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# AN OVERVIEW OF LYMPHATIC FILARIASIS LYMPHEDEMA

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*ABSTRACT*

*Filariasis is caused by thread-like nematode worms and is classified according to their presence in the vertebrate host. The lymphatic group includes* Wuchereria bancrofti, Brugia malayi, *and* Brugia timori. *Lymphatic filariasis, a mosquito-borne disease, has been one of the most prevalent diseases in tropical and subtropical countries and is accompanied by a number of pathological conditions. It is estimated that currently (after 13 years of the MDA programme) there are an estimated 67.88 million LF cases that include 36.45 million microfilaria carriers, 19.43 million hydrocele cases, and 16.68 million lymphedema cases. Adult filarial worms reside in the lymphatics and lymph nodes and induce changes that result in dilatation of lymphatics and thickening of the lymphatic vessel walls. Progressive lymphatic damage and pathology results from the summation of the effect of tissue alterations induced by both living and nonliving adult parasites. In recent years, there has been rapid progress in filariasis research, which has provided new insights into the pathogenesis of filarial disease, diagnosis, chemotherapy, the host-parasite relationship, and the genomics of the parasite. We examined the clinical manifestations of the disease, diagnosis, treatment, immune responses, and management including review of pharmaceutical agents against filariasis. Details on infection, safety profile, and status in clinical practices are also reported.*

**Keywords:** lymphedema, clinical management, lymphatic filariasis, surgical intervention in lymphatic filariasis lymphedema

The term "lymphatic filariasis" comprises infection with three closely related nematode worms – *Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*. All three parasites are transmitted by the bites of infective mosquitoes and have quite similar life cycles in humans with the adult worms living in the afferent lymphatic vessels while their progeny, the microfilariae, circulate in the peripheral blood and are available to infect mosquito vectors when they feed.

Lymphatic filariasis (LF) is a neglected mosquito-borne tropical disease. In 2014, 73 countries were considered to be endemic, among which 18 countries were at the surveillance stage and 55 were continuing to apply mass treatment (mass drug administration, MDA) (1). Lymphatic filariasis afflicts 68 million people in 73 countries, including 17 million persons living with chronic lymphedema. In India LF is endemic in 255 districts of 16 states and 5 Union Territories (UTs) of the country. Presently about 630 million of people in these endemic states/UTs are at-risk of LF (2-4). LF is responsible for 5.9 million disability adjusted

life years (DALYs) (5-7). These infections also lead to increased mortality (8-11). In addition to the economic loss due to lost productivity, there are negative social and cultural effects of the diseases (12). Elimination of lymphatic filariasis is possible by interrupting the transmission cycle.

Providing treatment on a large-scale to entire communities where the infection is present can stop the spread of infection. This strategy of preventive chemotherapy, called mass drug administration (MDA), involves a combined dose of 2 drugs given annually to an entire at-risk population in the following way: albendazole (400 mg) together with ivermectin (150-200 mcg/kg) or with diethylcarbamazine citrate (DEC) (6 mg/kg). These drugs have a limited effect on adult parasites but effectively reduce microfilariae from the bloodstream and prevent the spread of microfilariae to mosquitoes (13).

*Life Cycle of Lymphatic Filariasis*

All human filarial nematodes have a complex life cycle involving an insect vector, with Wuchereria and Brugia being transmitted by mosquitoes. Infection begins with the deposition of infectious-stage larvae or L3 larvae in the skin during a mosquito bite. The larvae then crawl in through the puncture wound and enter into the lymphatics and lymph nodes. They undergo a process of molting and development to form L4 larvae and then adult worms. The adult worms reside within the lymphatics and lymph nodes and following mating, release live progeny called microfilariae (mf), which circulate in the bloodstream. A mosquito can then ingest these microfilariae during a blood meal, wherein they undergo development to form L2 and finally L3 larvae, and the life cycle continues. The complex life cycle provokes a complicated host immune response, and it is this complexity of the host-parasite interaction that is thought to underlie the varied clinical manifestations of lymphatic filariasis.

*Clinical Manifestations*

The clinical manifestations of LF are varied. Traditionally, it has been accepted that people living in an endemic area can be classified into five groups: [1] endemic normals; [2] clinically asymptomatic, infected; [3] acute clinical disease; [4] chronic pathology, and [5] tropical pulmonary eosinophilia.

*Endemic normals*

In an endemic area, a proportion of the population remains uninfected despite exposure to the parasite. This group has been termed as endemic normals.

*Asymptomatic infection*

In areas endemic for lymphatic filariasis, many individuals exhibit no symptoms of filarial infection and yet, on routine blood examinations, demonstrate the presence of significant numbers of parasites or the presence of circulating parasite antigen (a surrogate for viable adult worms). These individuals are carriers of infection. With the availability of better imaging techniques (e.g., ultrasound, lymphoscintigraphy, MRI, CT), it has become apparent that almost everyone with active infection (e.g., microfilarial positivity) has some degree of lymphatic abnormality that may include: dilatation and tortuosity of lymph vessels with collateralization, increased or abnormal patterns of lymph flow (14-16), urogenital lymphangiectasia (17-18), and microscopic hematuria and/or proteinuria (19). At least half of all patients with lymphatic filariasis appear clinically asymptomatic. This asymptomatic presentation exists despite the presence of microfilariae in their blood and hidden damage to their lymphatics (20).

*Acute clinical disease*

Acute manifestations of lymphatic

filariasis are episodic attacks of lymphadenitis and lymphangitis (fever, pain in the affected part, tender red streaks) along with fever and malaise. Over 90% of cases with chronic manifestations will give a history of acute attacks. During acute infection, the microfilariae are transmitted by mosquitoes of various species. Occasionally the adult worms and their associated granulomatous reaction are manifested as lumps in the subcutaneous tissue, breasts, or testicles (20-22). Acute filariasis is characterized by episodic occurrence of inflammation of the lymph glands (lymphadenitis), inflammation of the lymph channels (lymphangitis), and subsequent swelling of the limbs or scrotum (lymphedema). Filariatic fever is often seen with headache and chills and will usually occur at the same time as lymphangitis. Lymphadenitis and lymphangitis are characteristic of both the *W. bancrofti* and *B. malayi* forms. The lymph nodes commonly involved are the inguinal, axillary, and epitrochlear nodes and the lymphatic system of the male genitals are frequently affected in *W. bancrofti* infection leading to funiculitis, epididymitis, and/or orchitis (23). The funiculo-epididymoorchitis, lymphadenitis and retrograde lymphangitis, has been termed acute dermatotolymphangitis, a process characterized by development of cutaneous or subcutaneous inflammation and accompanied by ascending lymphangitis and regional lymphadenitis. This manifestation is thought to result primarily from bacterial and fungal superinfections of the affected limbs (24).

Lymphadenitis and lymphangitis are characteristic of both the *W. bancrofti* and *B. malayi* forms (25). In lymphadenitis, the parasite essentially lodges inside the lymph nodes in the body, causing immune reaction and inflammation. Blockage and stretching of the lymph vessels by the adult worms make it difficult for lymph to flow out of the lymphatics and back into the blood stream. Inflammation of the lymph channels and lymph nodes along with a decreased draining efficiency leads to lymphedema. Lymphatic trunks become very painful and the skin on the arms and legs may show red streaks from the infected lymphatics. The distal end of the affected limb becomes swollen during the attack and remains swollen for several days. Usually the swelling is initially limited to a single limb.

*Chronic pathology*

The chronic pathology of lymphatic filariasis develops years after initial infection (26). The most commonly affected nodes are in the femoral and epitrochlear regions. Abscess formation may occur at the nodes or anywhere along the distal vessel. Infection with *Brugia timori* (*B. timori*) appears to result in more abscesses than infection with *B. malayi* (27) or *W. bancrofti* (28). The granulomas are characterized by macrophages (which develop into giant cells), with plasma cells, eosinophils, neutrophils, and lymphocytes and with hyperplasia of the lymphatic endothelium, occuring with repeated inflammatory episodes. The consequence is lymphatic damage and chronic leakage of protein-rich lymph in the tissues, thickening and verrucous changes of the skin, and chronic bacterial and fungal infections, which all contribute to the appearance of elephantiasis. *B. malayi* elephantiasis is more likely to affect the upper and lower limbs, with genital pathology and chyluria being rare. The current staging for filariasis-related lymphedema of the leg with defining symptoms is listed in *Table 1.*

*Tropical pulmonary eosinophilia*

Tropical pulmonary eosinophilia (TPE) is a distinct syndrome that develops in some individuals infected with *W. bancrofti* and *B. malayi* (29-30). Tropical pulmonary eosinophilia is an extreme immune response to filarial infection. High eosinophilia levels, asthma-like symptoms, and restrictive lung disease are characteristics of TPE. This manifestation occurs with low frequency in

**TABLE 1**
**Stages of Lymphedema of the Leg**

| STAGES | SYMPTOMS |
|---|---|
| Stage I | Swelling reverses at night<br>Skin folds-Absent<br>Appearance of Skin-Smooth, Normal |
| Stage II | Swelling not reversible at night<br>Skin folds-Absent<br>Appearance of skin-Smooth, Normal |
| Stage III | Swelling not reversible at night<br>Skin folds-Shallow<br>Appearance of skin-Smooth, Normal |
| Stage IV | Swelling not reversible at night<br>Skin folds-Shallow<br>Appearance of skin - Irregular,<br>* Knobs, Nodules |
| Stage V | Swelling not reversible at night<br>Skin folds-Deep<br>Appearance of skin – Smooth or Irregular |
| Stage VI | Swelling not reversible at night<br>Skin folds-Absent, Shallow, Deep<br>Appearance of skin *Wart-like lesions on foot or top of the toes |
| Stage VII | Swelling not reversible at night<br>Skin folds-Deep<br>Appearance of skin-Irregular<br>Needs help for daily activities - Walking, bathing, using bathrooms, dependent on family or health care systems |

endemic areas. Chest x-rays may be normal but generally show increased bronchovascular markings; diffuse miliary lesions or mottled opacities may be present in the middle and lower lung fields. Total serum IgE levels (10,000 to 100,000 ng/mL) and antifilarial antibody titers are characteristically elevated.

*Diagnosis of Lymphatic Filariasis*

Diagnosis of LF was once an extremely challenging task but with the advent of recent antigen-detection techniques, such as ICT and FST card test and ELISA-based on the Og4C3 monoclonal antibody, diagnosis has become much easier. Molecular xenomonitoring (MX), which detects filarial DNA in mosquitoes by PCR, is a highly sensitive assay. Ultrasonography (USG) and lymphoscintigraphy also revolutionized the diagnosis of the disease and may be very helpful in monitoring the success of chemotherapy. In TPE, serum antibodies like IgG & IgE will be extremely high and the presence of IgG4 antibodies indicate active infection. A brief review and summary of these techniques are:

1. New techniques for antigen detection represent the highest quality lab test for diagnosing infection by *W. bancrofti*. PCR tests are also of high specificity and sensitivity and detect parasite DNA in microfilariae in the blood of humans as well as in vectors in both bancroftian and brugian filariasis (31). Very high levels of specific IgG4 antibody in microfilaraemic patients have also been considered as a good diagnostic marker.

2. Immunochromatographic test (ICT) and Filaria Strip Test (FST), which are highly sensitive and specific filarial antigen detection assays, are available for the diagnosis of *W. bancrofti* infection (31, 32). With these tests, the parasite antigens can be detected independent of the microfilariae's periodicity. It is rapid (1-10 minutes), and no such test exists for Brugian filariasis. ELISA-based assay using the Og4C3 monoclonal antibody is equally sensitive and specific for detecting antigen in bancroftian infections.

3. Basic parasitologic testing of peripheral blood for microfilariae remains a diagnostic standby, keeping the periodicity of the microfilariae in mind (31).

4. Ultrasonography using a 7.5 or 10 MHz probe has helped to locate and visualize the movements of living adult filarial worms of *W. bancrofti* principally in the scrotal lymphatics of asymptomatic males with microfilaraemia (33-36).

5. Lymphoscintigraphy has been found useful in tracing lymphatic damage and dermal backflow after injecting radiolabeled proteins intradermally in both symptomatic and asymptomatic infections.

*Pathogenesis of Filarial Disease*

The most severe clinical manifestations of lymphatic filariasis are lymphedema and elephantiasis. Although the immune responses to filarial parasites have been well studied with respect to natural history, diagnosis, and treatment, there is a relative paucity of information in terms of the mechanisms underlying development of pathology.

The two major independent components of lymphatic filarial disease are lymphangiectasia and inflammatory reactions. While most infected individuals exhibit lymphangiectasia, clinically apparent lymphedema may not be common. It is also clear that with patent infection, lymphangiectasia develops in the vicinity of adult worm nests (37-39). Subclinical lymphangiectasia of the lymphatic vessels containing live adult worms has been shown to exhibit distention with no apparent inflammatory reactions in the vessel wall, with little or only a fleeting inflammatory response to living adult parasites. Further, the fact that lymphangiectasia is not restricted to the exact segment of lymphatics where the worms reside (40) suggests that this process is mediated by soluble products excreted or secreted by the parasite that act on the lymphatic endothelial cells. It is also clear that with the advent of adaptive immunity, the host inflammatory response against the dead or dying worm and the subsequent release of parasite products and inflammatory mediators, a stage of irreversible lymphatic dysfunction ensues (41-43). This then manifests clinically as progressive lymphedema. In addition, lymphatic dysfunction has been shown to predispose infected individuals to secondary bacterial and fungal infections and trigger inflammatory reactions in the skin and subcutaneous tissue that accelerates the progression of lymphedema and precipitates the development of elephantiasis (44-45).

Cells of the innate and adaptive immune system are important for the initiation of type 2 immunity, which are the hallmark of helminth infections. The key players in T helper (Th) 2-type immunity are CD4+ Th2 cells and involve the cytokines-IL-4, IL-5, IL-9, IL-10, and IL-13; the antibody isotypes-IgG1, IgG4, and IgE, and expanded populations of eosinophils, basophils, mast cells, and alternatively activated macrophages (46-47).

The importance of pro-inflammatory cytokines, possibly of innate origin, in the pathogenesis of lymphedema has been strengthened by a series of studies in humans with chronic pathology, either in early or late stages or lymphedema. Studies have shown that individuals with chronic lymphatic pathology have elevated levels of C-reactive protein (an acute phase protein, indicating an

acute inflammatory response) (48), pro-inflammatory cytokines such as TNF-α, IL-6 and soluble TNF receptor (49-50), endothelin-1 and IL-2 (51), as well as IL-8, MIP-1α, MIP-1β, MCP-1, TARC and IP-10 (75) in the peripheral circulation. Similarly, while patients with both acute and chronic manifestations of LF have elevated circulating levels of IL-6 and IL-8, only those with chronic disease manifestations have elevated levels of sTNF receptors (52).

The endothelium appears to be closely associated with pathogenesis of lymphatic disease and studies targeting the interaction between endothelial cells (blood vascular or lymphatic) and filarial parasites have been performed. Differentiation of LEC into tube-like networks was found to be associated with significantly increased levels of matrix metalloproteinases (MMPs) and inhibition of their endogenous inhibitors-TIMPs (tissue inhibitors of MPs) (53). Recent data suggest that an increase in circulating levels of MMPs and TIMPs is characteristic of the filarial disease process and that altered ratios of MMP/TIMP are an important underlying factor in the pathogenesis of tissue fibrosis in filarial lymphatic disease. Other studies have implicated the vascular endothelial growth factor (VEGF) family in lymphangiogenesis (54-56). Other angiogenic factors such as angiopoietins-1 and -2 are also found at elevated levels in individuals with filarial-induced pathology (57). A major factor involved in the initiation of the proinflammatory response and the increased production of VEGF-A and -C might be the endosymbiont, *Wolbachia*, present in most filarial nematodes (including *W. bancrofti* and the 2 *Brugia* spp) (55). Recently, it has been demonstrated that the increased levels of VEGF-C and sVEGF-R3 (observed in lymphedema patients) were reduced following doxycycline treatment (a regimen that eliminates *Wolbachia*) and that there was improvement in lymphedema (56).

Persistent immune activation is associated with elevations of circulating microbial products, acute-phase proteins, and the so-called microbial translocation molecules (58,59). However, intra and peri-lymphatic damage – an underlying feature of filarial disease – might also contribute to the presence of microbial translocation products in the bloodstream. Indeed, the increased circulating levels of LPS (which serves as a marker for microbial translocation) and decreased levels of LPS-binding protein (LBP) are characteristic features of filarial lymphatic pathology that in turn appear to cause immune activation. Since filarial lymphedema is known to be associated with increased bacterial and fungal loads in the lymphatics, our studies reveal that these damaged lymphatics may serve as a potential nidus for bacterial translocation through leaky lymphatic endothelium.

Multi-color flow cytometry analysis reveals that the frequency of Th1 cells (CD4+ T cells expressing either IFNγ or IL-2 or TNF-α) (60), Th9 cells (CD4+ T cells expressing IL-9 and IL-10) (61), Th17 cells (CD4+ T cells expressing IL-17) (62), and Th2 cells (CD4+ T cells expressing IL-22) is significantly enhanced in filarial pathology. This is accompanied by a concomitant decrease in the frequency of Th2 cells (CD4+ T cells expressing IL-4 or IL-5 or IL-13) both at homeostasis and following parasite antigen stimulation (63). Although less well studied than Th1 cells, Th17 cells might also have an important role in the pathogenesis of disease in filarial infection since PBMC from individuals with pathology (but not asymptomatic patients) express significantly higher levels of the Th17 associated cytokines as well as the master transcription factor – RORC at the mRNA level.

Finally, pathology in lymphatic filariasis is also associated with expanded frequencies of Th9 cells, CD4+ T cells that express both IL-9 and IL-10 but not IL-4, and this frequency exhibits a positive correlation with the severity of lymphedema in filarial infections.

*Wolbachia and its Role*

*Wolbachia* of filarial nematodes are the obligate intracellular alpha-proteobacteria and have some resemblances with insect *Wolbachia*. *Wolbachia* bacteria are vertically transmitted to the filarial progeny through the female germline (64). From the entry of the parasite to the establishment of the chronic disease, *Wolbachia* plays multiple roles, such as exacerbating proinflammatory pathogenesis and immunomodulation of the host, as well as enhancing survival of the filariae. *Wolbachia* can trigger a proinflammatory response through interaction with monocytes/macrophages, dendritic cells, and neutrophils (65-66). *Anti-Wolbachia* therapy with doxycycline (a semisynthetic derivative of the tetracycline family) has been recommended for the treatment of individuals with lymphatic filariasis (67-68). It allows the development of filariae in their vector to be blocked, thus arresting the transmission. *Wolbachia* thus prevents the degranulation of eosinophils by triggering an ineffective neutrophil response by the host (69). *Wolbachia* is being revealed as an important cause of pathology in filarial diseases. Symptoms are correlated with increases in the levels of circulating *Wolbachia* protein and DNA, and with the detection of antibodies directed against the endosymbiont (70-72).

*Elimination Program and Treatment*

The Global Program to Eliminate Lymphatic Filariasis (GPELF) recently released their progress report for 2014. The report summarized the work of the GPELF's first decade, which was focused on implementing mass drug administration (MDA) across all LF endemic regions. The report acknowledged that while MDA programmes have been particularly successful in reducing infection within communities, efforts to reduce morbidity associated with LF remain lacking. Currently, only 24 of the 73 endemic countries have morbidity programs. During 2000-2012, the MDA programme made remarkable achievements – a total of 6.37 billion treatments were offered and an estimated 4.45 billion treatments were consumed by the population living in endemic areas. Using a model based on empirical observations of the effects of treatment on clinical manifestations, it is estimated that 96.71 million LF cases, including 79.20 million microfilaria carriers, 18.73 million hydrocele cases and a minimum of 5.49 million lymphedema cases have been prevented or cured during this period. Consequently, the global prevalence of LF is calculated to have fallen by 59%, from 3.55% to 1.47%. The fall was highest for microfilaraemia prevalence (68%), followed by 49% in hydrocele prevalence and 25% in lymphedema prevalence. These programs focus on hygiene, skin care, hydrocele surgery, and exercises. The GPELF plan for 2010-2020 highlights the need for the establishment of morbidity management programs in all endemic regions. In particular, the plan identifies the need for the development of metrics to monitor and report on the outcomes of these programs.

The National Filaria Control Programme (NFCP) was launched in India in 1955. The control strategy was selective chemotherapy with diethylcarbamazine citrate (DEC) for 12 days at 6 mg/kg body weight for parasite carriers detected from the night blood survey, and larval control of vector mosquitoes. The major constraint of the NFCP was that it did not cover the vast majority of the population at risk residing in rural areas and that the strategy demanded detection of parasite carriers by night blood survey, which is less sensitive, expensive, time-consuming and poorly accepted by the community (73).

*Vector control*

Vector-control strategies in the last century were based on chemical agents and current ecological and environmental

protection standards largely no longer support such approaches due to adverse effects of many insecticides on non-target species (including humans), their environmental impact, contamination of soil and water, and development of selective processes and subsequent mosquito resistance to insecticides (74). New strategies therefore had to be created to replace the use of insecticides. Genetic control methods have now arisen as promising alternative strategies, based on two approaches: the replacement of a vector population by disease-refractory mosquitoes, and the release of mosquitoes carrying a lethal gene to suppress target populations. Genetically modified bacteria capable of colonizing a wide range of mosquito species may be a solution to this problem and another option for the control of these diseases. In the paratransgenic approach, symbiotic bacteria are genetically modified and reintroduced in mosquitoes, where they express effector molecules. In this approach, a genetic modified bacteria can act by: (a) causing pathogenic effects in the host; (b) interfering with the host's reproduction; (c) reducing the vector's competence; and (d) interfering with oogenesis and embryogenesis (75-76).

*Self-help groups or social helping groups*

Effective self-care implementation requires some degree of education, instruction or demonstration, and the role of the educated health worker or trained volunteer cannot be ignored. Studies which provided frequent monitoring and support were associated with greater improvements than studies which offered minimal or no support services. Study by Akogun and Badaki (77) where one group was able to alter the program design to suit their immediate cultural and social constraints reported good outcomes. A study by Wilson et al and others (78-81) reported that basic self-care improved skin integrity and prevented new infections while limb stage remained the same. Where a reduction in limb volume was reported in lymphedema, greater benefits were experienced among participants with early stages, suggesting that implementation of a self-care routine as soon as lymphedema is detected has the potential to curtail the number of cases that progress to advanced stages. Bernhard et al reported that limb volume reduction was significantly greater in the self-treating group compared to the therapist treated group. Douglass et al's review supported the adoption of remedial exercises in the management of lymphedema and a greater emphasis on self-treatment practices for people with lymphedema (105).

To eliminate lymphatic filariasis, the Indian Government has launched a substantial public health initiative in which they provide free prophylactic drugs to more than 400 million people in the country. The initiative includes providing an annual dose of preventive drugs (diethylcarbamazine and albendazole) to entire communities in the form of mass drug administration. To support this initiative, India's Ministry of Health and Family Welfare in collaboration with the Global Network for Neglected Tropical Diseases (an initiative of the Washington-based Sabin Vaccine Institute) has launched a public service advertising campaign called Hathipaon Mukt Bharat (Filaria Free India). The campaign includes a film entitled Giant footprints! in which a patient with lymphatic filariasis is shown delivering the message that the disease "can happen to anyone," that people should participate in the mass drug administration initiative, and that they should take the preventive medicines (which are free and safe) to make India filaria free. The campaign supports the Indian government's mass drug administration initiative, which is being implemented in 17 states (82).

*Tools for assessment of elimination*

Lymphatic filariasis is targeted for global elimination through treatment of entire

at-risk populations with repeated annual mass drug administration (MDA). Essential for program success is defining and confirming the appropriate endpoint for MDA when transmission is presumed to have reached a level low enough that it cannot be sustained even in the absence of drug intervention. Guidelines advanced by WHO call for a transmission assessment survey (TAS) to determine if MDA can be stopped within an LF evaluation unit (EU) after at least five effective rounds of annual treatment. The decision to stop MDA is complicated and a variety of tools have been suggested to guide the decision. The first step is to define the parameter(s) that will be measured and the best diagnostic tool for assessing it. At least eight diagnostic tests are currently available for detecting indicators of LF exposure and infection. These include Bm14, PanLF, Wb123, Urine SXP, ICT, Og4C3, Blood smear, and PCR

*Therapy for Lymphatic Filariasis*

Remarkable advances in the treatment of LF have recently been achieved focusing not on individuals but on communities with infection. The overall goal is to reduce mf in the community to levels below which successful transmission will not occur.

Drugs effective against filarial parasites
1. Diethylcarbamazine citrate (DEC)
2. DEC-Fortified salt
3. Ivermectin
4. Albendazole
5. Levamisole hydrochloride
6. Moxidectin

Treatment of microfilaraemic patients may prevent transmission of infection and may be repeated every 6 months till mf and/or symptoms disappears.

*Treatment and prevention of ADL*

The most distressing aspect of LF is the acute attacks of ADL, which result in considerable economic loss and deterioration of quality of life. Prompt treatment and prevention of ADL are of paramount importance. ADL may be seen both in early and late stages of the disease. It is due to the infection and inflammation of the skin and affected area from entry of bacteria or fungus through the entry lesions. The skin becomes warm, tender, painful, swollen, and red, and the patients can develop fever, headache, chills, and sometimes nausea and vomiting. They can also occasionally become septicemic. The first sign will be enlarged, tender, and painful swollen lymph nodes which lasts for 4-5 days. Peeling and darkening of skin is common and repeated attacks increase the size of the legs. Management includes symptomatic treatment like relieving pain, antibiotics to combat bacterial infection, care of entry lesions, etc. In patients with late stages of lymphedema, long term antibiotic therapy using oral Penicillin or long acting parentral Benzathil Penicillin are sometimes used to prevent ADL.

*Surgical treatment*

In the surgical aspect of lymphatic filariasis, grade I and grade II can be treated conservatively, whereas grade III and grade IV needs surgical correction together with regular antibiotics and chemotherapy with DEC. The old surgical techniques of excision and skin grafting are no longer practiced as it gives poor cosmetic results along with early recurrences. Thompson's, Kondolean, and Charles procedures are no longer utilized and newer techniques involving micro-vascular surgery like nodovenal shunt and lymphovenal shunt with reduction and sculpturing is being carried out without skin grafting or a flap cover. Patient's local skin itself has been salvaged and made to a better quality by manual lymph drainage (MLD), bandaging, and use of the same skin for reconstitution (83).

The future of lymphedema surgery will be supermicrovascular surgery with

lymphatico-venous anastomosis at multiple levels or a free microvascular lymph node transfer to the affected areas. The anastomosis can be performed either by glue or by laser. But our idea is to focus on prevention of lymphatic filariasis and elimination in future, which does not warrant any new surgical technique. We are concentrating on earlier detection of problems and creating awareness among the people and general precautions so that the infected people can be treated at an earlier reversible stage.

*Scrotal surgery*

Lymph scrotum almost always occurs in patients with a previous history of acute episodes of filariasis that are characterized by lymphangitis due to bacterial and/or fungal infection and who present chronic lymphangiectasia. Lymph scrotum or superficial scrotal lymphangiomatosis is a urogenital condition characterized by the presence of lymphatic vesicles on the surface of the scrotal skin that can easily rupture giving rise to drainage of the whitish fluid typical of the disease (84-88). This fluid serves as an excellent culturing medium that favors repeated bacterial infections. It may trigger progression of the condition to lymphedema and scrotal elephantiasis, the advanced stages of the disease. Lymph scrotum is a less frequent manifestation of LF, however it has important medical, psychological and socioeconomic repercussions for individuals who present this condition as it is seen as the complication of LF that produces the greatest incapacitation among men (88).

*Hydrocelectomy*

Chronic hydrocele is the accumulation of fluid around the testis leading to an increase in the volume of the scrotal contents. Depending on the volume of fluid, hydrocele can be disfiguring and even incapacitating. Chronic hydrocele has multiple etiologies, but irrespective of the cause, surgery is the standard form of treatment and this can be done using different surgical techniques. The prevalence of chronic hydrocele in bancroftian filariasis endemic areas-a parasitic disease transmitted by mosquito-is very high and represents the most common clinical manifestation of bancroftosis followed by swollen legs of lower limbs or lymphedema among women. The surgeons' preference is for surgical techniques in which the hydrocele sac is opened, averted with or without partial resection of the sac, and the edges sutured behind the testis. To avoid hydrocele recurrence, earlier recommendation was to a complete excision of hydrocele sac and when identified, leaking or leak-prone dilated lymphatic vessels should be sutured or excised.

By surgical practice, a simple reduction of scrotum and excision of penile skin with skin grafting has been done. Unfortunately, as there was no continuous drainage, these patients develop recurrences. Hence we came out with a new strategy of reducing the scrotum by doing hydrocelectomy, together with the excision of penile edematous skin and resurfacing of penis using the prepusal layer of the penis itself, followed by a bilateral nodo-venal shunt. The advantage of using this procedure is to avoid recurrence, retain the shape and sensation of the penis, and provide a more acceptable, functional, and aesthetic result for the genital region as it has been a neglected and important focus for the patients.

*Herbal treatments/yoga/traditional healing*

There are several herbs that have been prescribed by Ayurveda for the treatment of elephantiasis for centuries. The following are some of the herbs reported as having antifilarial activities i.e., *Vitex negundo L.* (roots), *Butea monosperma L.* (roots and leaves), *Ricinus communis L.* (leaves), *Aegle marmelos Corr.* (leaves) (89), *Canthium mannii (Rubiaceae)* (90), *Boerhaavia diffusa L.* (whole plant) (91). Two compounds, oleanonic acid and oleanolic acid, isolated

from hexane and chloroform fractions *in vitro* killed adult *B. malayi* (92). *Calotropis procera* R. Br. leaves was used as traditional home remedy to reduce pain and swelling during inflammatory episodes (93).

Narahari et al (94) developed a treatment protocol for lymphedema integrating ayurveda, biomedicine, and yoga. Yoga used as a major component of integrative treatment protocol in 14 Indian village camps improved quality-of-life in 425 lymphatic filariasis patients. Long standing lymphedema caused altered gait and joint deformities in small and large volume limbs. This was mostly due to the inactivity causing muscle weakness and edema within and around the muscles. Yoga postures improve movements and helped the patients to negotiate with these deformities (95). Narahari et al showed that the lymph drainage achieved in these patients was plausible because of breathing, movements coordinated with breathing, and stimulation of autonomic system. There is no evidence that breathing facilitates the lymphatic drainage in much dilated human truncal lymphatics. Their study included a total of 730 patients (851 limbs) from two LF endemic districts of south India -Gulbarga in Karnataka and Alleppey in Kerala- and all patients were given training in the integrative procedure which involved patient education and the domiciliary protocol. At completion of the three and half month follow up, there was a statistically significant reduction up to mid-thigh level volume measurement for both small and large limbs. Yoga offers a self-care management tool for lymphedema albeit there is lack of evidence that breathing actually achieves lymphatic drainage (96).

*Treatment and Prevention of Lymphedema and Elephantiasis*

Early treatment with drugs may destroy the adult worms and logically prevent the later development of lymphedema. Once lymphedema is established there is often no complete cure, but the "foot care programme" may offer relief, some amelioration, and prevention of acute attacks and thus limitation of further progression of the swelling.

*Current control strategy of LF*

In view of achieving the global elimination of LF, the program in India has been made a part of the NVBDCP in 2003, under the National Health Policy 2002, and set a target for elimination of LF by 2015. The strategy for achieving this goal was initially by annual MDA single dose DEC (6 mg/kg body wt.) for at least five years to the entire population of an endemic district (excluding children under two years, pregnant women and severely ill patients), and home-based management of lymphedema cases and hydrocelectomy operations in identified Community Health Centres (CHCs) and hospitals.

MDA with DEC was launched as a pilot project in 13 districts of seven states in the year 1996 (97). The NVBDCP upscaled the MDA to cover a population of 77 million in 2002 from 41 million in1996-97. During the year 2004, a population of about 468 million from 202 districts was targeted for MDA. There have been several reviews of the use of Albendazole (Alb) for MDA towards the elimination of LF (98-102). A large-scale trial on the feasibility and impact of co-administration of DEC and Alb in selected districts in the country was carried out in 2000-05, with the support of Indian Council of Medical Research (ICMR) Task Force. It therefore recommended the co-administration (DEC 6 mg/kg/ body wt. and Alb 400 mg) strategy for all endemic districts in India. A new trial using triple drug therapy (DEC+ Albendazole+ Ivermectin) has started in Karnataka and is being conducted by VCRC to evaluate the efficacy of triple drug therapy annually compared to DEC+ Albendazole annually. If effective, the national programme might implement triple drug therapy for MDA for the remaining endemic areas in India.

*Disease Management*

Filarial patients with skin lesions often have more bacteria on the skin than usual. The large number of bacteria on the skin, multiple skin lesions, slow lymph fluid movement from the damaged lymphatics, and the reduced ability of lymph nodes to filter the bacteria cause inflammation characteristic of an acute attack. Repeated bacterial infections precipitate frequent acute attacks, which further damage lymphatic vessels in the skin, reducing their ability to drain fluid. This vicious cycle continues, aggravating the condition of the patient.

Lymphedema management involves the following components: washing, prevention and cure of entry lesions, elevation of the foot, exercise, wearing proper footwear, and management of acute attacks.

The GPELF aims to provide access to a minimum package of care for every person with associated chronic manifestations of lymphatic filariasis in all areas where the disease is present, thus alleviating suffering and promoting improvement in their quality of life. Success in 2020 will be achieved if patients have access to the following minimum package of care: treatment for episodes of adenolymphangitis (ADL); guidance in applying simple measures to manage lymphedema and hydrocele to prevent progression of lymphedema and debilitating, inflammatory episodes of ADL; surgery for hydrocele; treatment with antifilarial medicines to destroy any remaining worms and microfilariae by preventive chemotherapy or individual treatment; and doxycycline for early stage lymphedema.

*Washing and skin care*

Good hygiene and treatment of entry lesions are important measures for managing lymphedema. The patients should be encouraged to practice skin care and hygiene. The skin must be checked for entry lesions, including very small lesions between the toes that can hardly be seen which may cause itching. Scratching can further damage the skin and can provoke an acute attack. Toenails should be trimmed in such a way that the skin is not injured. Do not try to clean under the nails with sharp objects as these can cause entry lesions. It is important to check the skin every time the leg is washed because entry lesions allow bacteria to enter the skin and this will cause acute attacks. If entry lesions are found, they should be cleaned carefully.

Washing the leg includes: (i) Wet the leg with clean water at room temperature. Do not use hot water to wash the leg; (ii) Begin soaping at the highest point of swelling (usually around the knee); (iii) Wash down the leg towards the foot; (iv) Gently clean between all skin folds and between the toes, preferably using a small cloth or cotton swab, and paying particular attention to the entry lesions. Brushes should not be used as they can damage the skin; (v) Rinse with clean water; (vi) Repeat this careful washing until the rinse water is clean; (vii) Wash the other leg in the same way, even if it looks normal.

Drying the skin includes: (i) Patting the area lightly with a clean towel. Do not rub hard because this can cause damage to the skin; (ii) carefully dry between the toes and between skin folds using a small cloth, gauze or cotton swab. Wet areas between the toes, skin folds and entry lesions promote bacterial and fungal growth leading to frequent acute attacks.

*Prevention and cure of entry lesions*

Entry lesions are common in patients with lymphedema and are most frequently found between the toes and deep skin folds and around the toenails. Entry lesions, such as wounds, can also be found on the surface of the skin. Both fungi and bacteria can cause entry lesions. Fungal infections frequently damage the skin and create entry lesions, especially between the toes, and may cause itching. The entry lesions allow bacteria to

enter the body through the skin and this can cause acute attacks. Fungi and bacteria can cause bad odor.

*Fungal infections*

Fungal infections are usually white or pink in color and do not leak fluid. Bacterial infections may leak fluid that is thin and clear or thick and colored. Antifungal and antibacterial creams can be used for local application.

*Elevation*

Elevation is important for patients with lymphedema of the leg. It helps prevent fluid from accumulating in the leg by improving the flow in the elevated position. The knee should be slightly bent and a pillow placed under the knee for support. While sitting, raise the foot as high as is comfortable, preferably as high as the hip. If sitting on the floor, place a small pillow under the knees. If lying down, the foot can be raised by placing a pillow under the mattress.

*Exercise*

Exercise is useful for patients with lymphedema and in general, the more they exercise the better they are. Exercise helps by pumping the fluid and improving drainage. However, patients should not exercise during acute attacks.

Walking short distances and standing up on toes exercise is a common approach. Patients can stand with both feet slightly apart, holding on to a wall, a person, or other support and then raise on to the toes of both feet at the same time and then sink back down to flat feet. While sitting or lying down, they can point toes towards the floor, then bend (extend) the toes upwards, and finally move the foot in a circle to the right and left. If patients are sitting on the floor, it is good to protect the heel with a flat pillow. Modern lymphedema management strategies (based on regular washing, careful drying, and treatment, with antifungal, antibiotic, or emollient creams, of the affected limbs, limb elevation, exercise, and use of footwear) has not yet reached all study communities and the local physicians are not aware of them (103-105).

*Wearing proper footwear*

Proper footwear protects feet from injury and counseling the patients is important.

*Management of acute attacks*

The reduction in the frequency of the acute attacks is an indication that the patient's condition is improving. An acute attack is painful. The patient may complain of fever, nausea, headache, and soreness of the lymph nodes. Most patients can easily care for their acute attack. The patient should rest and elevate the leg comfortably as much as possible at home.

The following simple procedures can alleviate the symptoms: (1) A cloth soaked in water and placed around the leg can relieve pain. The leg can also be soaked in bucket of cold water; (2) The leg should be washed with soap and clean water, but gently and carefully; (3) After drying, antiseptic can be applied to the skin and medicated cream; (4) The patient should drink plenty of water; (5) Paracetamol can be taken for fever every six hours until the fever lessens; and (6) Oral antibiotics which can shorten the attack are recommended.

*CONCLUSION*

In this review we have focused on the epidemiology of LF, clinical manifestations, pathogenesis of LF and immune response, current strategy for clinical management, and disease management. The creation of GAELF has shown that it is possible to bring different organizations and donations together under one umbrella to coordinate and streamline global activities aiming at

eliminating LF transmission by 2020. In the endemic countries, progress has mostly been satisfactory, leading to lower numbers of infected people and to interrupted transmission. Mosquito control is a supplemental strategy supported by WHO. It is used to reduce transmission of lymphatic filariasis and other mosquito- borne infections. Depending on the parasite-vector species, measures such as insecticide-treated nets, indoor residual spraying or personal protection measures may help protect people from infection. Vector control has in select settings contributed to the elimination of lymphatic filariasis in the absence of large-scale preventive chemotherapy.

*Key Points*

- Lymphatic filariasis is a neglected mosquito-borne tropical disease which is caused by filarial worms, *Wuchereria bancrofti, Brugia malayi*, or *B. timori*. It is endemic in 58 countries, putting 1.2 billion people at risk globally with an estimated 120 million infected.
- Filariasis causes relatively low mortality but has a high incidence of morbidity that has a major social impact causing heavy economic loss in developing countries.
- It is the second leading cause of permanent or long-term disability with over 40 million infected people suffering from pathological manifestations like lymphedema, hydrocoele, chyluria, and elephantiasis
- The standard method for diagnosing active infection is by finding the microfilariae via microscopic examination. This may be difficult, as in most parts of the world microfilariae only circulate in the blood at night. For this reason, blood has to be collected nocturnally. The blood should be in the form of a thick smear and stained with Giemsa. Testing the blood for filarial antigen has been transformative in enabling the rapid and accurate diagnosis of LF.
- The clinical manifestations of LF are varied, Traditionally, it has been accepted that people living in an endemic area can be classified into five groups: (1) endemic normals; (2) clinically asymptomatic, infected; (3) acute clinical disease; (4) chronic pathology and (5) tropical pulmonary eosinophilia (TPE)
- While filarial infection does induce expression of immune cells in humans, early interaction of parasites or parasite antigens leads to a predominantly pro-inflammatory response with expression of mainly pro-inflammatory cytokines including TNF$\alpha$, IL-6 and IL-1$\beta$, as well as genes involved in inflammation and adhesion.
- Increase in circulating levels of MMPs and TIMPs is characteristic of the filarial disease process and altered ratios of MMP/TIMP are an important underlying factor in the pathogenesis of tissue fibrosis in filarial lymphatic disease.
- Elevated levels of VEGF-A, VEGF-C, and endothelin-1 have been observed in the serum of filarial-infected individuals.
- Multi-color flow cytometry has shown that the frequency of Th1 cells (CD4+ T cells expressing either IFN$\gamma$ or IL-2 or TNF-$\alpha$); Th9 cells (CD4+ T cells expressing IL-9 and IL-10); Th17 cells (CD4+ T cells expressing IL-17) and Th2 cells (CD4+ T cells expressing IL-22) is significantly enhanced in filarial pathology.
- Chronic pathology in lymphatic filariasis is also associated with expanded frequencies of Th9 cells, CD4+ T cells that express both IL-9 and IL-10.
- A basic, recommended package of care can alleviate suffering and prevent further disability among lymphatic filariasis patients.
- Treatments for lymphatic filariasis differ depending on the geographic location of the endemic area (i.e., in some areas of the world, albendazole is used with diethylcarbamazine). Geo-targeting treatments is part of a larger strategy to eventually eliminate lymphatic filariasis by 2020.
- Lymphatic filariasis can be eliminated by stopping the spread of infection through preventive chemotherapy with single doses of

2 medicines for persons living in areas where the infection is present.

*REVIEW CRITERIA*

An exhaustive search strategy using keyword and subject headings was applied to PubMed.

Search Criteria:

Search Keywords used to search databases in pubmed.

Search 1: [(lymphedema or lymphedema or elephantiasis) and (filariasis)]

Search 2: [(lymphedema or lymphedema or elephantiasis) and (Immunology of Lymphatic filariasis)]

Search 3: Clinical management and treatment methods for lymphatic filariasis

Search 4: (self-care or "self care" or basic-care or "basic care" or "community based home care" or "community-based home-care" or "self-management" or self-management or self-treatment or "self treatment" or self-massage or "self massage" or "partner massage" or home-care or "home care" or limb-care or "limb care" or foot-care or "foot care" or hygiene or breathing or exercise)

Search 5: 3 AND 4

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*CONFLICT OF INTEREST AND DISCLOSURE*

All authors declare that no competing financial interests exist.

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