservoir of *A. duodenale* and *N. americanus*; cats, dogs, and humans are the main reservoirs of *A. ceylanicum*.[8]

FIGURE 2. *ANCYLOSTOMA DUODENALE* LIFE CYCLE



Created with BioRender.com

*This is a schematization of the *A. duodenale* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where ancylostomiasis is endemic, the main risk factors for acquiring the disease include low socioeconomic status, lack of sanitation, open defecation, using human feces as fertilizers, walking barefoot, drinking untreated water, and consuming unwashed, unpeeled, or raw vegetables. Ancylostomiasis affects men more frequently than women and is most common in children than adults.[1,9]

Clinical Manifestations

The incubation period of the disease ranges from weeks to months. Afterward, some infected individuals can remain asymptomatic if the parasite load is low or

may become symptomatic if the parasite load is high. Clinically, the disease develops through four distinct stages:

- **Cutaneous stage.** When larvae penetrate the skin, they can cause a pruritic erythematous maculopapular or papulovesicular rash in feet, known as "ground itch." When they migrate through the subcutaneous tissues, they can also leave intracutaneous serpiginous tracks. This stage appears in the first or second week after skin penetration.
- **Respiratory stage.** When larvae reach the lungs, they can cause fever, sore throat, cough, and wheezing. They can also cause paroxysmal attacks of fever, dyspnea, cough, hemoptysis, pleurisy, and eosinophilic pulmonary infiltrates (known as "Loeffler's syndrome") or pharyngeal itching, hoarseness, dyspnea, cough, nausea, vomiting, and eosinophilia (known as "Wakana disease"); the latter occurs when transmission is by oral ingestion. This stage appears in the second week after skin penetration.
- **Gastrointestinal stage.** When larvae reach the gastrointestinal tract, they can cause anorexia, nausea, vomiting, abdominal discomfort, abdominal pain, flatulence, and diarrhea. They can also lead to gastrointestinal bleeding if the parasite load is very high. Gastrointestinal clinical manifestations tend to be intense during the initial infection and gradually disappear in case of reinfections. This stage appears in the fifth week after skin penetration.
- **Chronic nutritional stage.** When larvae have been living in the host for a long time, they can cause chronic blood loss and iron deficiency that leads to anemia and protein loss in which fatigue, syncope, headache, dyspnea, palpitations, melena, edema of the limbs, and pallor may be experienced. It can also lead to low birth weight and retardation in growth and mental development if pregnant women and children are left untreated. This stage appears in the first month after skin penetration.[10, 11]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of eggs of *Ancylostoma* spp. or *Necator americanus* is required for confirmation, and several laboratory tests are available for this

purpose. Direct microscopic examination of stool samples can demonstrate the presence of hookworm eggs. Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low; flotation techniques such as the FLOTAC technique may be performed to separate the eggs from stool. Quantitative techniques such as the Kato-Katz technique (KKT) may be used to estimate the infection intensity. Direct microscopic examination combined with FECT, FLOTAC, or KKT is the preferred approach for diagnosis. However, hookworm eggs cannot be detected during the acute stage of the disease. Moreover, the eggs of *A. duodenale* and those of *N. americanus* are very similar and cannot be distinguished. Although rare, hookworms can occasionally pass with the stools, and their morphology can be distinguished.[12] Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can be used to diagnose the acute stage and identify DNA sequences specific to the infecting species. These methods are highly sensitive and specific but are not widely available yet. Serological techniques currently are under development and not recommended for diagnosis at this point.[13, 14]

Differential diagnosis should always be conducted to rule out other causes of dermal penetration, including dracunculiasis and cutaneous larva migrans; other causes of pulmonary disease such as ascariasis and strongyloidiasis; other causes of gastrointestinal manifestations such as dientamoebiasis, giardiasis, and strongyloidiasis; and other causes of chronic nutritional impairment, including ascariasis, enterobiasis, and trichuriasis.[11]

Treatment

Treatment consists of administering anthelmintic drugs and providing nutritional support:

- **Anthelmintic treatment.** The first-line treatment is albendazole (400 mg orally in a single dose). The second-line treatment is mebendazole (500 mg orally in a single dose or 100 mg orally twice a day for 3 days). The one-day regimen is less effective than the 3-day regimen. Pyrantel pamoate (11 mg/kg orally once a day for 3 days) is an alternative anthelmintic drug that can be used when albendazole and mebendazole are not available or in case of treatment failure.

- **Nutritional support.** Iron supplementation with ferrous gluconate, ferrous fumarate, or ferrous sulfate should be administered according to the severity of the anemia, especially in underdeveloped countries where iron deficiency is common. Blood transfusions may be necessary in severe cases.

Follow-up at 1, 4, and 12 months is recommended to assess the absence of clinical manifestations, hookworm eggs in stool samples, and anemia in blood samples.[14, 15]

Prevention

No vaccine to prevent ancylostomiasis is currently available. The main preventive strategies include improving sanitation, strengthening hygiene, avoiding barefoot walking, treating water before watering vegetable crops, consuming only well-cooked vegetables, drinking potable water, and administering preventive drug therapy in high-risk populations.[1, 15]

Conclusion

Ancylostomiasis is a parasitic soil-borne disease acquired by direct contact with contaminated soil or by ingesting vegetables contaminated with filariform larvae. It is endemic to African, American, and Asian countries where poor sanitation and lack of disease awareness prevail. The clinical manifestations develop through various stages that lead to malnutrition and substantial morbidity. Pregnant women and children are especially vulnerable. Diagnosis is usually based on the epidemiological background, clinical manifestations, and direct microscopic examination. Molecular methods are not widely available, and serological techniques are still under development. Treatment consists of administering anthelmintic drugs, which are highly effective and safe, but resistance has been reported and reinfections are common. Until vaccines are available, prevention and control strategies must be strengthened.

References

1. World Health Organization. Soil-transmitted helminth infections. [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections
2. Power HJ. History of Hookworm. Encycl Life Sciences 2002; 1: 1.
3. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013 Lancet; 386 (9995): 743-800.
4. Walana W, Aidoo EN, Tay SC. Prevalence of hookworm infection: a retrospective study in Kumasi. Asian Pac J Trop Biomed 2014; 4 (1): S158-S161.
5. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014; 7 (37): 1-19.
6. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.
7. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
8. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Parasites of Public Health Concern. Hookworm (Intestinal). [Internet]. U.S. Department of Health & Human Services. [Updated: September 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/dpdx/hookworm/index.html
9. Jiraanankul V, Aphijirawat W, Mungthin M, et al. Incidence and risk factors of hookworm infection in a rural community of central Thailand. Am J Trop Med Hyg 2011; 84 (4): 594-598.
10. Ghodeif AO, Jain H. Hookworm. [Internet]. StatPearls Publishing. [Updated: January 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK546648/
11. Weller PF, Leder K, Ryan ET, Baron EL. Hookworm infection. [Internet]. UpToDate. Wolters Kluwer. [Updated: September 2019; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/hookworm-infection?search=hookworm&source=search_result&selectedTitle=1~50&usage_type=default&display_rank=1#H3
12. Loukas A, Hotez P, Diemert D, Yazdanbakhsh M, McCarthy JS, Correa-Oliveira R, et al. Hookworm infection. Nat Rev Dis Primers 2016; 2: 1-18.

13. Khurana S, Sethi S. Laboratory diagnosis of soil transmitted helminthiasis. Trop Parasitol 2017; 7 (2): 86-91.

14. Centers for Disease Control and Prevention. Resources for Health Professionals. Parasites - Hookworm. [Internet]. U.S. Department of Health & Human Services. [Updated: August 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/hookworm/health_professionals/index.html

15. The Center for Food Security & Public Health, Institute for International Cooperation in Animal Biologics, Iowa State University. Zoonotic Hookworms. [Internet]. The Center for Food Security & Public Health, Institute for International Cooperation in Animal Biologics, Iowa State University. [November: 2013; Reviewed: January 2021]. Available at: https://www.cfsph.iastate.edu/Factsheets/pdfs/hookworms.pdf

ASCARIASIS

Introduction

Ascariasis, also known as roundworm disease, is a parasitic soil-borne disease caused by *Ascaris spp*. that primarily affects the respiratory and gastrointestinal tracts. Ascariasis mostly affects people living in tropical countries with warm and humid climates, but it can also affect people during the rainy season in dry climates. Infection is more prevalent in children due to the lack of disease awareness and poor hygiene habits. Infected people experience chronic malnutrition that impairs their mental and physical development, compromising their present and future well-being.[1]

Historical Background

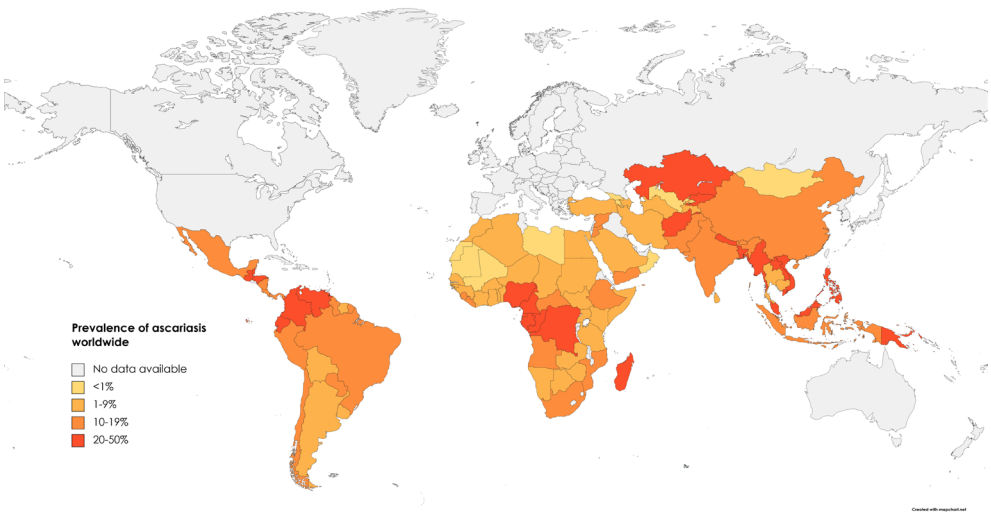
The earliest evidence of the disease can be traced back to the *Eber Papyrus* (1550 BC), which describes two intestinal parasites (roundworms and tapeworms) found in the gastrointestinal tract of an infected individual. Several archaeologists have found the parasite in coprolites, mummies, latrines, and soil from burial sites in Africa (800 BC). Moreover, several biologists, philosophers, and physicians, including Hippocrates (5th century BC), Aristotle (3rd century BC), Galen (2nd century AD), Chang Chi (3rd century AD), Avicenna (10th century AD), and Francesco Redi (17th century AD), have described their characteristics, mechanisms of

transmission, and treatments.[2] However, it was until 1758 that Carolus Linnaeus described and formally named the parasite *Ascaris lumbricoides*.[3] Later, Casimir Davaine identified its transmission mechanism in 1862, and Shimesu Koino described the life cycle of the parasite in 1922.[4]

Epidemiology

About 820 million people are estimated to be infected, and almost 5 billion are at risk of acquiring the disease worldwide. Ascariasis is widely distributed but is endemic to Africa, America, and Asia. Among the species with the potential to infect humans, *A. lumbricoides* accounts for most of the cases. In 2010, Rachel Pullan et al. estimated its prevalence (Figure 1); of the regions studied, the highest prevalence was found in Asia (589.0 million cases), followed by sub-Saharan Africa (117.9 million cases), Latin America and the Caribbean (86.0 million cases), North Africa and Middle East (24.3 million cases), and Oceania (1.9 million cases).[5] The 2010 *Global Burden of Disease Study* estimated that roundworm disease accounted for 1.32 million disability-adjusted life years, 1.11 years lived with disability, and 0.22 years of life lost.[6]

FIGURE 1. PREVALENCE OF ASCARIASIS WORLDWIDE



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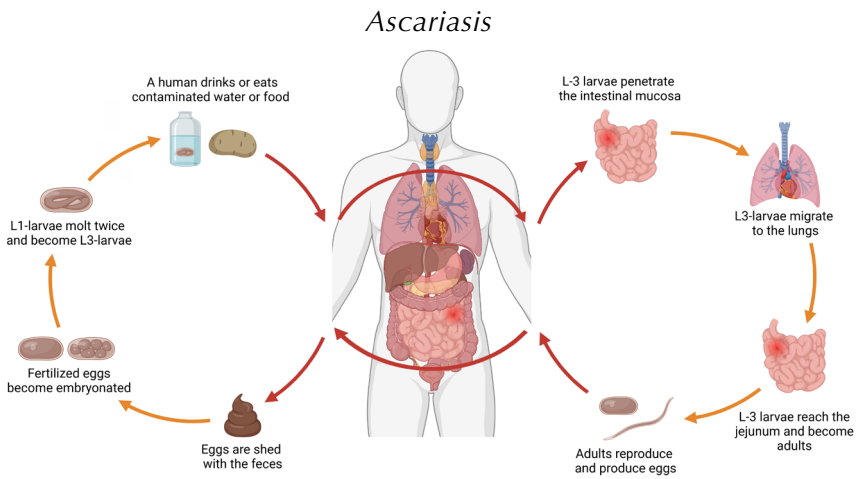
Adapted from: Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014; 7 (37): 1-19.

Etiology

Ascariasis is caused by parasites named *Ascaris lumbricoides* and *Ascaris suum,* which belong to the phylum Nematoda, class Chromadorea, order Rhabditida, suborder Spirurina, infraorder Ascaridomorpha, superfamily *Ascaridoidea*, family *Ascarididae*, and genus *Ascaris*.[7] The disease is soil-borne. Transmission occurs by ingesting contaminated soil; unwashed, unpeeled, or raw vegetables; or drinking untreated water that contains embryonated eggs with encysted larvae. Afterward, they travel through the gastrointestinal tract to reach the small intestine. Upon reaching the duodenum, the embryonated eggs hatch and release larvae, which penetrate the intestinal mucosa and travel through the bloodstream to reach the heart and lungs. Upon reaching the lungs, they mature and penetrate the alveoli to ascend through the tracheobronchial tree and reach the oropharynx, where they get expelled or swallowed. Upon reaching the jejunum, the larvae mature into adult worms, which establish in the lumen, and undergo sexual reproduction to produce fertilized eggs that are excreted with the feces onto the soil. Subsequently, they embryonate and larvae become infective. The cycle is completed when an uninfected individual ingests contaminated soil; unwashed, unpeeled, or raw vegetables; or drinks untreated water that contains embryonated eggs with encysted larvae (Figure 2).[8] Humans are the main reservoir of *A. lumbricoides*; humans and pigs are the main reservoirs of *A. suum*.[9]

FIGURE 2. *ASCARIS LUMBRICOIDES* LIFE CYCLE



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*This is a schematization of the *A. lumbricoides* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where ascariasis is endemic, the main risk factors for acquiring the disease include low socioeconomic status, lack of sanitation, open defecation, using human feces as fertilizers, raising livestock, and consuming unwashed, unpeeled, or raw vegetables. Ascariasis affects men and women equally but is more common in children than adults.[1, 10]

Clinical Manifestations

The incubation period of the disease ranges from weeks to months. Infected individuals can remain asymptomatic if the parasite load is low or may become symptomatic if the parasite load is high. Clinically, the disease develops through two distinct stages:

- **Respiratory stage.** When larvae reach the lungs, they can cause paroxysmal attacks of fever, dyspnea, cough, hemoptysis, pleurisy, and eosinophilic pulmonary infiltrates (known as a "Loeffler's syndrome"). This stage is usually severe during the initial infection but is absent in reinfections. This stage appears in the first week after parasite ingestion.
- **Gastrointestinal stage.** When larvae reach the gastrointestinal tract, they can cause anorexia, nausea, vomiting, abdominal discomfort, abdominal pain, flatulence, and diarrhea. Roundworms may be observed in the stool. Chronic infection can also lead to several complications:
  - ◊ **Malnutrition.** A high load of roundworms in the small intestine leads to impaired absorption of carbohydrates, lipids, proteins, minerals, and vitamins, growth retardation, and impaired cognitive development in children.
  - ◊ **Hepatobiliary and pancreatic involvement.** Migration of roundworms to the biliary tree leads to ascending cholangitis, pyogenic cholangitis, acalculous cholecystitis, hepatitis, and liver abscesses. Migration of roundworms to the pancreatic duct leads to pancreatitis.
  - ◊ **Intestinal obstruction.** A high load of roundworms in the small intestine causes intestinal obstruction, volvulus, ileocecal intussusception, intestinal perforation, and peritonitis.

This stage appears from the sixth week after parasite ingestion.[11, 12]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Ascaris* spp. is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of sputum or gastric aspirates can demonstrate the presence of roundworm larvae; stool samples can show the presence of roundworm eggs. Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low, and flotation techniques such as the FLOTAC method may be performed to separate the eggs from stool. Quantitative methods such as the Kato-Katz technique (KKT) may be needed to estimate the infection intensity. Direct microscopic examination combined with FECT, FLOTAC, or KKT is the preferred approach for diagnosis. Roundworm larvae can be detected in sputum or gastric aspirates during the acute stage of the disease; roundworm eggs can be detected in stool during the chronic stage. The eggs of *A. lumbricoides* are very similar to those of *A. suum* and cannot be distinguished. Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect roundworm-specific DNA sequences and are useful to identify the infecting species. However, these methods are expensive and not widely available. Serological techniques are not recommended for diagnosis as there is cross-reactivity with antibodies produced against other parasites.[13, 14]

Supplementary examination with X-rays (to detect bilateral migratory round infiltrates in chest X-rays or a large collection of adult roundworms and a "whirlpool" effect in abdominal X-rays), computer tomography (to detect a large collection of adult roundworms in the biliary tree or the liver, or "bull's eye" appearance in cross-section abdominal CT), magnetic resonance imaging (to detect a large collection of adult roundworms in the biliary or pancreatic ducts in MRI cholangiopancreatography), or ultrasonography (to detect curved strips, tubular echogenic structures, or a "target" sign) should be performed to assess the presence of parasites.[12]

Differential diagnosis should always be conducted to rule out other diseases with similar pulmonary manifestations, including ancylostomiasis, eosinophilic pneumonitis, and strongyloidiasis; and other diseases that cause similar gastrointestinal manifestations, including acute appendicitis, acute cholangitis, acute pancreatitis, ascending cholangitis, bowel obstruction, cholecystitis, enterobiasis, giardiasis, strongyloidiasis, and trichuriasis, among others.[11]

Treatment

Treatment depends on the disease progression. Patients may require a combination of anthelmintic therapy and surgical interventions:

- **Anthelmintic treatment.** The first-line treatment is albendazole (400 mg orally in a single dose), which is effective in almost 100% of the cases. The second-line treatment is mebendazole (500 mg orally in a single dose or 100 mg orally twice a day for 3 days), which is effective in almost 95% of the cases. Pyrantel pamoate (11 mg/kg orally once a day for 3 days) is an alternative anthelmintic drug that can be used when albendazole and mebendazole are not available, in case of pregnancy, or in case of treatment failure.
- **Surgical interventions.** Surgery is required when patients experience chronic complications of the disease that cannot be managed with pharmacological treatment or when improvement requires surgical intervention. Adequate assessment by an experienced surgeon is recommended.

Follow-up at 2 weeks is recommended to assess the absence of clinical manifestations and roundworm larvae or eggs in stool samples.[12, 15]

Prevention

No vaccine to prevent ascariasis is currently available. The main preventive strategies include improving sanitation, strengthening hygiene, treating water before watering vegetables, consuming only well-cooked vegetables, drinking potable water, and administering preventive drug therapy in high-risk populations.[1, 17]

Conclusion

Ascariasis is a parasitic soil-borne disease endemic to African, American, and Asian countries with warm and humid climate. Ascariasis is caused by two species in the genus *Ascaris*, of which *A. lumbricoides* accounts for most cases. The disease develops into stages. The intensity of clinical manifestations depends on the parasite load and on whether it is primo- or re-infection. Infected individuals tend to underestimate the severity of their disease until they see roundworms in their feces. Diagnosis is made based on the epidemiological background, clinical

manifestations, and direct microscopic examination of stool. Molecular or serological techniques are useful when available. Supplementary examination with imaging techniques is valuable. Treatment consists of administering anthelmintic drugs to eliminate roundworms and surgical interventions to cure chronic complications. Disease awareness and preventive drug therapy are the best options currently available until a safe and effective vaccine is developed.

References

1. World Health Organization. Soil-transmitted helminth infections. [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections
2. Stewart IE. Helminths in History. The Scientific Monthly. Jun 1951; 72 (6): 345-352.
3. Leles D, Gardner SL, Reinhard K, Iñiguez A, Araujo A. Are Ascaris lumbricoides and Ascaris suum a single species? Parasit Vectors 2012; 5: 42.
4. Cox FEG. History of Human Parasitology. Clin Microbiol Rev 2002; 15 (4): 595-612.
5. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014; 7: 37.
6. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.
7. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
8. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Parasites of Public Health Concern. Ascariasis. [Internet]. U.S. Department of Health & Human Services. [Updated: July 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/dpdx/ascariasis/index.html
9. Asaolu SO, Ofoezie IE. Global water pathogen project. Part three. Specific excreted pathogens: environmental and epidemiology aspects. Ascaris spp. [Internet]. United Nations Educational, Scientific and Cultural Organization. [Updated: April 2018; Reviewed: January 2021]. Available at: https://www.waterpathogens.org/sites/default/files/Ascaris%20spp._2.pdf
10. Yang D, Yang Y, Wang Y, Yang Y, Dong S, Chen Y, et al. Prevalence and Risk Factors of Ascaris lumbricoides, Trichuris trichiura and Cryptosporidium Infections in Elementary School Children in Southwestern China: A School-Based Cross-Sectional Study. Int J Environ Res Public Health 2018; 15 (9): 1809.

11. De Lima-Corvino D, Horrall S. Acariasis. [Internet]. StatPearls Publishing. [Updated: July 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430796/
12. Leder K, Weller PF, Ryan ET, Baron EL. Ascariasis. [Internet]. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/ascariasis?search=ascariasis&source=search_result&selectedTitle=1~44&usage_type=default&display_rank=1#H1
13. Lamberton PH, Jourdan PM. Human Ascariasis: Diagnostics Update. Curr Trop Med Rep.2015; 2 (4): 189-200.
14. Centers for Disease Control and Prevention. DPDx - Laboratory Identification of Parasites of Public Health Concern. Ascariasis. [Internet]. U.S. Department of Health & Human Services. [Updated: July 2019; Reviewed: January 2021]. Available at: https://www.cdc.gov/dpdx/ascariasis/index.html
15. Médecins Sans Frontières. Clinical guidelines / Chapter 6: Parasitic diseases. Nematode infections. [Internet]. Médecins Sans Frontières.. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/nematode-infections-16689807.html
16. Centers for Disease Control and Prevention. Parasites – Ascariasis. Prevention & Control. [Internet]. U.S. Department of Health & Human Services. [Updated: February 2018; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/ascariasis/prevent.html

TRICHURIASIS

Introduction

Trichuriasis, also known as whipworm disease, is a parasitic soil-borne disease caused by *Trichuris* spp. that primarily affects the gastrointestinal tract. Trichuriasis is widely distributed, and the persons most affected are those living in tropical climates with warm and moist weather where lack of awareness, inadequate sanitation, and poor hygiene habits prevail. Infection is more common in children than adults, and clinical manifestations depend on the parasite load.[1]

Historical Background

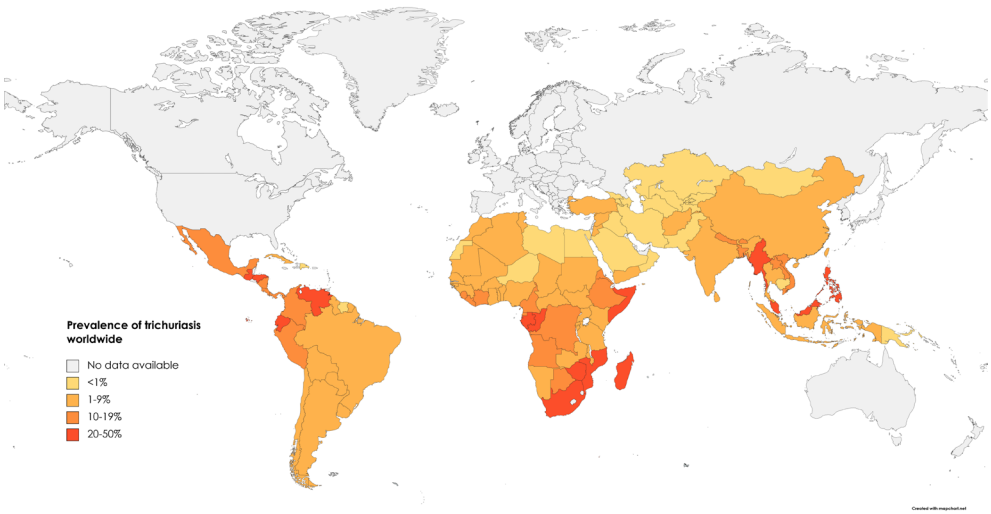
The earliest evidence of the disease can be traced back thousands of years. Paleoparasitological studies have found *Trichuris* spp. eggs in mummies, latrines, and copro-

lites.[2] However, the first description of trichuriasis dates from 1740, when Giovanni Morgagni identified adult whipworms in the colon of an infected individual. Later, Johann Roeder produced an accurate description of the parasite morphology with drawings in 1761, and Linnaeus formally named it *Trichuris trichiura* in 1771.[3]

Epidemiology

About 800 million people are estimated to be infected, and almost 5 billion are at risk of acquiring the disease.[4] Trichuriasis is widely distributed but is endemic to Africa, America, and Asia. Among the species that infect humans, *T. trichiura* accounts for most cases. In 2010, Rachel Pullan et al. estimated its prevalence (Figure 1); of the regions studied, the highest prevalence was found in Asia (282.3 million cases), followed by sub-Saharan Africa (100.8 million cases), Latin America and the Caribbean (72.2 million cases), North Africa and the Middle East (8.7 million cases), and Oceania (0.6 million cases).[5] The 2010 *Global Burden of Disease Study* estimated that the whipworm disease accounted for 0.64 million disability-adjusted life years, 0.64 years lived with disability, and 0 years of life lost.[6]

FIGURE 1. PREVALENCE OF TRICHURIASIS WORLDWIDE



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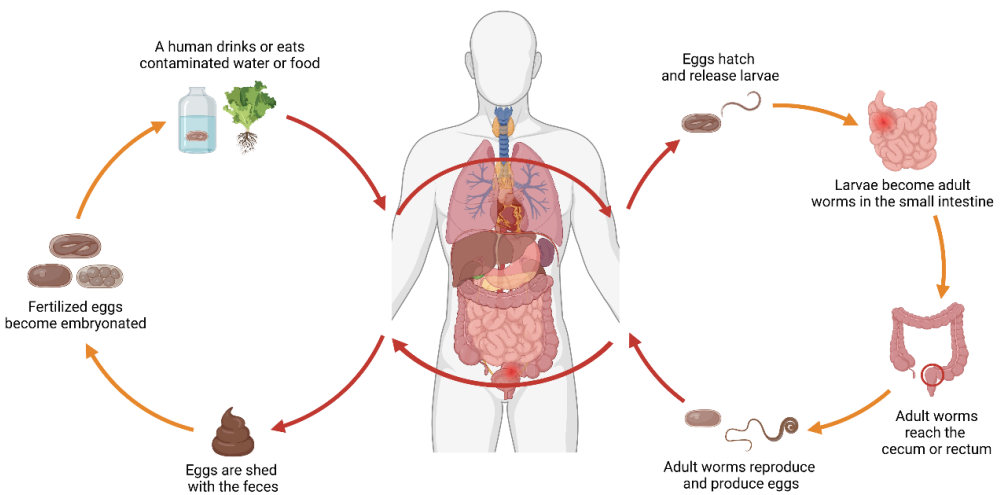
Adapted from: Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014; 7 (37): 1-19.

Etiology

Trichuriasis is caused by parasites named *Trichuris suis, Trichuris trichiura,* and *Trichuris vulpi*, which belong to the phylum Nematoda, class Enoplea, subclass Dorylaimia, order Trichinellida, family *Trichuridae*, and genus *Trichuria*.[7] *T. trichuris* is the most prevalent one; case reports of trichuriasis caused by *T. suis* or *T. vulpi* in humans are sporadic. The disease is soil-borne. Transmission occurs by ingesting contaminated soil; ingesting unwashed, unpeeled, or raw vegetables; or drinking untreated water that contains embryonated eggs with encysted larvae. Afterward, they travel through the gastrointestinal tract to reach the small intestine, where they hatch, release larvae, and mature into adult worms. The adult worms then migrate and establish from the cecum to the rectum, depending on the parasite load, and undergo sexual reproduction to produce fertilized eggs that are excreted with the feces onto the soil. Subsequently, they embryonate and larvae become infective. The cycle is completed when an uninfected individual ingests contaminated soil; unwashed, unpeeled, or raw vegetables; or drinks untreated water that contains embryonated eggs with encysted larvae (Figure 2). Humans and primates are the main reservoirs of *T. trichiura*.[4, 8]

FIGURE 2. *TRICHURIS TRICHIURA* LIFE CYCLE

Trichuriasis



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*This is a schematization of the *T. trichiura* life cycle, but the icons are not fidedign copies of the parasite morphologic features.

Risk Factors

In countries where trichuriasis is endemic, the main risk factors for acquiring the disease include low socioeconomic status, lack of sanitation, open defecation, using human feces as fertilizers, and consuming unwashed, unpeeled, or raw vegetables. Trichuriasis affects men and women equally and is most prevalent in children than adults.[9, 10]

Clinical Manifestations

The incubation period of the disease ranges from weeks to months. Afterward, infected individuals can remain asymptomatic when the parasite load is low or may become symptomatic if the parasite load is high. Anorexia, nausea, vomiting, abdominal discomfort, abdominal pain, flatulence, diarrhea (more commonly at night), dysentery, dyschezia, tenesmus, and rectal prolapse can be experienced. A high load of whipworms in the small intestine leads to impaired absorption of nutrients, secondary anemia due to iron deficiency, and weight loss. Growth retardation and impaired cognitive development may occur in children.[8, 11]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Trichuris* spp. is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of stool samples can demonstrate the presence of whipworm eggs. Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low, and flotation methods like the FLOTAC technique may be performed to separate the eggs from stool. Quantitative methods such as the Kato-Katz technique (KKT) can be used to estimate the infection intensity. Direct microscopic examination combined with FECT, FLOTAC, or KKT is the preferred approach for diagnosis. However, whipworm eggs are not shed with feces until months after the onset of disease. Molecular methods such as the polymerase chain reaction can detect DNA sequences specific of *Trichuris* spp. and are useful to identify the infecting species, but these methods are expensive and not widely available.[8, 12]

Supplementary examination with X-rays (to detect tiny pinwheel-shaped or target-shaped collections of barium and thickening of the colonic wall in abdominal X-rays with barium enema), computer tomography (to detect irregular and nodular thickening of the colonic wall in abdominal CT), ultrasonography (to detect thickening of the colonic wall and "whipworm dance"), or colonoscopy (to detect thread-like forms with an attenuated end) should be performed to assess the presence of parasites.[13, 14]

Differential diagnosis should always be conducted to rule out other diseases that cause similar gastrointestinal manifestations, including acute appendicitis, acute cholecystitis, acute colitis, ancylostomiasis, ascariasis, giardiasis, and strongyloidiasis, among others.[11]

Treatment

Treatment depends on the disease progression. Patients may require a combination of anthelmintic therapy, nutritional support, and surgical intervention:

- **Anthelmintic treatment.** The first-line treatment is mebendazole (100 mg orally twice a day for 3 days). The second-line treatment is albendazole (400 mg orally once a day for 3 days). Ivermectin (200 mcg//kg orally once a day for 3 days) is an alternative anthelmintic drug that can be used in case of pregnancy, when mebendazole and albendazole are not available, or in case of treatment failure.
- **Nutritional support.** Iron supplementation with ferrous gluconate, ferrous fumarate, or ferrous sulfate must be administered according to the severity of the anemia, especially in developing countries where iron deficiency is common. Blood transfusions may be necessary in severe cases.
- **Surgical interventions.** Surgery is required when patients experience chronic complications of the disease that are not resolved with pharmacological treatment or require surgical intervention for improvement. Adequate assessment by an experienced surgeon is recommended.

Follow-up at 2 weeks is recommended to assess the absence of clinical manifestations and whipworm larvae or eggs in stool samples.[8, 15]

Prevention

No vaccine to prevent trichuriasis is currently available. The main preventive strategies include improving sanitation, strengthening hygiene, implementing veterinary public health strategies, treating water before watering vegetables, consuming well-cooked vegetables, drinking potable water, and administering preventive drug therapy in high-risk populations.[1, 9]

Conclusion

Trichuriasis is a parasitic soil-borne disease endemic to African, American, and Asian countries where warm and moist weather prevails. Trichuriasis is caused by three species in the genus *Trichuris*, with *T. trichiura* accounting for most cases. Most infected individuals remain asymptomatic, but others develop gastrointestinal disease. Diagnosis can be made by direct microscopic examination about two months after infection, but new diagnostic tools are necessary to detect the disease more promptly. A short course of anthelmintic drugs can clear the infection, but follow-up is needed. Prevention can be achieved by improving sanitation and hygiene habits.

References

1. The Center for Food Security & Public Health, Institute for International Cooperation in Animal Biologics, Iowa State University. Trichuriasis.Internet] The Center for Food Security & Public Health, Institute for International Cooperation in Animal Biologics, Iowa State University. [Updated: January 2019; Reviewed: January 2021]. Available at: https://www.cfsph.iastate.edu/Factsheets/pdfs/trichuriasis.pdf
2. Betson ME, Soe MJ, Nejsum P. Human Trichuriasis: Whipworm Genetics, Phylogeny, Transmission and Future Research Directions. Current Trop Med Reports 2015; 2: 209-217.
3. Stanford. Trichuriasis. History of Discovery. [Internet]. Stanford Education. [Updated: 2002; Reviewed: January 2021]. Available at: https://web.stanford.edu/group/parasites/ParaSites2002/trichuriasis/Tirchhod.html
4. Centers for Disease Control and Prevention. DPDx – Laboratory Identification of Parasites of Public Health Concern. Trichuriasis. [Internet]. U.S. Department of Health & Human Services. [Updated: December 2017; Reviewed: January 2021]. Available at: https://www.cdc.gov/dpdx/trichuriasis/index.html

5. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014; 7 (37): 1-19.

6. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.

7. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

8. Leder K, Weller PF, Ryan ET, Edwards MS, Baron EL. Enterobiasis (pinworm) and trichuriasis (whipworm). [Internet]. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/enterobiasis-pinworm-and-trichuriasis-whipworm?search=trichuriasis&source=search_result&selectedTitle=1~27&usage_type=default&display_rank=1#H15

9. World Health Organization. Soil-transmitted helminth infections. [Internet]. World Health Organization. [Updated: March 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections

10. Centers for Disease Control and Prevention. Parasites – Trichuriasis (also known as Whipworm Infection). Epidemiology & Risk Factors. [Internet]. U.S. Department of Health & Human Services. [Updated: December 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/whipworm/epi.html

11. Viswanath A, Yarrarapu SNS, Williams M. Trichuris Trichiura. [Internet]. StatPearls Publishing. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507843/

12. Barda BD, Keiser K, Albonico M. Human Trichuriasis: Diagnostics Update. Current Trop Med Reports 2015: 2: 201-208.

13. Tokmak N, Koc Z, Ulusan S, Koltas IS, Bal N. Computed tomographic findings of trichuriasis. World J Gastroenterol 2006; 12 (26): 4270-4272.

14. Baldisserotto M. Trichuriasis colitis detected by Doppler sonography. Pediatr Radiol 2010; 40 (1): 95-97.

15. Centers for Disease Control and Prevention. Parasites – Trichuriasis (also known as Whipworm Infection). Resources for Health Professionals. Treatment. [Internet]. U.S. Department of Health & Human Services. [Updated: December 2020; Reviewed: January 2021]. Available at: https://www.cdc.gov/parasites/whipworm/epi.html

Chapter 18. Taeniasis/Cysticercosis

Authors

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Introduction

Taeniasis is a parasitic disease caused by *Taenia* spp. that affects the gastrointestinal tract, whereas cysticercosis is a devastating disease that primarily affects the central nervous system (CNS). Both tend to affect people living in developing countries that depend on farming for subsistence. Taeniasis is considered the leading cause of death from food-borne diseases, whereas cysticercosis is the leading preventable cause of epilepsy worldwide.[1]

Historical Background

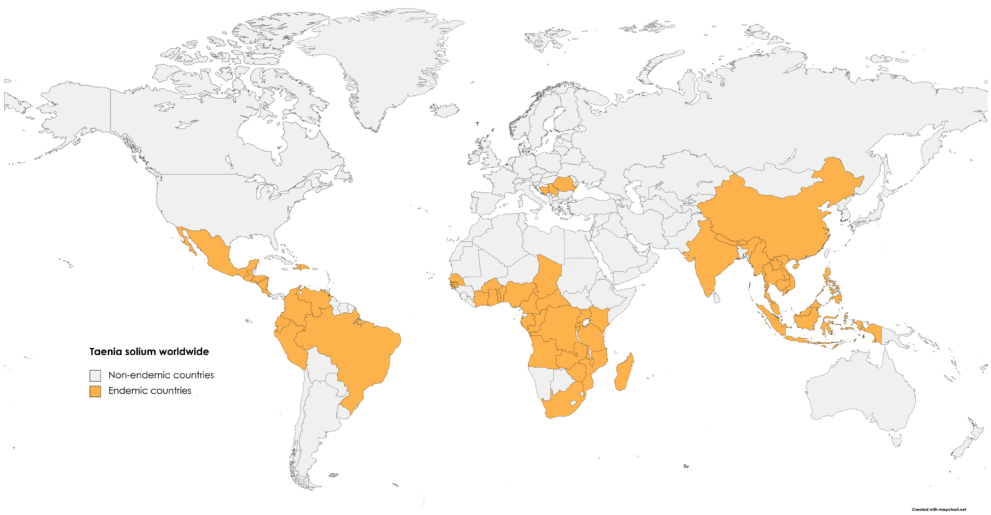
The earliest evidence of the disease can be traced back to the *Ebers Papyrus* (1500 BC), which depicts tapeworms and their eggs within the intestines of ancient mummies. Later, several philosophers and physicians described tapeworms, including Hippocrates (5th century BC), Aristotle (3rd century BC), and Theophrastus (3rd century BC). In 1550, Paranolli suggested that cysts could be found in the brain; in 1558 Rumler confirmed their presence in the CNS; and in 1650 Paracelsus related them to epilepsy. Subsequently, Marcello Malpighi described the nature of cysts in 1697, and Friedrich Küchenmeister identified the transmission mechanism in 1855.[2]

Epidemiology

About 50 million people are estimated to be infected, and 50,000 deaths are caused each year worldwide.[3] Taeniasis/cysticercosis is endemic to Africa (An-

gola, Benin, Burkina Faso, Burundi, Cabo Verde Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, the Democratic Republic of the Congo, Gabon, Gambia, Ghana, Guinea-Bissau, Kenya, Madagascar, Malawi, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Togo, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe), America (Brazil, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Peru, and Venezuela), Asia (Bhutan, Cambodia, China, India, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Nepal, Philippines, Thailand, and Vietnam), and Europe (Bosnia and Herzegovina, Romania, and Serbia) (Figure 1).[4] The 2010 *Global Burden of Disease Study* estimated that taeniasis/cysticercosis accounted for 0.50 million disability-adjusted life years, 0.46 years lived with disability, and 0.05 years of life lost.[5]

FIGURE 1. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR TAENIA SOLIUM



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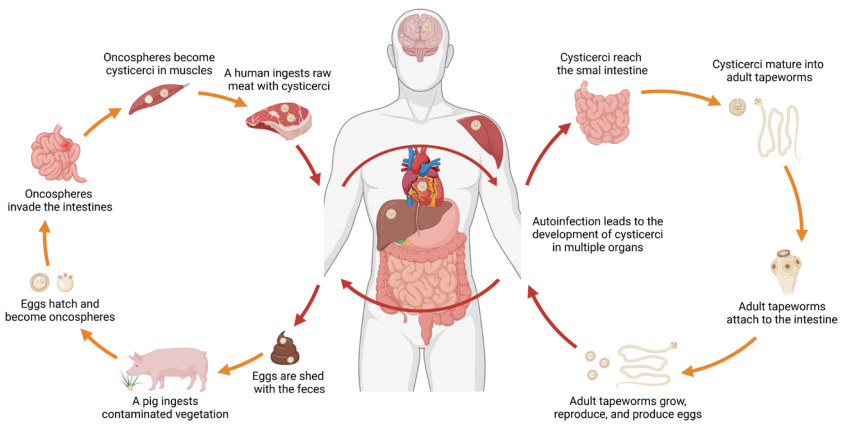
Adapted from: World Health Organization. Taenia solium - Status of endemicity of Taenia solium. Data by country. [Internet]. World Health Organization. [Updated: December 2018; December: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDTSOL1?lang=en

Etiology

Taeniasis/cysticercosis is caused by parasites named *Taenia solium*, *Taenia saginata*, and *Taenia asiatica*, which belong to the phylum Platyhelminthes, class Cestoda, subclass Eucestoda, order Cyclophyllidea, family *Taeniidae*, and genus *Taenia*.[6] Of the species that infect humans, *T. solium* accounts for most cases. Transmission occurs when an uninfected cow (*T. saginata*) or pig (*T. solium*) ingests vegetation contaminated with gravid proglottids or embryonated eggs. Afterward, they travel through the gastrointestinal tract to reach the small intestine, where they hatch and release oncospheres. The oncospheres then penetrate the intestinal wall and migrate through the bloodstream to reach the striated muscles, where they differentiate into cysticerci. Transmission continues when an uninfected individual ingests raw or undercooked meat containing cysticerci. Later, they travel through the gastrointestinal tract to reach the small intestine, where they mature into adult tapeworms. The adult tapeworms then attach to the intestinal wall, undergo sexual reproduction, and produce proglottids. Subsequently, they differentiate, become gravid, detach from the tapeworm, and are shed with feces. The cycle is completed when an uninfected cow or pig ingests vegetation contaminated with gravid proglottids or embryonated eggs (Figure 2). Autoinfection may occur via the fecal-oral route when hygiene is poor, leading to the development of cysticerci in the brain, eyes, heart, liver, and striated muscles.[7] Several herbivores, including pigs, act as intermediate hosts by harboring the larval stage of the parasite; carnivores and humans serve as definitive hosts by harboring the adult egg-producing stage of the parasite.[1]

FIGURE 2. *TAENIA SOLIUM* LIFE CYCLE



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Risk Factors

In rural areas of countries where taeniasis/cysticercosis is endemic, the main risk factors for acquiring the disease include inadequate sanitation, poor hygiene, raising livestock, eating raw or undercooked meat, drinking contaminated water, and history of intestinal taeniasis. Taeniasis/cysticercosis is more prevalent in men than women and in adults than children.[7, 8]

Clinical Manifestations

The incubation period of the disease is 56 days on average. Afterward, infected individuals can remain asymptomatic or may become symptomatic. Clinically, the disease can be divided into two major forms:

- **Taeniasis.** It is characterized by the presence of *T. solium* in the small intestine, which can cause nausea, vomiting, abdominal discomfort, abdominal pain, diarrhea, constipation, and weight loss. Proglotides may be observed in feces. Complications such as appendicitis, bladder perforation, and bowel or pancreatic obstruction have been reported.[9, 10]
- **Cysticercosis.** It is characterized by the presence of cysticerci in organs and tissues. These are mainly found in the SNC, where they can cause a wide range of clinical manifestations, depending on their location, number, and size:
  - ◊ **Intraparenchymal cysticerci.** Seizures and headaches are common. Altered mental status and visual impairment may be experienced. Meningoencephalitis and encephalitis have been reported.
  - ◊ **Extraparenchymal cysticerci.** Headache, nausea, and vomiting are common. Altered mental status and visual impairment can be experienced in case of intraventricular lesions; cranial nerve palsies and vascular involvement, in case of subarachnoid lesions; neurological deficit and transverse myelitis, in spinal lesions; and chorioretinitis and retinal detachment, in ocular lesions.

Other parts of the body where cysticerci can be found include the subcutaneous tissues (painless nodules), muscles (acute myopathy), and heart (arrhythmias and conduction abnormalities).[9, 11]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but detection of *Taenia* spp. is required for confirmation, and several laboratory tests are available for this purpose. Direct microscopic examination of stool samples can demonstrate the presence of eggs or proglottids of *Taenia* spp. Concentration methods such as the formalin-ether concentration technique (FECT) may be necessary when the parasite load is low. Quantitative methods such as the Kato-Katz technique (KKT) can be used to estimate the infection intensity. Direct microscopic examination combined with FECT or KKT is the preferred approach for diagnosis. However, eggs are not shed with feces before the third month from the onset of disease, and it is impossible to distinguish between the eggs of *Echinococcus* spp. and those of *Trichuris* spp. On the other hand, although the species can be identified by counting the uterine branches of proglottids, these are rarely seen. Molecular methods such as loop-mediated isothermal amplification and polymerase chain reaction can detect DNA sequences specific to *Taenia spp*. and are useful to identify the infecting species but are rarely available in the field. Serological techniques can detect antigens and antibodies weeks before the eggs are shed and are useful during the early stages of the disease. However, these techniques show cross-reactivity with other parasites.[11-13]

Supplementary examination with techniques such as endoscopy can demonstrate the presence of taenia; imaging techniques (e.g., X-rays, computerized tomography, and magnetic resonance imaging) can demonstrate the presence of cysticerci.[14]

Differential diagnosis should always be conducted to rule out other causes of intestinal diseases, such as ancylostomiasis, ascariasis, difilobotriasis, hymenolepiasis, and strongyloidiasis, as well as other causes of neurological disease, such as aspergillosis, coccidioidomycosis, cryptococcosis, echinococcosis, toxoplasmosis, syphilis, and tuberculosis, among others.[9]

Treatment

Treatment of taeniasis/cysticercosis depends on the form of the disease:

- **Taeniasis.** Treatment consists of administering anthelmintic drugs. The first-line treatment is praziquantel (10 mg/kg orally in a single dose) or ni-

closamide (500 mg orally in a single dose for children under 2 years, 1 g orally in a single dose for children aged 2 to 6 years, and 2 g orally in a single dose for children over 6 years and adults). Albendazole (400 g orally once a day for 3 days) has been used as an alternative anthelmintic drug.[1, 10]

- **Cysticercosis.** Treatment consists of administering antiepileptic, anthelmintic, and corticosteroid drugs. Antiepileptic drugs must be administered in case of seizures and should be selected based on availability, interactions, and side effects. Anthelmintic drugs must be administered in case of viable or degenerating cysts and should be avoided in cases of high cysticercus loads or calcified cysts. Albendazole (15 mg/kg orally divided into two doses for up to 10 to 14 days) must be administered when the patient has 1 or 2 cysticerci; albendazole (15 mg/kg orally divided into two doses for up to 10 to 14 days) plus praziquantel (50 mg/kg orally divided in three doses for up to 10 to 14 days) should be administered when the patient has more than two cysticerci. Corticosteroids (dexamethasone 0.1 mg/kg orally once a day or prednisone 1 mg/kg orally once a day) must be administered at least one day prior to and during the anthelmintic drug therapy, and the dosage should be tapered when finishing it. Supportive treatment must be maintained.[15]

Prevention

No vaccine to prevent taeniasis/cysticercosis is currently available. The main preventive strategies include improving sanitation, strengthening hygiene, vaccinating pigs, improving inspection and processing of meat products, consuming well-cooked beef and pork meat, and administering preventive drug therapy in high-risk populations.[1]

Conclusion

Taeniasis is an intestinal disease caused by tapeworms, while cysticercosis is a non-organ-specific disease caused by cysticerci. Three tapeworm species cause taeniasis, but *T. solium* is the most relevant species in man. Most infected individuals remain asymptomatic for a long time until clinical manifestations arise. Autoinfection leads to the dissemination of cysticerci, which can reach the CNS

and cause life-threatening complications. Diagnosis can be performed through a combination of detection methods, but new affordable, widely available tools are necessary to detect taeniasis in the early stages. Imaging techniques are required to confirm cysticercosis. Anthelmintic drugs are effective for treating the disease, but adequate supportive measures and close follow-up are needed. Prevention can be achieved by improving living conditions of animals and humans.

References

1. World Health Organization. Taeniasis/cysticercosis.Internet]. World Health Organization. [Updated: June 2019; Revised: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/taeniasis-cysticercosis
2. Del Brutto OH, García HH. Cysticercosis of the Human Nervous System. J Neurol Sci 2015; 15: 359 (1-2): 392-395.
3. Bouteille B. Épidémiologie de la cysticercose et de la neurocysticercose [Epidemiology of cysticercosis and neurocysticercosis]. Med Sante Trop 2014; 24 (4): 367-74.
4. World Health Organization. Taenia solium - Status of endemicity of Taenia solium. Data by country. [Internet]. World Health Organization. [Updated: December 2018; December: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDTSOL1?lang=en
5. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.
6. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.
7. Centers for Disease Control and Prevention. Parasites – Taeniasis. Biology. [Internet]. U.S. Department of Health & Human Services. [Updated: 2019; Revised: December 2020]. Available at: https://www.cdc.gov/parasites/taeniasis/biology.html
8. Conlan JV, Vongxay K, Khamlome B, Khamlome B, Dorny P, Sripa B, et al. A cross-sectional study of Taenia solium in a multiple taeniid-endemic region reveals competition may be protective. Am J Trop Med Hyg 2012; 87 (2): 281-291.
9. Lesh EJ, Brady MF. Tapeworm [Internet]. StatPearls Publishing. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537154/

10. Leder K, Weller PF, Ryan ET, Baron EL. Tapeworm infections. [Internet]. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/tapeworm-infections?source=history_widget

11. White AC, Weller PF, Baron EL. Cysticercosis: Clinical manifestations and diagnosis. [Internet]. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/cysticercosis-clinical-manifestations-and-diagnosis?search=cysticercosis&source=search_result&selectedTitle=1~26&usage_type=default&display_rank=1

12. Okello AL, Thomas LF. Human taeniasis: current insights into prevention and management strategies in endemic countries. Risk Manag Healthc Policy 2017; 10: 107-116.

13. Centers for Disease Control and Prevention. Parasites - Taeniasis. Resources for Health Professionals. [Internet]. U.S. Department of Health & Human Services. [Updated: 2019; Revised: December 2020]. Available at: https://www.cdc.gov/parasites/taeniasis/health_professionals/index.html#dx

14. Moyano LM, O'Neal SE, Ayvar V, Gonzalvez G, Gamboa R, Vilchez P, et al. High Prevalence of Asymptomatic Neurocysticercosis in an Endemic Rural Community in Peru. PLoS Negl Trop Dis 2016; 10 (12): e0005130.

15. White AC, Weller PF, Baron EL. Cysticercosis: Treatment. [Internet]. UpToDate. Wolters Kluwer. [Updated: January 2021; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/cysticercosis-treatment?search=cysticercosis%20treatment&source=search_result&selectedTitle=1~26&usage_type=default&display_rank=1

Chapter 19. Trachoma

Authors

Jorge-Alberto Ascencio-Aragón, Diego-Abelardo Álvarez-Hernández, Leticia Sidauy-Adissi, Simran Mangwani-Mordani

Introduction

Trachoma is a chronic bacterial disease caused by *Chlamydia trachomatis* that affects the eyes. It is the leading infectious cause of blindness worldwide and is a significant public health issue in developing countries and emerging economies. Infected individuals tend to underestimate the severity of the disease and defer medical attention until non-reversible complications have developed.[1]

Historical Background

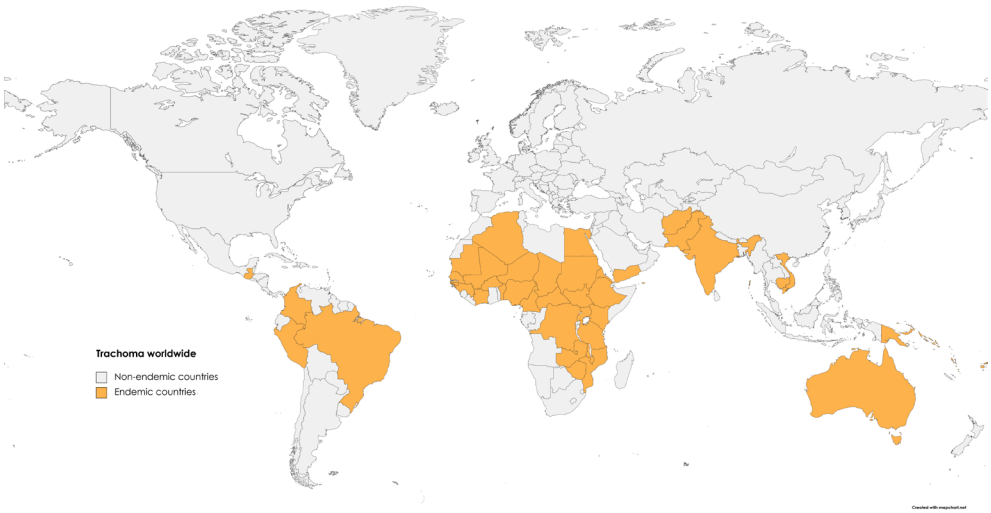
The earliest evidence of the disease can be traced back to medical writings from ancient China (2600 BC) and the *Eber Papyrus* from ancient Egypt (1500 BC). Several philosophers and physicians, including Celsus and Dioscorides (1st century AD) and Galen (2nd century AD), described the characteristics of the disease. Several conflicts and wars, including the Egyptian Campaign and the Napoleonic Wars (18th–19th century AD), spread the disease from previously endemic areas. It was not until 1954 that Tang first isolated the etiological agent.[2]

Epidemiology

About 84 million people are estimated to be infected, and almost 138 million are at risk of acquiring the disease worldwide.[3] Trachoma is endemic to Africa (Algeria, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Côte d'Ivoire, the Democratic Republic of the Congo, Egypt, Eritrea, Ethiopia, Guinea, Guinea-Bissau, Kenya, Malawi, Mali, Mauritania, Mozambique,

Niger, Nigeria, Senegal, South Sudan, Sudan, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe), America (Brazil, Colombia, Guatemala, and Peru), Asia (Afghanistan, Cambodia, India, Pakistan, Vietnam, and Yemen), and Oceania (Australia, Fiji, Kiribati, Nauru, Papua New Guinea, Solomon Islands, and Vanuatu), but it can be found worldwide (Figure 1).[4] The 2010 *Global Burden of Disease Study* estimated that trachoma accounted for 0.33 million disability-adjusted life years, 0.33 years lived with disability, and 0 years of life lost.[5]

FIGURE 1. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR *CHLAMYDIA TRACHOMATIS*



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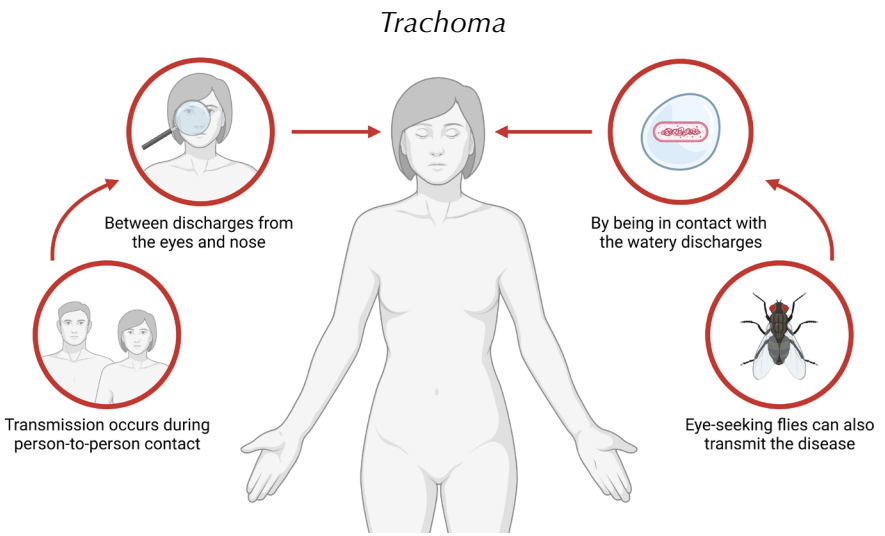
Adapted from: World Health Organization. Trachoma. Status of elimination of trachoma as a public health problem: 2020. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://apps.who.int/neglected_diseases/ntddata/trachoma/trachoma.html

Etiology

Trachoma is caused by a bacteria named *Chlamydia trachomatis,* which belongs to the phylum Chlamydiae, class Chlamydiia, order Chlamydiales, family *Chlamydiaceae*, and genus *Chlamydia*.[6] *C. trachomatis* is a Gram-negative, obligate intracellular bacterium that has been subdivided into 19 serovars: A–K and L1–

L3. Serovars A to C cause visual impairment, serovars D to K cause pelvic inflammatory disease, and serovars L1 to L3 cause lymphogranuloma venereum. Transmission occurs mainly from an infected to an uninfected individual during close contact through the direct spread of discharges from the eyes and nose. Transmission by indirect spread through fomites and by eye-seeking flies in the genus *Musca* has also been reported (Figure 2). Humans are the sole reservoir of the disease.[7, 8]

FIGURE 2. *CHLAMYDIA TRACHOMATIS* LIFE CYCLE



Risk Factors

In countries where trachoma is endemic, the main risk factors for acquiring the disease include low socioeconomic status, inadequate sanitation and basic infrastructure, crowded conditions, poor hygiene habits, and high density of flies. Trachoma affects both sexes equally during the active stage but causes blindness more frequently in women than men. It is more prevalent in adults than children.[9, 10]

Clinical Manifestations

The incubation period of the disease ranges between 1 and 2 weeks. Afterward, the disease develops through two distinct stages:

- **Active stage.** It affects mainly children and is characterized by mild and self-limiting follicular conjunctivitis. Conjunctival hyperemia, photophobia, and watery or mucopurulent discharge are common. Severe cases can lead to papillary hypertrophy or pronounced inflammatory thickening of the conjunctiva. Secondary infections may be experienced.
- **Cicatricial stage.** It affects mainly adults and is characterized by chronic inflammation and eyelid scarring that eventually leads to entropion, trichiasis, and corneal opacification if left undiagnosed and untreated.[11, 12]

The simplified trachoma grading system published by the World Health Organization (WHO) classifies trachoma into five categories for diagnostic and therapeutic purposes (Table 1).[13]

TABLE 1. FEATURES USED FOR ASSESSING TRACHOMA

WHO Simplified trachoma grading system	
Stage	**Characteristics**
Trachomatous inflammation-follicular	Presence of 5 or more follicles >0.5 mm in diameter in the upper tarsal conjunctiva. Involution of follicles in limbal area may result in depressions named Herbert pits
Trachomatous inflammation-intense	Pronounced inflammatory thickening and papillary hypertrophy of the upper tarsal conjunctiva that obscure more than 50% of the deep tarsal vessels
Trachomatous scarring	Presence of linear or stellate scars to thick distortion bands of fibrosis in the tarsal conjunctiva with fornix shortening and symblepharon
Trachomatous trichiasis	Ingrowth of at least one eyelash touching the eyeball or evidence suggesting that in-turned eyelashes have been recently removed
Corneal opacity	Clearly visible corneal opacity over the pupil, blurring its margin

Adapted from: World Health Organization. The simplified trachoma grading system, amended. Internet. World Health Organization. [Updated: December 2019; Reviewed: January 2021]. Available at: https://www.who.int/bulletin/volumes/98/10/19-248708/en/

Diagnosis

The epidemiological background and clinical manifestations are sufficient to make the diagnosis in the field. Several laboratory tests can detect *C. trachomatis* to confirm the diagnosis, but these are mainly used for research purposes. Direct microscopic examination of Giemsa-stained smears of conjunctival cells can demonstrate the presence of Halberstaedter-Prowazek bodies. Culture techniques such as *in-vivo* cell culture in HeLa or McCoy cells can grow *C. trachomatis* colonies. Molecular methods, including nucleic acids amplification test and polymerase chain reaction, can detect *C. trachomatis*-specific DNA sequences. Serological techniques such as the enzyme-linked immunosorbent assay can recognize antigens produced by *C. trachomatis* and antibodies produced by the host against it in biological samples.[2, 12]

Differential diagnosis should always be conducted to rule out other causes of chronic follicular conjunctivitis such as allergic conjunctivitis, bacterial conjunctivitis, inclusion conjunctivitis, and viral conjunctivitis; as well as other causes of cicatricial conjunctivitis including chemical injuries, distichiasis, epiblepharon, mucous membrane pemphigoid, Stevens-Johnson syndrome, and systemic sclerosis.[9]

Treatment

Treatment consists of implementing a multifaceted package of interventions, known as the "SAFE strategy":

- **Surgical treatment.** It is indicated to treat entropion and trachomatous trichiasis. Eyelash removal can relieve the pain caused by rubbing the lashes against the eye. The recurrence rate ranges between 40 and 60%.
- **Antimicrobial treatment.** It is indicated to clear the ocular infection. The first-line treatment is azithromycin (20 mg/kg orally in a single dose). An alternative antibiotic drug is 1% tetracycline eye ointment (1 application intraocularly twice a day for 6 weeks).
- **Facial cleanliness.** It is indicated to prevent further transmission. The cleansing of ophthalmic and nasal discharges prevents eye-seeking flies from approaching and fomites from spreading to clothes and bedsheets.

- **Environmental improvement.** It is indicated to prevent further transmission. Improving sanitation and hygiene habits lowers the prevalence of the disease.[14, 15]

Prevention

No vaccine to prevent trachoma is currently available. The main preventive strategies include improving sanitation and strengthening hygiene.[1]

Conclusion

Trachoma remains the leading infectious cause of blindness worldwide. It is acquired primarily during childhood, in which repeated follicular conjunctivitis leads to visual impairment during adulthood. Diagnosis is performed clinically, and treatment requires several interventions to prevent further complications, but recurrences are common. Prevention can be achieved by improving the living conditions of people. The global response that has been active over the past decades has allowed making progress on preventing the transmission of trachoma. However, efforts should continue, and no patient should be left behind.

References

1. World Health Organization. Trachoma. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/trachoma
2. Mohammadpour M, Abrishami M, Masoumi A, Hashemi H. Trachoma: Past, present and future. J Curr Ophthalmol 2016; 28 (4): 165-169.
3. Dawson CR, Schachter J. Trachoma. In: Guerrant RL, Walker DH, Weller PF. Tropical Infectious Diseases: Principles, Pathogens and Practice. 3rd edition. United States; Elsevier: 2011.
4. World Health Organization. Trachoma. Status of elimination of trachoma as a public health problem: 2020. [Internet]. World Health Organization. [Updated: December 2020; Reviewed: January 2021]. Available at: https://apps.who.int/neglected_diseases/ntddata/trachoma/trachoma.html

5. Hotez PJ, Alvarado M, Basáñez MG, Bollinger I, Bourne R, Boussinesq M, et al. The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases. PLoS Negl Trop Dis 2014; 8 (7): 1-9.

6. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

7. Elwell C, Mirrashidi K, Engel J. Chlamydia cell biology and pathogenesis. Nat Rev Microbiol 2016; 14: 385-400.

8. Faris R, Andersen SE, McCullough A, Gourronc F, Klingelhutz AJ, Weber MM. Chlamydia trachomatis Serovars Drive Differential Production of Proinflammatory Cytokines and Chemokines Depending on the Type of Cell Infected. Front Cell Infect Microbiol 2019; 9: 399.

9. Burton MJ. Trachoma: an overview. British Medical Bulletin 2007; 84: 99-116.

10. Roba AA, Patel D, Zondervan M. Risk of trachoma in a SAFE intervention area. Int Ophthalmol 2013; 33: 53-59.

11. Ahmad B, Patel BC. Trachoma. [Internet]. StatPearls Publishing. [Updated: June 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559035/#:~:text=Trachoma%20is%20a%20bacterial%20infection,causes%20of%20blindness%20worldwide%20today.

12. Last A, Hu V, Mabey D, Burton M, Weller PF, Baron EL. Trachoma. [Internet]. UpToDate. Wolters Kluwer. [Updated: November 2020; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/trachoma?search=trachoma&source=search_result&selectedTitle=1~21&usage_type=default&display_rank=1#H483986778

13. World Health Organization. The simplified trachoma grading system, amended. Internet. World Health Organization. [Updated: December 2019; Reviewed: January 2021]. Available at: https://www.who.int/bulletin/volumes/98/10/19-248708/en/

14. World Health Organization. Weekly epidemiological record. Weekly Epidemiol Record 2017; 26: 357-368.

15. Médecins Sans Frontières. Clinical guidelines / Chapter 5. Eye diseases. Trachoma [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/trachoma-16689733.html

Chapter 20. Yaws

Authors

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Introduction

Yaws, also known as endemic treponematosis, is a chronic, debilitating, and disfiguring bacterial disease caused by *Treponema pallidum* subsp. *pertenue* that primarily affects the skin and bones. It is the most common of a group of chronic infections known as endemic treponematoses, also including bejel and pinta. Yaws is widely distributed but mostly affects children living in poor, neglected communities in warm, humid climates. It develops through distinct stages associated with increasing morbidity and stigmatization.[1]

History

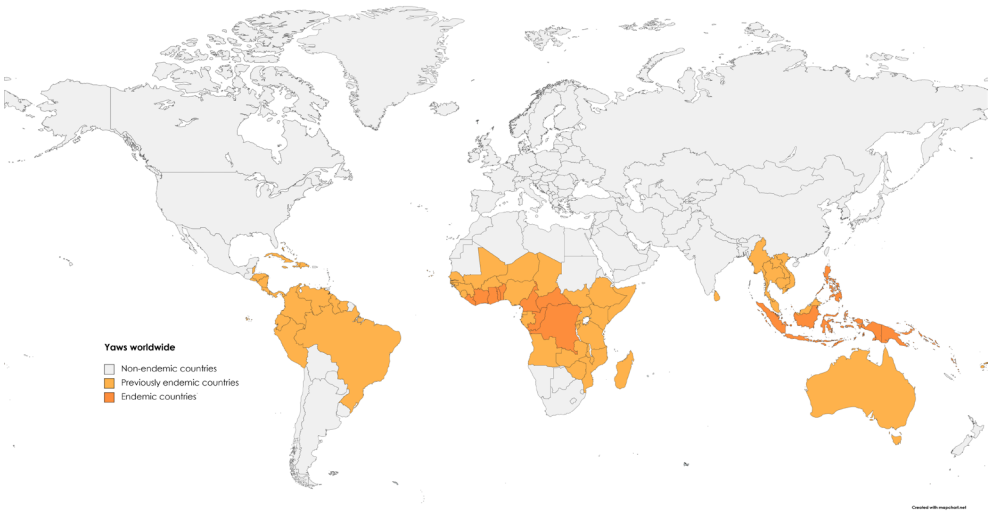
The first evidence of the disease can be traced back to skeletal remains from the Middle Pleistocene (1.5 million years ago) found in Africa. Yaws-related changes were described in skeletal remains dated 850 AD found in Oceania.[2] However, it was until 1905 that Aldo Castellani isolated the etiological agent from skin lesions of infected individuals in former Ceylon (current Sri Lanka); he named it *Spirochaeta pertenuis*. The same year, Frederick Wellman isolated *S. pertenuis* from skin lesions of infected individuals in Africa.[3]

Epidemiology

The precise prevalence and incidence of the disease are unknown, but a total of 80,247 suspected cases were reported in 2018;[4] 1,117 of those cases were confirmed by laboratory tests. The confirmed cases were reported in 9 countries:

Ghana (448 cases), Indonesia (353 cases), Cameroon (150 cases), Vanuatu (140 cases), Côte d'Ivoire (30 cases), The Democratic Republic of the Congo (27 cases), Liberia (24 cases), Benin (4 cases), and Timor-Leste (1 case).[5] Yaws is endemic to Africa (Benin, Cameroon, Central African Republic, Congo, Côte d'Ivoire, The Democratic Republic of the Congo, Ghana, Liberia, and Togo) and Asia (Indonesia, Papua New Guinea, Philippines, Solomon Islands, Timor-Leste, and Vanuatu). The current status of 72 previously endemic countries (Figure 1)[6] and the global burden of yaws are unknown.

FIGURE 1. ENDEMIC AND NON-ENDEMIC COUNTRIES FOR *TREPONEMA PALLIDUM* SUBSP. *PERTENUE*



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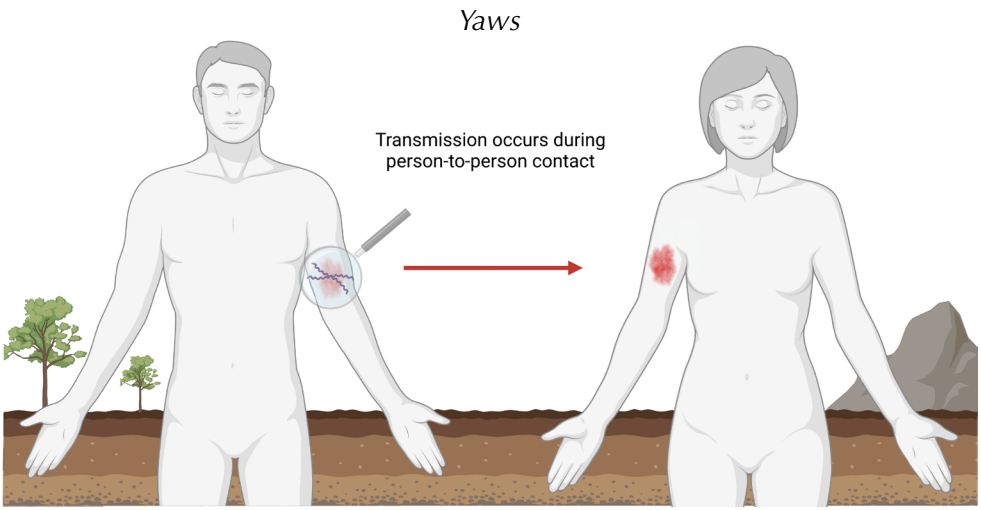
Adapted from: World Health Organization. Global Health Observatory data repository. Status of endemicity for yaws. Data by country. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDYAWSEND?lang=en

Etiology

Yaws is caused by a bacteria named *Treponema pallidum* subsp. *Pertenue*, which belongs to the phylum Spirochaetes, class Spirochaetia, order Spirochaetales, family *Spirochaetaceae*, genus *Treponema*, and species *Treponema pallidum*.[7] *T.*

pallidum subsp. *pertenue* is a Gram-negative bacterium that exhibits characteristic corkscrew-like motility and divides slowly; it grows in hot, humid, and moist climates but cannot survive outside a mammalian host. Transmission occurs by direct contact between an infected and an uninfected individual (Figure 2). Flies have been proposed as vectors, and humans are the sole reservoir, although there have been case reports in non-human primates.[8, 9]

FIGURE 2. MECHANISM OF TRANSMISSION FOR YAWS



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Risk Factors

In countries where yaws is endemic, the main risk factors for acquiring the disease include low socioeconomic status, inadequate sanitation and basic infrastructure, crowded conditions, and poor hygiene habits. Yaws affects both sexes equally and is more prevalent in adults than children.[1, 8]

Clinical Manifestations

The incubation period of the disease ranges between 10 and 90 days. Afterward, the disease develops through several distinct stages:

- **Primary stage.** It is characterized by the development of a primary lesion (mother yaw) at the initial infection site, mainly on the lower extremities. Other parts of the body where it can be found include the face, arms, hands, and buttocks. This lesion is a papule that can grow to become a 2–5 cm nodule; it is not painful but can cause pruritus and eventually ulcerate. The ulceration can be distinguished by its raised dark margins and moist erythematous center. The primary lesion heals spontaneously after 3 to 6 months since the onset of the disease, leaving a hypopigmented pitted scar. The primary lesion may still be present when the secondary stage develops, weeks to years after the onset of the disease.
- **Secondary stage.** It is characterized by the dissemination of *T. pallidum* subsp. *pertenue* through the bloodstream and lymphatic vessels. Secondary lesions (daughter yaws) develop near the primary lesion and can be papules, nodules, ulcers, or plaques, mainly in the lower extremities. Secondary lesions are painful and can lead to altered weight bearing on the external side of the foot (crab-yaws) or osteoperiostitis of phalanges (dactylitis) or long bones (fibula, tibia, radius, and ulna). Secondary lesions can resolve with the administration of antibiotics. However, when infected individuals do not receive adequate treatment, their immune system may control the infection, and the disease enters a latency stage.
- **Latency stage.** It is characterized by the absence of symptomatology while testing positive on serological tests. Relapses may occur once or twice a year, with lesions developing near the mouth, axillae, or anus. Rarely, untreated infected individuals progress to the tertiary stage 5 to 10 years after the onset of the disease.
- **Tertiary stage.** It is characterized by the development of gummatous lesions on the skin and bones. Exostoses of the maxillary bones (goundou), destructive osteitis of the septum and palate (rhinopharyngitis mutilans) with secondary infection (gangosa), and osteoperiostitis of the tibia (saber shin) can be experienced.[10, 11]

Diagnosis

The epidemiological background and clinical manifestations should be considered for diagnosis, but laboratory confirmation is required, and several labora-

tory tests are available for this purpose. Dark-field microscopic examination of lesion scrapings can demonstrate the presence of treponemes. Molecular methods can detect DNA sequences specific to *T. pallidum* subsp. *pertenue* in exudates from ulcers but are not widely available in endemic countries. Serological techniques can recognize non-treponemal and treponemal antibodies in blood samples. Screening can be done with non-treponemal agglutination tests (rapid plasma reagin or venereal disease research laboratory) to detect non-treponemal antibodies; confirmation should be performed with treponemal tests (fluorescent treponemal antibody-absorbed test, treponemal chemiluminescent immunoassay, treponemal enzyme immunoassay, treponemal hemagglutination assay, or treponemal particle agglutination assay) to detect treponemal antibodies. However, these tests cannot distinguish between syphilis and yaws, and it is difficult to run them in low-resource settings. To overcome this issue, several point-of-care tests have become available, which are highly sensitive and specific, and are useful for diagnosis and surveillance.[11, 12]

Imaging studies such as X-rays can be performed to identify periostitis in secondary yaws and osteoperiostitis in tertiary yaws.[13]

Differential diagnosis should always be conducted to rule out a variety of skin diseases, including chromomycosis, leishmaniasis, leprosy, molluscum contagiosum, psoriasis, sarcoidosis, and scabies, among others, as well as a variety of bone lesions such as bacterial osteomyelitis, bejel, histoplasmosis, sickle cell anemia, syphilis, and tuberculosis, among others.[12]

Treatment

Treatment consists of wound cleansing and administering antibiotics. The first-line treatment is azithromycin (30 mg/kg orally in a single dose). The second-line treatment is benzathine penicillin (0.6 million IU intramuscularly in a single dose for children under 10 years of age and 1.2 million IU intramuscularly in a single dose for children over 10 years and adults). Follow-up is recommended for at least 1 month after completing antibiotic treatment to confirm clearance of the infection, identify underlying complications, and observe any recurrence.[1, 14]

Prevention

No vaccine to prevent yaws is currently available. The main preventive strategies include improving personal hygiene and curbing the transmission through early diagnosis and adequate treatment at individual and community levels.[1]

Conclusion

Yaws has been set as the second neglected tropical disease to be eradicated. However, it remains an issue in poor and marginalized communities across the world. Yaws causes a chronic disease characterized by highly contagious primary and secondary cutaneous lesions and non-contagious tertiary destructive lesions of the bones. The infection can become latent at any time, and relapses can occur up to a decade later. Diagnosis of yaws has historically been based on careful analysis of the epidemiological background and clinical manifestations due to the unavailability of reliable tests in endemic regions. The development of affordable and reliable point-of-care tests has been a major step forward. A single dose of azithromycin or benzathine penicillin can entirely cure the disease. Therefore, it is unacceptable that people still suffer the consequences of this disease. As we progress towards achieving its eradication, the affected countries should commit to diagnose and adequately treat the remaining cases.

References

1. World Health Organization. Yaws. [Internet]. World Health Organization. [Updated: April 2019; Reviewed: January 2021]. Available at: http://www.who.int/media-centre/factsheets/fs316/en/
2. Rose M. Yaws Origin. Archeology 1996; 49 (3): 1.
3. Stamm LV. Yaws: 110 years after Castellani's discovery of Treponema pallidum subspecies pertenue. Am J Trop Med Hyg 2015; 93 (1): 4-6.
4. World Health Organization. Global Health Observatory data repository. Number of suspected yaws cases reported. Data by country. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDYAWSNUMSUSP?lang=en
5. World Health Organization. Global Health Observatory data repository. Number of confirmed yaws cases reported. Data by country. [Internet]. World Health Organi-

zation. [Updated: August 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDYAWSNUMCONF?lang=en

6. World Health Organization. Global Health Observatory data repository. Status of endemicity for yaws. Data by country. [Internet]. World Health Organization. [Updated: August 2020; Reviewed: January 2021]. Available at: https://apps.who.int/gho/data/node.main.NTDYAWSEND?lang=en

7. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. Database (Oxford) 2020; 2020: baaa062.

8. Marks M, Lebari D, Solomon AW, Higgins SP. Yaws. Int J STD AIDS 2015; 26 (19): 696-703.

9. Perine PL, Hopkins DR, Niemel PLA, St. John R, Causse G, Antal GM. Handbook of endemic treponematoses: yaws, endemic syphilis. 1st edition. Geneva; World Health Organization: 1984.

10. Maxfield L, Corley JE, Crane JS. Yaws. [Internet]. StatPearls Publishing. [Updated: July 2020; Reviewed: January 2021]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK526013/

11. Mijta O, Mabey D, Ryan ET, Baron EL. Trachoma. [Internet]. UpToDate. Wolters Kluwer. [Updated: September 2019; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/yaws-bejel-and-pinta?source=history_widget

12. Giacani L, Lukehart SA. The Endemic Treponematoses. Clinical Microbiology Reviews 2014; 27 (1): 89-115.

13. Mitjà O, Hays R, Ipai A, Wau B, Bassat Q. Osteoperiostitis in early yaws: case series and literature review, Clin Infect Dis 2011; 52: 771-774.

14. Médecins Sans Frontières. Clinical guidelines / Chapter 4. Skin diseases. Endemic treponematoses. [Internet]. Médecins Sans Frontières. [Updated: 2018; Reviewed: January 2021]. Available at: https://medicalguidelines.msf.org/viewport/CG/english/endemic-treponematoses-16689682.html

Chapter 21. Snakebite Envenoming

Authors

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Introduction

Snakebite envenoming was the first non-infectious disease acknowledged as a neglected tropical disease (NTD) by the World Health Organization (WHO). It mainly affects people living in poor, neglected communities with inadequate healthcare services. Although there is a highly effective treatment to prevent death from snakebite envenoming, people in need do not always receive it.[1]

Historical Background

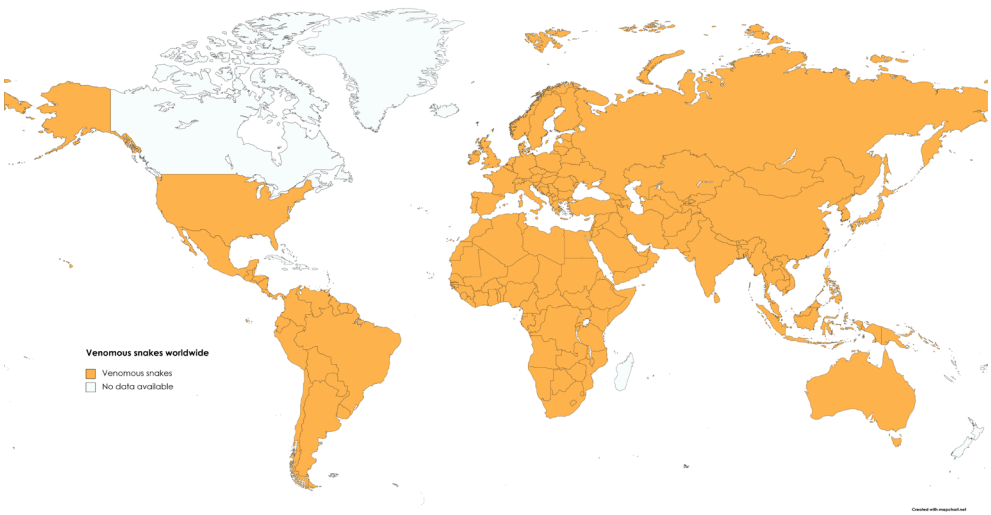
Snakebite envenoming has occurred since the beginning of humankind, and most individuals who got bitten by a venomous snake developed a permanent disability or died. Throughout history, several remedies were proposed and administered unsuccessfully until 1887, when Henry Sewall demonstrated that pigeons could be immunized against the pygmy rattlesnake venom. In 1894, Albert Calmette developed the first antivenom serum derived from hyperimmunized horses to treat cobra venom poisoning, and he started producing it commercially in 1898, making it widely available in Vietnam. Since then, several sources of antivenom serum have been developed and tested with varying success. Recent advances in technology have made them highly effective.[2]

Epidemiology

Each year, snakes are estimated to bite about 5.4 million people, almost 2.3 million suffer snakebite envenoming, approximately 0.4 million become disabled,

and nearly 0.1 million die worldwide. Although snakebite envenoming occurs across the world, most cases are reported in Africa, America, and Asia.[3, 4] In 2018, Joshua Longbottom et al. mapped hotspots of vulnerability to snakebite envenoming and estimated that 6.86 billion people live in areas that are home to at least one of the 278 known species of venomous snakes, especially in Latin America, Southeast Asia, and the Congo Basin in Africa (Figure 1). Some 750.19 million of these persons live more than 1 hour away from high-density areas, increasing the probability of not getting access to adequate healthcare services, which highlights the importance of addressing this global threat immediately. Detailed information on this issue can be found in the source document.[5]

FIGURE 1. COUNTRIES WITH VENOMOUS SNAKE SPECIES



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Adapted from: Longbottom J, Shearer FM, Devine M, Alcoba G, Chappuis F, Weiss DJ, et al. Vulnerability to snakebite envenoming: a global mapping of hotspots. Lancet 2018; 392 (10148): 673-684.

Etiology

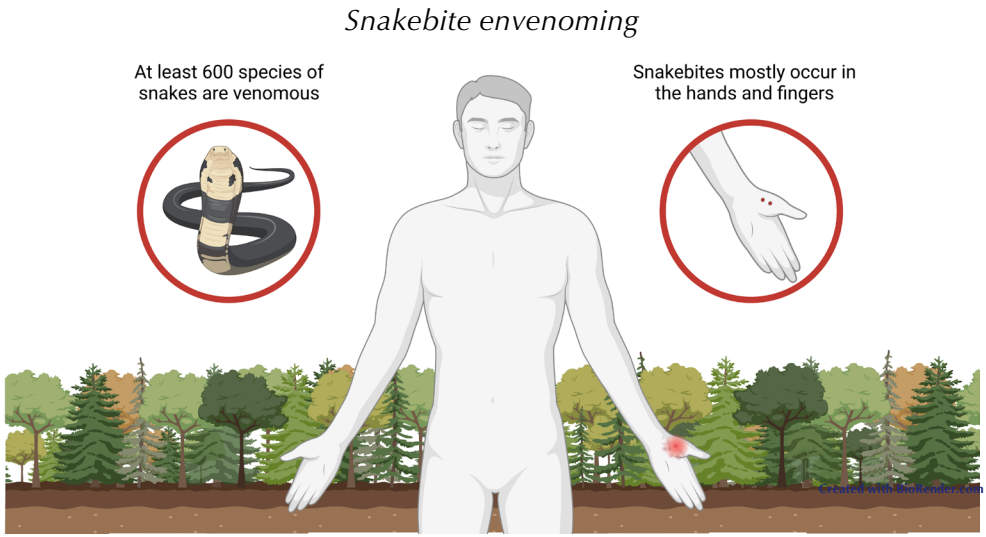
There are more than 3,000 known species of snakes in the world, over 600 of which are venomous, and nearly 200 are medically relevant (Figure 2). The med-

ically relevant snakes can be classified into two categories based on the level of risk they pose for humans:

- **Category I.** This category includes common or widespread highly venomous snakes that bite frequently, causing high morbidity, disability, or mortality.
- **Category II.** This category includes uncommon or not widespread but highly venomous snakes that do not bite frequently or for which epidemiological or clinical data are lacking, although with the potential to cause high morbidity, disability, or mortality.[6]

Table 1 shows the detailed list of category I and category II venomous snakes provided by the WHO.

FIGURE 2. MECHANISM OF TRANSMISSION FOR SNAKEBITE ENVENOMING



Risk Factors

In rural areas, the main risk factors for acquiring the disease include low socioeconomic status and occupational activities (agriculture, fishing, and plantation work). Snakebite envenoming is more prevalent in men than women and in children than adults.[8]

TABLE 1. WHO LIST OF CATEGORY I MEDICALLY IMPORTANT SNAKE SPECIES PER REGION

WHO medically important venomous snakes – Category I	
Region	**Family and species**
Africa and the Middle East	**Atractaspididae:** *Atractaspis andersonii* **Elapidae:** *Dendroaspis angusticeps, D. jamesoni, D. polylepis, D. viridis, Naja anchietae, N. annulifera, N. arabica, N. ashei, N. haje, N. katiensis, N. melanoleuca, N. mossambica, N. nigricincta, N. nigricollis, N. nivea, N. oxiana, N. senegalensis* **Viperidae:** *Bitis arietans, B. gabonica, B. nasicornis, B. rhinoceros, Cerastes cerastes, C. gasperettii, Daboia mauritanica, D. palaestinae; Echis urkini, E. carinatus, E. coloratus, E. jogeri, E. leucogaster, E. ocellatus, E. omanensis, E. pyramidum, Macrovipera lebetina, Montivipera xanthine, Pseudocerastes persicus*
America and the Caribbean	**Viperidae:** *Agkistrodon bilineatus, A. contortrix, A. piscivorus, A. taylori, Bothrops alternatus, B. asper, B. atrox, B. bilineatus, B. brazili, B. caribbaeus, B. diporus, B. jararaca, B. jararacussu, B. lanceolatus, B. leucurus, B. mattogrossensis, B. moojeni, B. pictus, B. venezuelensis, Crotalus adamanteus, C. atrox, C. durissus, C. horridus, C. oreganus, C. simus, C. scutulatus, C. totonacus, C. viridis, Lachesis muta*
Asia and Australasia	**Elapidae:** *Acanthophis laevis Bungarus caeruleus, B. candidus, B. magnimaculatus, B. multicinctus, B. niger, B. sindanus, B. walli, Naja atra, N. kaouthia, N. mandalayensis, N. naja, N. oxiana, N. philippinensis, N. samarensis, N. siamensis, N. sputatrix, N. sumatrana, Notechis scutatus, Oxyuranus scutellatus, Pseudechis australis, Pseudonaja affinis, P. mengdeni, P. nuchalis, P. textilis* **Viperidae:** *Calloselasma rhodostoma, Cryptelytrops albolabris, C. erythrurus, C. insulari, Daboia russelii, D. siamensis, Deinagkistrodon acutus, Echis carinatus, Gloydius blomhoffii, G. brevicaudus, G. halys, Hypnale hypnale, Macrovipera lebetina, Protobothrops flavoviridis, P. mucrosquamatus, Viridovipera stejnegeri*
Europe	**Viperidae:** *Vipera ammodytes, Vipera aspis, Vipera berus*

Adapted from: World Health Organization. WHO Guidelines for the Production, Control, and Regulation of Snake Antivenom Immunoglobulins. 1st edition. Geneva, Switzerland; WHO: 2010.

Clinical Manifestations

Clinical manifestations depend on the snake species. Some individuals may not even notice that they were bitten until life-threatening complications have developed, whereas others may develop local and progressive systemic symptomatology. Fang marks, pain, erythema, ecchymosis, swelling, blistering, and necrosis may occur at the wound site; lymph node enlargement indicates that the venom has spread; and anxiety, lethargy, sweating, syncope headache, tachypnea, tachycardia, nausea, vomiting, abdominal pain, acroparesthesia, and carpopedal spasm may be experienced in case of systemic involvement.

Depending on the toxins in the venom, several complications can appear:

- **Venom-induced neurotoxicity.** It is characterized by dysfunction of the neuromuscular junction, leading to cranial nerve palsies (mydriasis, diplopia, ptosis, facial palsy, drooling, and dysphagia) and descending flaccid neuromuscular paralysis (limb weakness or paralysis, decreased or absent reflexes, gait disturbance, and respiratory failure), among others. Some species first induce cranial nerve palsy that proceeds with generalized involvement, whereas the neurotoxicity induced by other venoms presents with both simultaneously.
- **Venom-induced coagulopathy.** It is characterized by dysfunction of the hemostatic system, which leads to overt bleeding (epistaxis, gingival bleeding, hemoptysis, hematemesis, hematochezia, hematuria, and oozing in venipuncture sites) and prothrombotic states (cerebral infarction, pulmonary embolism, and deep vein thrombosis), among others. Some species readily induce coagulopathies, and others cause this symptom slowly; coagulopathies induced by some species reverse spontaneously, while others require the administration of antivenom for reversal.
- **Venom-induced cardiac vasculopathy.** It is characterized by dysfunction of the cardiovascular system, leading to shock (altered mental status, tachycardia, hypotension, prolonged capillary refill, and decreased urinary output are common). Species capable of causing cardiac vasculopathy can also cause coagulopathies and myopathies.
- **Venom-induced myopathy.** It is characterized by direct damage to muscles, leading to rhabdomyolysis (myalgia, myasthenia, and hematuria). Some cases may present with compartment syndrome (myasthenia, myal-

gia upon passive stretching, tenderness upon palpation, aching or burning pain that does not respond to opioids, and absence of color or pulse) or acute kidney injury (oliguria and red to brown colored urine). Species capable of causing myopathies can also cause coagulopathies and cardiac vasculopathy.

The time elapsed from the snakebite to the onset of clinical manifestations also depends on the snake species. Local clinical manifestations such as swelling appear two to four hours after the snakebite, blistering in 2 to 12 hours, and necrosis in 12 to 24 hours. Systemic clinical manifestations such as syncope, tachypnea, tachycardia, nausea, and vomiting appear within minutes after the snakebite. Venom-induced neurotoxicity may appear within minutes after the snakebite and venom-induced coagulopathy, coagulopathy, and myopathies, within hours.[9, 10]

Diagnosis

The epidemiological background and clinical manifestations are essential to make the diagnosis. However, some individuals may not recall having been bitten or, if they do, they could not have identified the biting species. The clinical history, physical examination, and vital signs of the affected person help suspect snakebite envenoming, but specific supplementary tests should be performed to confirm the presence of specific complications:

- **Venom-induced neurotoxicity.** An edrophonium test may indicate postsynaptic paralysis and whether this is responsive to anticholinesterase and antivenom serum.
- **Venom-induced coagulopathy.** A complete blood count can reveal anemia and thrombocytopenia; a whole blood coagulation test can indicate whether the international normalized ratio, prothrombin time, or activated partial thromboplastin time are too long. Fibrinogen levels may decrease, and D-dimer levels may increase.
- **Venom-induced cardiac vasculopathy.** A complete blood count can reveal anemia, hemodilution, hemoconcentration, and thrombocytopenia; a central venous pressure line can show sudden changes in blood pressure.

- **Venom-induced myopathies.** A rapid urine dipstick may show the presence of blood; blood chemistry testing may reveal increased potassium, serum creatinine kinase, and blood-urea nitrogen. An electrocardiogram may reveal hyperkalemia-related changes. Myoglobin may be present in urine.

When the biting species cannot be identified, venom antigens must be detected and quantified in biological samples of the bitten individual to provide an adequate antivenom and assess the prognosis. This can be done by obtaining wound aspirates or swabs and using serological methods such as antibody microarrays, DNA fingerprinting, enzyme-linked immunosorbent assay, and liquid chromatography-mass spectrometry with time-of-flight. Molecular methods such as reverse transcription-polymerase chain reaction are under development.[9, 11]

Treatment

Treatment of patients bitten by a snake begins in a pre-hospital setting and continues through in-patient therapy:

- **Pre-hospital setting.** Immobilization of the affected area, removal of accessories around or near the bitten extremity, and direct pressure over the bite wound must be performed immediately. Afterward, analgesics such as acetaminophen or opioids should be administered by a health professional to relieve the pain.
- **In-patient treatment.** Oxygen supplementation and intravenous resuscitation must be started according to the clinical condition of the patient. Careful assessment must be performed to identify whether snakebite envenoming is ongoing to administer either monovalent or polyvalent antivenom, according to whether the biting species is or is not known, respectively. The dosage depends on the manufacturer, and patients must remain under observation after administration due to the potential risk of anaphylaxis.

Specific measures to be taken in case of venom-mediated complications:

- **Venom-induced neurotoxicity.** Administration of **s**pecific antivenom to neutralize the toxins plus atropine and neostigmine to improve neuro-

muscular transmission are necessary. Management and support of the airways, breathing, and circulation with regular reassessment must be performed.

- **Venom-induced coagulopathy.** Administration of specific antivenom to neutralize the toxins plus blood or blood-derived transfusions to revert hemodilution are necessary. Management and support of the airways, breathing, and circulation with regular reassessment should be performed.
- **Venom-induced cardiac vasculopathy.** Specific antivenom to neutralize the toxins plus intravenous resuscitation with isotonic solutions and vasoactive drugs to maintain blood pressure are required. Management and support of the airways, breathing, and circulation with regular reassessment must be performed.
- **Venom-induced myopathies.** Intravenous resuscitation with isotonic solutions to restore urinary output is required. Hemodialysis in case of acute kidney injury may be needed.

All cases warrant proper wound cleansing and administration of antibiotics in case of deep injuries. Patients should be discharged only when there is clinical improvement and when no risk of delayed complications is anticipated. Follow-up is recommended 5 to 15 days after antivenom administration, and rehabilitation is strongly encouraged.[9, 10]

Prevention

The main preventive strategies currently available include disease awareness, wearing protective clothing, avoiding walking in areas covered by tall grass, staying away from snakes, innovative and intensified disease management, and avoiding handling piles of leaves, rocks, or logs.[12]

Conclusion

NTDs have traditionally included infectious diseases. However, snakebite envenoming was included in the list of NTDs because of the shortage of antivenom production, among other reasons. Snakes are distributed worldwide, but coun-

tries located between the tropics harbor the largest variety of species. Persons who are bitten in rural areas are at increased risk of high morbidity, disability, and mortality due to poor healthcare services. If they manage to reach adequate healthcare facilities, sometimes antivenoms are in short supply. Increasing antivenom production and widening their scope will save many preventable deaths around the world.

References

1. Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease! J Venom Anim Toxins incl Trop Dis 2017; 23: 38.
2. Lalloo DG, Theakston DG. Snake Antivenoms. J Toxicol 2003; 41 (3): 277-290.
3. World Health Organization. Snakebite envenoming. [Internet]. World Health Organization. [Updated: April 2019; Reviewed: January 2021]. Available at: https://www.who.int/news-room/fact-sheets/detail/snakebite-envenoming
4. Longbottom J, Shearer FM, Devine M, Alcoba G, Chappuis F, Weiss DJ, et al. Vulnerability to snakebite envenoming: a global mapping of hotspots. Lancet 2018; 392 (10148): 673-684.
5. World Health Organization. Global snakebite burden. [Internet]. World Health Organization. [Updated: March 2018; Reviewed: January 2021]. Available at: https://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_17-en.pdf
6. World Health Organization. Venomous snakes distribution and species risk categories. [Internet]. World Health Organization. [Updated: 2020; Reviewed: January 2021]. Available at: https://apps.who.int/bloodproducts/snakeantivenoms/database/default.htm
7. World Health Organization. WHO Guidelines for the Production, Control, and Regulation of Snake Antivenom Immunoglobulins. 1st edition. Geneva, Switzerland; WHO: 2010.
8. Hossain J, Biswas A, Rahman F, Rahmnan-Mashreky S, Dalal K, Rahman A. Snakebite Epidemiology in Bangladesh – A National Community Based Health and Injury Survey. Health 2016; 8: 479-486.
9. White J, Danzl DF, Traub SJ, Wiley JF. Snakebites worldwide: Clinical manifestations and diagnosis. [Internet]. UpToDate, Wolters Kluwer. [Updated: December 2020; Reviewed: January 2021]. Available at: https://www.uptodate.com/contents/snakebites-worldwide-clinical-manifestations-and-diagnosis?search=snake&source=search_result&selectedTitle=2~61&usage_type=default&display_rank=2#H1544315

10. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrel DA. Snakebite envenoming. Nature Rev Dis Primers 2017; 3: 17063.

11. Feola A, Marella GL, Carfora A, Pietra BD, Zangani P, Campobasso CP. Snakebite Envenoming a Challenging Diagnosis for the Forensic Pathologist: A Systematic Review 202; 12: 699.

12. Oregon Health & Science University. Snake bite prevention. [Internet]. Oregon Health & Science University. [Updated: 2020; Reviewed: January 2021]. Available at: https://www.ohsu.edu/sites/default/files/2019-10/SNAKE-BITE-PREVENTION-TOOLKIT_0.pdf