WHAM evidence summary: Lymphatic filariasis: Treatment

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CLINICAL QUESTION

What is the best available evidence on the treatment of filariasis?

SUMMARY

Lymphatic filariasis is a parasitic infection spread by mosquito in tropical countries.[1-18] The disease course is primarily asymptomatic but includes episodic acute disease that can become chronic. Prevention of disease is the most effective management strategy. Once contracted, management focuses on reducing severity and frequency of acute outbreaks with combination chemotherapy (albendazole plus either diethylcarbamazine [DEC] or ivermectin)[1] (*Level 1*), doxycycline[2] (*Level 1*) and/or comprehensive regimens that include skin hygiene, disinfection of skin lesions, leg elevation and range of motion exercises[3] (*Level 4*).

CLINICAL PRACTICE RECOMMENDATIONS

All recommendations should be applied with consideration to the wound, the person, the health professional and the clinical context.

In patients with active filariasis, a single dose of combination chemotherapy (albendazole plus either diethylcarbamazine or ivermectin) is recommended to eradicate infection and reduce the spread of disease (Grade A).

Daily leg care that includes washing, leg elevation and range-of-motion exercises is recommended to reduce episodes of acute lymphatic filariasis (Grade A).

Consider a course of doxycycline (200mg daily for 4 to 6 weeks) to reduce episodes of acute lymphatic filariasis (Grade B).

SOURCES OF EVIDENCE

This summary was conducted using methods published by the Joanna Briggs Institute (JBI). This evidence summary is based on a structured database search using the search terms lymphoedoema, filariasis, lymphatic filariasis and Bancroftian filariasis. The evidence sources are described in Table 1.

BACKGROUND

Epidemiology

Lymphatic filariasis is a parasitic infection of threadlike worms that is spread by female mosquito bite. Mosquitoes become infected after feeding on blood from people infected with microfilariae (juvenile worms). When the mosquito moves to another person and feeds,

Table 1: Sources of evidence and the level

Level 1 Evidence	Level 2 Evidence	Level 3 Evidence	Level 4 Evidence	Level 5 Evidence
Experimental Designs	**Quasi-experimental Designs**	**Observational – Analytic Designs**	**Observational – Descriptive Studies**	**Expert Opinion/ Bench Research**
1.a Systematic review of RCTs[1,18] 1.b A systematic review including trials of various methodologies[15] 1.c RCTs[2,8-13]	2.d Pre-test post-test or historic/retrospective control group study[17]	Nil	4.c case series[3]	5.c Expert opinion[4-7, 14,16]

the microfilariae enter the skin and migrate to the lymphatic system were they develop into macrofilariae (mature worms) and continue breeding. The resulting microfilariae then return to the bloodstream. The time frame from infection to production of microfilariae in the blood steam is six to twelve months.[1, 4]

Three different roundworms are implicated in lymphatic filariasis, *Wuchereria bancrofti* (found in tropical regions of Africa, Asia, China and Pacific Islands), *Brugia timori* (Asia) and *Brugia malayi* (Indonesia).[1]

Lymphatic filariasis is endemic in 58 countries, but 80% of people who are at risk of exposure live in one of the following ten countries: Bangladesh, Côte d'Ivoire, Democratic Republic of Congo, India, Indonesia, Myanmar, Nigeria, Nepal, Philippines and the United Republic of Tanzania.[5]

Clinical presentation

Clinical course of lymphatic filariasis falls into three broad categories: asymptomatic disease, acute phase and chronic disease.

Filariasis is primarily asymptomatic; however, even people without clinical symptoms can experience pathological changes to the lymphatic system with the widening of lymphatic vessels (lymphangiectasia).[1] In the acute phase, patients experience sudden, episodic onset of signs and symptoms including fever, enlarged inguinal and axillary lymph nodes (adenolymphangitis), and lymphoedema, with skin exfoliation often occurring at the resolution of an acute episode.[3,5,6] Repeated episodes of acute bacterial adenolymphangitis (ADL) are associated with progression of the severity of lymphatic filariasis.[3] Chronic lymphatic filariasis is characterised by chronic and irreversible lymphoedema and elephantiasis of the limbs, scrotum and breasts.[1,5,6]

Diagnostic methods include:[6]

- establishing history of exposure,
- antigen detection assay to detect adult worms and, most reliably,
- microfilariae detection using venous blood smears, usually done at night when the microfilariae are most active in the bloodstream.

CLINICAL EVIDENCE

Chemotherapy for treating active filarial infection

The World Health Organisation recommends management of active lymphatic filariasis with a single dose of combination therapy (albendazole plus either DEC or ivermectin) for eradication of microfilariae and prevention of spread of disease.[7] (Level 5).

Chemotherapy is only recommended for active lymphatic filariasis as determined by observation of microfilariae in blood smear[4] (*Level 5*). It is not effective for treatment of lymphoedema or elephantitis where there is no active filarial infection[8] (*Level 1*).

The three primary treatments for eradication of microfilariae and macrofilariae are albendazole, ivermectin and diethylcarbamazine (DEC), either alone or in combination with each other. Albendazole is used to treat adult worms, DEC is used to treat both adult worms and microfilariae and ivermectin treats microfilariae and may have a role in sterilising adult worms. Medications are generally given in a single dose (albendazole 400mg, DEC 6mg/kg body weight or ivermectin 150 to 200µg/kg body weight).[1, 8-14]

The evidence on effectiveness of these three chemical treatments has been reported in a comprehensive Cochrane review in which three randomised controlled trials (RCTs) reported outcome measures in participants with active disease. The trials were conducted in child and adult populations with follow-up varying from three months to two years.[1] The findings, which are presented in more detail below, suggested that there is no significant differences between various chemotherapy regimens.[1]

The following evidence is available on the efficacy of chemotherapy for reducing microfilariae prevalence:

- One meta-analysis[1] of two small RCTs[8, 9] found no significant difference between albendazole (n=100) compared with placebo (n=95) for reduction in microfilariae prevalence in participants who were positive at baseline (risk ratio [RR] 0.97, 95% confidence interval [CI] 0.87 to 1.09, p=0.60)[1] (*Level 1*).
- A systematic review of studies of various methodology found ivermectin administered as a single dose (20 to 400µg/kg body weight) were effective in reducing microfilariae, with higher doses having greater and more sustained effect[15] (*Level 1*).

- In two RCTs there was no significant difference between DEC combined with albendazole and DEC alone for microfilariae prevalence in participants positive at baseline at any duration follow-up (three months to two years)[11, 12] (*Level 1*).
- A meta-analysis of two small studies[8, 9] found ivermectin (n=98) was slightly more effective that albendazole (n=100) for microfilariae prevalence in participants who were positive at baseline (RR 0.84, 95% CI 0.72 to 0.98, p=0.02)[1] (*Level 1*).
- Ivermectin in combination with albendazole (n=180) was not significantly different to ivermectin alone (n=168) at 12 month follow-up for microfilariae prevalence in participants who were positive at baseline (RR 1.00, 95% CI 0.88 to 1.13, p=0.94)[1] (*Level 1*). Individual RCTs had mixed findings on the comparison between ivermectin alone compared with ivermection combined with albendazole for reducing the density of microfilariae[8, 9, 13] (*Level 1*).

The following evidence is available for chemotherapy for reducing lymphoedema symptoms:

- A small RCT conducted in Ghana found no difference between albendazole (n=13) and placebo (n=9) in improving lymphoedema symptoms. The same trial found no significant difference for improving hydrocele; however this study was small and had wide confidence intervals[8] (*Level 1*).
- The same RCT conducted found no difference between ivermectin (n=13) and albendazole (n=13) for improving the clinical course of lymphoedema[8] (*Level 1*).

Six RCTs found there was no serious adverse events associated with albendazole, ivermectin or DEC. In one RCT that used much higher doses of medications there was a high incidence of scrotal syndrome (scrotal pain, epididymis enlargement and fever) in participants with albendazole[1] (*Level 1*).

Chemotherapy for reducing episodic lymphatic filariasis

Doxycycline may also be effective in reducing episodes of acute lymphatic filariasis[4] (*Level 5*) and [2] (*Level 1*). Evidence comes from a short report of an RCT:

- One placebo-controlled RCT (n=149) reported on effectiveness of a six week course of doxycycline (200mg daily) compared with amoxicillin (1,000mg daily) or placebo for reducing the acute episodes of lymphatic filariasis in patients with bancroftian filariasis and lymphoedema (stage 1 to 5) who were negative for active microfiliae. Participants received leg hygiene training at commencement of the study. At two year follow-up there was a significant reduction in acute episodes for participants receiving doxycycline compared to the other treatment groups[2] (*Level 1*).

Basic hygiene for reducing episodic lymphatic filariasis

Repeat acute episodes are associated with progress of lymphatic filariasis to chronic lymphoedema and elephantiasis. Effective management of acute episodes is therefore critical. The core components of treatment include skin care and hygiene, leg elevation and exercise[4, 7, 16] (*Level 5*). There is evidence that suggests these strategies are effective in reducing episodic ADL:

- In a case series study (n=175) conducted in Haiti, episodes of ADL were significantly lower when treatment focused on preventing recurrence using basic hygiene strategies compared with focusing on reduction of leg volume using compression bandaging. Patients followed a basic lymphoedema management plan that included leg washing, management of skin lesions with antibiotic cream and/or potassium permanganate, daily range of motion exercises and elevation of the legs (overnight and whenever possible during the day). Self-reported episodes of ADL significantly decreased (p=0.006) from 2.35 episode per person-year with no treatment and 1.56 episodes per person-year when compression was the primary management strategy to 0.56 episodes per person-year with the preventive hygiene plan (mean follow-up 22 months)[3] (*Level 4*).
- A community-based, multi-modal intervention that included skin wash, an Ayurvedic skin soak (*Rubia cordifolia*), Indian manual lymphatic drainage, yoga and breathing exercise, compression therapy, and a counselling and education program was trialled in two endemic regions of south India (n=1663 attended a one day education and counselling session, n=1008 entered the research study, n=730 achieved follow up). After 3 months there was a significant reduction in ADL (odds ratio [OR] 0.3, 95% CI 0.2 to 0.4, p<0.0001). Significant improvements (p<0.01) were also observed in mobility, self-care, pain, limb volume and overall quality of life[17] (*Level 2*).

There is some evidence on concordance with multi-modal interventions. For one intervention that included a one day counselling and education camp, 84.6% of participants were concordant with the treatment regimen[17] (*Level 2*). In another multi-modal intervention, high levels of concordance were achieved for skin hygiene (88%) and daytime leg elevation (69.7%), but lower adherence was reported for exercise (38.3%) and sleeping with foot of bed elevated (49.7%)[3] (*Level 4*).

To prevent spreading infected lymph through nodes, manual lymphatic drainage (self-massage) should be avoided when swelling is associated with infection[16] (*Level 5*).

Benzo-pyrones for reducing lymphoedema

Benzo-pryones, particularly the plant-derived coumarin, have been used for reducing lower limb oedema associated with lymphatic filariasis. Benzo-pryones limit fluid filtration but do not stimulate drainage of fluid. A Cochrane review[18] reported three low quality RCTs that investigated benzo-pryones alone or in combination with DEC. In individual trials, participants reported improved symptoms; however, the reviewers did not identify significant impact of treatment on objective measures of limb volume and suggested that the method of action of benzo-pyrones does not adequately address underlying pathophysiological issues (i.e. reduced fluid drainage). No pooling of results was conducted and no overall conclusions on treatment effectiveness could be made[18] (*Level 1*).

ABOUT WHAM EVIDENCE SUMMARIES

WHAM evidence summaries are consistent with methodology provided in detail in resources published by the Joanna Briggs Institute as cited in this evidence summary. WHAM evidence summaries undergo peer-review by an international review panel. More information on the website: http://WHAMwounds.com

WHAM evidence summaries provide a summary of the best available evidence on specific topics and make suggestions that can be used to inform clinical practice. Evidence contained within this summary should be evaluated by appropriately trained professionals with expertise in wound prevention and management, and the evidence should be considered in the context of the individual, the professional, the clinical setting and other relevant clinical information.

PUBLICATION

This evidence summary has been published in:

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