Lymphatic Filariasis

Akre M Adja*, Sina Helbig, Alia Tayea, Neil Arya**

Prepared as part of an education project of the Global Health Education Consortium and collaborating partners

*First author **Corresponding author
7.1 Epidemiology: Lymphatic Filariasis

- Lymphatic Filariasis (LF) is caused by **two main types** of vector-borne filarial nematodes:
  - **TYPE 1** *Wuchereria bancrofti* (Bancroftian filariasis): tropical Africa, Americas, Asia, Pacific - represents most of global burden
  - **TYPE 2** *Brugia malayi* (SE Asia, India), *B. timori* (Indonesia)

- Endemic in **more than 80 countries** in Asia, Africa, Central & South America, with over 120 million infected (~40% of infected people live in India and ~33% of infected people live in Africa)
Areas in red indicate LF presence (photo credit: CDC)

Photo from http://www.cdc.gov/parasites/lymphaticfilariasis/epi.html
7.1 Epidemiology: Lymphatic Filariasis

- LF is a main cause of long-term disability worldwide
- Results in a spectrum of clinical/subclinical disease
  - Asymptomatic **microfilaremia** (infection of the blood with microfilariae)
  - Chronic lymphadenitis with elephantiasis (swelling of dependent limb or scrotum)
  - Tropical pulmonary eosinophilia

Gardener in Nigeria with elephantiasis

Photo credit: WHO/TDR/Crump (1995)
7.1 Epidemiology: Lymphatic Filariasis

- Even in microfilaremic patients who appear healthy, there is some degree of suppression of the immune system
  - Infected people are thus more vulnerable to other infections such as TB
  - Specific effects of HIV infection on LF are largely unknown
  - One study showed that the replicative capacity of HIV is significantly enhanced in peripheral blood mononuclear cells from patients with untreated LF
  - Many also have evidence of impaired renal function
7.2 Risk factors: Lymphatic Filariasis

- LF is transmitted by **mosquitoes**, so risk factors include those that are conducive to the life cycle of mosquitoes
- Poor drainage, vector breeding sites
- Poor sanitation
- Vulnerability to mosquito bites due to low **insecticide-treated net** (ITN) use, etc.
- Inadequate case treatment, resulting in accumulation of disability and persistence of infection reservoir
- Interruption of LF-eradication, vector control programmes

7.3 Biology: Lymphatic Filariasis

- **Mosquito vectors**
  - *Anopheles spp.*: most common vector in Africa
  - *Culex spp.*: most common vector in the Americas
  - *Aedes spp.*: can transmit in Asia & Pacific regions
  - *Mansoninae spp.*: can transmit in Asia & Pacific regions

- **Adult worms reside in the lymphatic system of the human host**
  - Female *W. bancrofti*: 80-100 x 0.25 mm
  - Male *W. bancrofti*: 40 x 0.1 mm
  - *Brugia spp* are only half of this size
7.3 Biology: Lymphatic Filariasis

- Microfilarial periodicity
  - Periodicity in concentration of microfilariae in blood of the host – corresponding with biting habits of principal vector
  - *W. bancrofti* and *B. malayi*: mostly nocturnal with peak blood concentrations around midnight

Photo:http://www.the-travel-doctor.com/filari12.gif
7.3 Life cycle

- Microfilaria are produced from ova in the uterus of the female worm
- Development takes 10-12 days
- Mature infective larvae then migrate to the mouthparts of the mosquito from where they enter the skin of the human host
- Larvae migrate to the lymphatics and develop to adult worms. Adult worms live in tissue
- Microfilariae appear in the blood after about 8 months (*W bancrofti*) and 3 months (*Brugia malayi*)
- The adult worm may live and produce microfilariae for up to 20 years
- Microfilariae have lifespan of ~ 1 year

This illustration depicts the life cycle of Brugia malayi, one of the parasitic worms that cause the tropical disease lymphatic filariasis. Credit: CDC
7.4 Symptoms: Lymphatic Filariasis

- Wide range of clinical presentations

- Asymptomatic microfilaremia in individuals:
  - Who have not been sufficiently exposed to be infected
  - With prepatent infection, adult worm infection without microfilaremia
  - Who have cleared the infection

- Acute manifestations: adenolymphangitis (filarial fever)
  - Characteristic of both Bancroftian and Malayan filariasis
  - Episodic attacks of fever, malaise, chills (resembles malaria)
  - Enlarged painful lymph nodes draining the affected part
  - Duration usually 1 wk, may recur multiple times within 1 yr
  - May also have filarial abscess; pus sterile or with bacteria
7.4 Symptoms: Lymphatic Filariasis

- **Chronic manifestations**
  - Hydrocele
  - Lymphedema
  - Elephantiasis (mainly lower limbs, less commonly arms, genitals, breast)
  - Chyluria
  - Tropical pulmonary eosinophilia

- **Brugian filariasis**
  - Less genital involvement
  - Elephantiasis usually restricted to areas below the knee
7.4 Symptoms

30yr old male from Papua New Guinea with bilateral elephantiasis

Photo credit: WHO/TDR/Crump (1995)
7.4 Symptoms

Photo credit: CDC
7.5 Diagnosis

• Based on symptoms

• Parasitological
  o Microfilariae in patient’s blood at peak time of concentration (at night)
    ▪ Measured by counting chamber
    ▪ Staining techniques (Giemsa or hematoxylin and eosin)
    ▪ Membrane filtration technique (Nucleopore) – high sensitivity, but costly filters
      ▪ Knott concentration technique
  o Adult worm usually not detectable
  o Absence of microfilaremia does not exclude filarial disease, nor does microfilaremia denote it
  o Microfilariae in hydrocele fluid, sometimes urine or other fluid
7.5 Diagnosis

- Immunological and PCR
  - Serology only has a role in visitors to the area
  - IgG4 Antibody = marker of active infection
  - Periodicity – independent
  - PCR - need at least one microfilaria in blood volume

- Ultrasonography
  - Detection of *W. bancrofti* filarial worms in lymphatic vessels of limbs and scrotum of infected males
  - Less reliable in female genitals
7.6 Treatment

- Treatment consists of drugs directed against microfilariae (microfilaricidal) and adult worms (macrofilaricidal) combined with symptomatic treatment to relieve already caused by the disease.

- Diethylcarbamazine (DEC)
  - Microfilaricidal: most common agent used since >50 yrs
  - Macrofilaricidal: capable to kill a proportion of adult *W. bancrofti* and *Brugia* spp.

- Ivermectin
  - Microfilaricidal, not macrofilaricidal
  - Since not macrofilaricidal repeated doses every 6 months or yearly are needed

- Symptomatic
  - Bandaging
  - Physiotherapy
  - Infection-prevention
  - Treatment of secondary bacterial infection (e.g. in filarial abscess)
7.6 Treatment

- Surgery
  - Hydrocele drainage
  - Surgical intervention in elephantiasis of limbs has proven unsuccessful

- Promising research
  - Depletion of filarial worms of endosymbiontic *Wolbachia* bacteria
  - Trials with doxycycline

7.7 Control

• Avoiding mosquito bites
  o Sleeping under an ITN
  o Use of repellent/long clothing between dusk and dawn

• Awareness raising in high-risk and endemic areas

• Annual mass community treatment
  o Reduces microfilarial load and diminishes transmission
  o Added benefit of this as drugs used also help control other helminthic infections!
Onchocerciasis

River blindness
8.1 Epidemiology

- Vector-borne filarial infection and 2\textsuperscript{nd} leading infectious cause of blindness worldwide
- Est. 50 million people at risk of onchocerciasis
- Est. 37 million infected with \textit{O. volvulus}, 270,000 blind as a result\textsuperscript{1}, 500,000 have some degree of visual impairment
- Mainly endemic to sub-Saharan Africa, but some foci in the Arabian Peninsula (mainly Yemen) and Latin America
- In endemic regions it is a major cause of disfiguring skin changes and damaging eye lesions

8.1 Epidemiology

- Also associated with epilepsy in high-prevalence areas (e.g. parts of Uganda\textsuperscript{1}, Cameroon\textsuperscript{2})
- Prior to Onchocerciasis Control Project (1974-2002) in West Africa, huge areas of fertile land were abandoned in because of the disease
- In some communities, onchocerciasis cause of large prevalence of blindness
  - E.g. up to 35% in some villages in Burkina Faso
  - In addition to morbidity, other results are loss of productivity for both the infected and their families

8.1 Epidemiology - Affecting lives

Child leading a blind man in a village where onchocerciasis is endemic

Photo: http://www.onchohki.org
8.1 Epidemiology/distribution

Photo credit: http://mectizan.org/onchocerciasis-maps
8.2 Risk factors

- Communities living near flowing rivers and streams that form breeding grounds to the blackfly of the *Simulium* species

- Mainly rural agricultural areas

A flowing river, habitat for the *Simulium spp.* vector, in an onchocerciasis-endemic district of southern Malawi. (Photo credit: Alia Tayea, 2006)
8.3 Biology

• Infection by *Onchocerca volvolus*

• Humans are the natural hosts

• Vectors: blackfly (*Simulium* spp.)

• Adult worms: slender, white
  o Males: 2-5 cm x 0.2 mm
  o Females: 35-70 cm x 0.4 mm
  o Microfilariae: 300 μm x 8 μm

• Adult worms produce larvae in body throughout their lifespan

http://www.parasitologie.nl/assets/images/galerie_plaatjes/781/nem_00310_onchocerca_volvulus.jpg
8.3 Life cycle

**Onchocerca volvulus**

**Blackfly Stages**

1. Blackfly (genus Simulium) takes a blood meal (L3 larvae enter bite wound)
2. Migrate to head and blackfly’s proboscis
3. L3 larvae
4. Microfilariae penetrate blackfly’s midgut and migrate to thoracic muscles
5. Blackfly takes a blood meal (ingests microfilariae)
6. Subcutaneous tissues
7. Adults in subcutaneous nodule
8. Adults produce unsheathed microfilariae that typically are found in skin and in lymphatics of connective tissues, but also occasionally in peripheral blood, urine, and sputum.

**Human Stages**

1. Infective Stage
2. Diagnostic Stage
8.4 Symptoms

- Main manifestations
  - Skin lesions
  - Nodule formation
  - Severe itching due to body’s inflammatory response
  - Eye lesions (late)

- Lymphedema, hydrocele, hanging groin

- Long exposure is usually required to develop symptoms – many cases are asymptomatic

- Severity depends on intensity of infection
8.4 Symptoms - skin

- Lesions occur when microfilariae undergo destruction of skin
  - Few papules to large nodules
  - Extensive pigmentary and texture changes due to inflammatory reaction to *O. volvulus* antigens
  - Intense itching
  - Chronic atrophic, fibrotic changes
  - Often different stages are present at the same time

Photo: http://www.who.int/apoc/media/skin.gif
8.4 Symptoms - skin

• Early symptoms
  o Itching (filarial itch)
  o Rash (consists of raised papules = microabscesses)

• Later symptoms
  o Heavy lichenification (lizard skin)
  o Loss of elastic fibers in skin of the groin (hanging groin)
  o Leopard skin (loss of pigment, degeneration of dermal collagen, thinning of epidermis) – mainly pretibial region
  o Onchocercomata = granulomas resulting from a tissue reaction around adult worms
8.4 Symptoms - skin

62 yr old in Uganda with “leopard skin” resulting after many years of infection

Photo: WHO/APOC/TDR/Crump, 2001
8.4 Symptoms - eyes

- Ocular involvement as a result of microfilariae migrating through, collecting and dying in eye tissue

- Damage caused by microfilariae and inflammatory response to these, particularly dying/dead microfilariae

- May progress to blindness

- Anterior and posterior segment can be involved
8.4 Symptoms – eyes

- Anterior segment lesions
  - Punctuate keratitis (snowflake opacities)
    - Acute inflammatory reaction around microfilariae more common in younger age
    - Reversible
  - Sclerosing keratitis
    - Vascular infiltrates begin at limbus and pass inwards resulting in excessive scarring → blindness
  - Iridocyclitis – caused by dying microfilariae

- Posterior segment lesions
  - Optic nerve atrophy: choroidoretinitis → blindness
  - Acceleration of optic nerve damage may follow treatment with DEC
8.4 Symptoms – eyes

Sclerosing keratitis in a man blinded by onchocerciasis in West Africa

Photo credit: WHO/TDR
8.5 Diagnosis

- Clinical - skin/eye lesions, subcutaneous nodules

- Ultrasonography - detection of nodules in tissues, follow up of drug effects on worms

- Mazzotti test - administration of small dose of DEC p.o. if itching/rash develops could be diagnostic for infection

- DEC patch test (historically used but no longer recommended)
  - Gauze soaked in 20% DEC solution applied to skin (hip), site later checked for inflammatory reaction
  - Less risk of systemic inflammatory reaction than Mazzotti test
  - Good test for re-emergence of infection
8.5 Diagnosis

- Parasitological diagnosis
  - Demonstrating microfilariae that have emerged from bloodless skin snips (biopsy preferred from iliac crest or below) – immersion of snips in isotonic saline, counting of emerging microfilariae

- Immunologic and PCR based diagnosis
  - Antibody detection to crude Ag is of limited practical use
  - Specific IgG4 Antibodies
  - PCR – identification of worm DNA and distinction between various strains
8.6 Treatment

- Removal of nodules/onchocercomas
- Ivermectin – drug of choice
  - Single dose 150 μg/kg bodyweight
  - Rapid elimination of microfilariae from skin. Low level is obtained over 6-12 months; retreatment may be required
  - Beneficial effect on eye (slower elimination) except chorioretinitis (no effect)
  - No long-lasting effect on mature worms; treatment required for life-span of adult worm (10-14 yrs)
- Suramin – largely macrofilaricidal with some microfilaricidal effect
  - Due to toxicity and severe adverse effects¹ reserved for severe hyperreactive onchodermatitis not responding to ivermectin

¹ Including haemolytic anaemia, thrombocytopenia, neutropenia, optic atrophy
8.6 Treatment

- DEC is no longer recommended for use due to severe adverse reactions
  - Especially in severely infected people (inflammatory reaction to parasite death)
  - Potential worsening of eye lesions

- Potential new targets for chemotherapy with antibiotics - endosymbiotic *Wolbachia* bacteria
  - Doxycycline 100mg/day x 4-6 weeks resulted in long term sterilization of, and increased dead proportion of adult worms
  - Doxycycline 200mg/day x 6 weeks resulted in even higher (~70%) proportion of dead adult worms after >24 months
  - Kills parasites over extended timeframe, less parasite-mediated inflammatory reactions

1Taylor, MJ, Hoerauf, A, and Bockarie, M (2010); Lymphatic filariasis and onchocerciasis; The Lancet, 376(9747), p.1175 - 1185, 2 October 2010
8.7 Control

- No vaccine for onchocerciasis
- Vector control: spraying of blackfly habitats with insecticide to kill larvae
- Community directed treatment with ivermectin (donated by Merck & Co. Inc. since 1987)
  - One of NTD success stories
  - 6-monthly or yearly mass treatment with ivermectin in at-risk communities
- Sustained vigilance in at-risk areas, along with multi-stakeholder cooperation to ensure capacity for diagnosis and treatment at community level
8.7 Control

CDTI poster in a rural health centre in Thyolo District, Malawi

Photo credit: Alia Tayea, 2007
8.8 Treatment

Slow extraction of adult female worm after emergence from blister

8.8 Treatment

- Surgical extraction of the guinea worm prior to eruption – has resulted in less associated disability
  - However, not widely available in problematic area

- No curative antihelminthnic treatment is available
  - Niridazole has been reported to decrease inflammation around the worm, allowing for easier extraction
  - Metronidazole, thiabendazole (adults) also used as adjunct to stick removal; however to be used with caution due to one study’s finding that these were associated with aberrant migration of worms

Photo: http://www.tumblr.com/tagged/guinea-worm
8.9 Control

• Community education on disease & transmission
  o Educating affected individuals not to immerse the affected areas in water which is used for public consumption

• Promotion and provision of safe drinking water sources

• Boiling water

• Point-of-use filtration of drinking water to “strain” copepods
  o Nylon filters, straw filters
  o Low-cost methods effective, e.g. filtration through clean cloth

• Larvicide to kill copepods
8.9 Control

Simple filtration of water to remove copepod vectors

(Photo: Carter Center/L. Gubb)
Pipe filters: portable, for use anytime and at any water source available.

Photo: Carter Center/L. Gubb
Acknowledgments

• Thanks to Jenna Kelly, Shazeen Bandukwala and Melissa Whaling for critical editing.
• We appreciate Tim Brewer and Jackeline Alger for thoughtful review.
Credits

Akre M Adja¹, Sina Helbig², Alia Tayea³, Neil Arya⁴

1: Institut Pierre Richet, Université de Cocody Abidjan
2: Boston University School of Medicine, Division of Infectious Diseases, Boston, MA, USA
3: Médecins Sans Frontières
4: Western University, University of Waterloo, McMaster University

Contact narya@uwaterloo.ca
The Global Health Education Consortium and the Consortium of Universities for Global Health gratefully acknowledge the support provided for developing teaching modules from the:

**Margaret Kendrick Blodgett Foundation**

**The Josiah Macy, Jr. Foundation**

**Arnold P. Gold Foundation**

This work is licensed under a [Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 United States License](https://creativecommons.org/licenses/by-nc-nd/3.0/us/).