Evidence Summary: Lymphatic filariasis: Treatment

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QUESTION

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

SUMMARY

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

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, the microfilariae enter the skin and migrate to the lymphatic system where 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 stream is six to 12 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 10 countries: Bangladesh, Côte d'Ivoire, the Democratic Republic of Congo, India, Indonesia, Myanmar, Nigeria, Nepal, the Philippines, and the United Republic of Tanzania[5].

Clinical presentation

The 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 the 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 BOTTOM LINE

Chemotherapy for treating active filarial infection

The World Health Organization 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 5b evidence).

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

The three primary treatments for eradication of microfilariae and macrofilariae are albendazole, ivermectin and 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 400 mg, DEC 6 mg/kg body weight or ivermectin 150 to 200 µg/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 seven randomised controlled trials (RCTs) reported outcome measures in participants with active disease. These trials were designed primarily to assess treatment of individuals, and 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].

Efficacy in 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 1a evidence).
- A systematic review of studies of various methodologies found ivermectin administered as a single dose (20 to 400 µg/kg body weight) were effective in reducing microfilariae, with higher doses having greater and more sustained effect[15] (Level 1b evidence).
- 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 of follow-up (three months to two years)[11,12] (Level 1c evidence).
- 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 1a evidence).
- 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 1a evidence). 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 1c evidence).

Efficacy of chemotherapy in 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 1c evidence).
- The same RCT conducted found no difference between ivermectin (n=13) and albendazole (n=13) for improving the clinical course of lymphoedema[8] (Level 1c evidence).

Chemotherapy adverse events

- 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 1c evidence).

Doxycycline for reducing episodic lymphatic filariasis

Doxycycline may also be effective in reducing episodes of acute lymphatic filariasis[4] (Level 5b evidence) and [2] (Level 1.c evidence). 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 (200 mg daily) compared with amoxicillin (1,000 mg 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 1c evidence).

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] (Level 5b evidence). There is evidence that suggests these strategies are effective in reducing episodic ADL:

- In a case series study (n=175) in Haiti, patients were followed for a mean duration of 22 months. 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, a 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[3] (Level 4c evidence).
- High levels of adherence (defined as reporting at 75% or more appointments that the intervention had been performed every day since the last appointment) were achieved for skin hygiene (88%) and leg elevation in the daytime (69.7%), but lower adherence was reported for exercise (38.3%) and sleeping with foot of bed elevated (49.7%)[3] (Level 4c evidence).

CHARACTERISTICS OF THE EVIDENCE

This evidence summary is based on a structured database search using the search terms lymphoedoema, filariasis, lymphatic filariasis and Bancroftian filiariasis. The evidence comes from:

- A systematic review of RCTs[1] (Level 1a).
- A systematic review of studies of varied methodologies[15] (Level 1b).
- RCTs (some reported in the above systematic reviews)[2,8-13] (Level 1c).
- A case series study[3] (Level 4c).
- Opinion-based resources[4-7,14] (Level 5b).

BEST PRACTICE RECOMMENDATIONS

- In patients with active filariasis, a single dose of combination therapy (albendazole plus either DEC or ivermectin) is recommended to eradicate infection and reduce the spread of disease (Grade A).
- Daily leg care that includes washing, management of skin lesions, leg elevation and range-of-motion exercises is recommended to reduce episodes of acute lymphatic filariasis (Grade B).
- Consider a course of doxycycline (200 mg daily for four to six weeks) to reduce episodes of acute lymphatic filariasis (Grade B).

Related evidence summary

JBI ES Lymphatic filariasis: Prevention

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