2.3 LF DISEASE—CLINICAL MANAGEMENT

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Summary of Prioritized Research Needs

- 1) Investigate effects of MDA alone on progression or reversal of LF disease (lymphedema, filaricercle, acute adenolymphangitis [ADL]),
- 2) Evaluate comparative studies of filaricercle surgical techniques for a) relapse rates, b) surgical costs and duration, c) post-operative complications,
- 3) Refine and standardize (through a consensus conference) clinical definitions of LF disease, and describe epidemiology of LF disease with these new definitions,
- 4) Improve differential diagnosis of pediatric LF disease, and initiate studies to define measures to prevent its progression,
- 5) Investigate the value of traditional medicine approaches to lymphedema and urogenital disease,
- 6) Increase understanding of the skin barrier function, entry lesions, and ways of preventing the bacterial complications of LF disease,
- 7) Define epidemiology, risk factors, complications, and optimal management of chyluria.

2.3.1 Overview

LF disease management today.

In May, 1997, the World Health Assembly called for a global effort “to eliminate lymphatic filariasis as a public health problem.” Unlike most other infectious disease eradication or elimination programs, which focus only on interrupting transmission, two essential program components, or “pillars,” were envisioned for LF elimination: mass treatment with antifilarial drugs to interrupt transmission of the parasite, and care for those who already suffer from lymphedema or hydrocoele.¹ This clinical care component is believed to be important for the success of the overall programs; the antifilarial drugs themselves are thought to provide little benefit to people with chronic filarial disease, which is usually life-long;² and reducing the suffering of those with filarial disease enhances program acceptance and maximizes population coverage with antifilarial drugs.

Proper surgery can cure hydrocoele. For lymphedema of the leg, simple, inexpensive self-care measures have been shown to reduce the frequency of acute bacterial adenolymphangitis (a major factor in disease progression),^{3,4} stop progression of lymphedema to elephantiasis, and improve quality of life.^{5,6} These measures, which can be readily incorporated into the daily routine of people with lymphedema, include hygiene, skin care, range-of-motion movement or exercise, elevation of the leg, and wearing proper shoes to protect the feet from injury.⁷

Despite the availability of these simple and effective strategies for hydrocoele surgery and lymphedema management, thus far a relatively small proportion of people with filarial

disease worldwide has had access to them.⁸ With initiatives in several countries, this situation is beginning to change. Renewed effort is now underway at the program level to implement morbidity control interventions that are based on current knowledge of LF disease.⁹ However, research—basic, clinical, epidemiologic, social science, and operational—remains extremely important.

2.3.2 Research Needs

Epidemiologic assessments based on standardized definitions and techniques.

Considerable progress has been made during the last decade in our understanding of LF disease. However, particularly in the area of urogenital disease, these new findings have not been widely applied to epidemiologic research or to clinical or surgical management. For example, the relative frequency of hydrocoele, lymphocele, chylocele, and hematochylocele, all indistinguishable by clinical examination and all characterized by fluid inside the scrotal sac, is unknown. In addition, the clinical assessment of treatment outcomes has not been standardized. For example, adult worm death has been inferred by the disappearance of filarial antigenemia,¹⁰ detection of scrotal nodules,¹¹ and cessation of the filaria dance sign,¹² among other techniques. Ultrasound is being used increasingly, but techniques and procedures need to be standardized, and its potential value in women and children with *W. bancrofti* and in all individuals with *Brugia* infections still needs to be defined. Therefore,

- a consensus conference should be held both to establish case definitions for clinical and epidemiologic research in LF, and to identify and standardize the most appropriate diagnostic approaches for clinical research in individuals of all ages,
- epidemiologic studies should be carried out using the refined clinical definitions to describe the frequency, severity, geographic and age distributions of clinical conditions caused by LF (including less well-defined conditions of filarial arthritis and glomerulonephritis),
- through these studies the impact of disease should be measured, especially as it relates to disability (including psychological), since this information will be essential for planning for morbidity control, for advocacy, and for gaining further understanding of the pathogenesis and progression of filarial disease.

Effect of MDAs on filariasis morbidity.

Data on the impact of antifilarial MDAs on filariasis morbidity are inconsistent. Several studies report surprising reductions in acute attacks, lymphedema, and/or hydrocoele following MDAs,¹³ but a roughly equal number of studies reports no such association. Many of these studies are limited by inadequate or non-standardized case definitions and intermittent or incomplete follow-up. Few studies included control groups. Assessing the public health impact of mass treatment

** Other contributors in this working group are listed in Annex 2.

with antifilarial drugs is a critically important issue for program advocacy and for planning morbidity control strategies. The MDAs also induce transient adverse reactions, which, when DEC is used, may include lymphatic inflammatory reactions and hydrocoele. Therefore,

- the impact of MDAs on the prevalence and incidence of ADL, lymphedema, and hydrocoele should be studied both acutely and chronically using rigorous case definitions, close clinical assessment and control groups; they should be conducted both in areas using DEC/albendazole and in areas using ivermectin/albendazole.

Pediatric LF disease.

Pediatric LF remains under-recognized, misunderstood, and misdiagnosed. Physicians in filariasis-endemic areas need to be trained in differential diagnosis of swollen limbs. Guidelines are needed for referral from the peripheral level to reference centers, particularly for children with lymphedema or hydrocoele.

Most LF morbidity control activities currently focus on reducing severity or stopping progression of existing disease, and they do not address the prevention of clinical disease in persons who may already have subclinical disease. Lack of efforts to address prevention represents a major gap in current morbidity control efforts. Therefore, studies of pediatric, endemic-area populations are needed

- to define the extent and character of subclinical disease in children,
- to assess the effectiveness of early anti-filarial treatment on the development of subclinical and clinical lesions,
- to determine the degree to which bacterial ADL and lymphedema can be prevented through education programs focused on hygiene, maintenance of the skin barrier function through good skin care, and recognition and treatment of entry lesions,
- to assess the effectiveness of educational materials and school curricula developed to help prevent pediatric filarial disease.

Urogenital disease.

Clinical research and observation in filariasis-endemic areas, especially in Recife, Brazil, has revealed that fluid inside the scrotal sac, which was considered as hydrocoele, actually is comprised of several distinct entities: true hydrocoele, lymphocele, chylocele, and hematochylocele. Indeed, the term filaricele has been suggested recently to encompass all of these conditions. The implications for surgical management and for risk of compromised testicular function vary considerably for these different conditions. Little is known about the relative frequency of these conditions, and techniques and markers to discriminate among them are currently inadequate. Therefore,

- clinical studies are needed to define the epidemiology and assess the risk factors for various causes of filaricele,
- laboratory and diagnostic studies are urgently needed to develop simple, inexpensive, easy-to-use markers to distinguish among various causes of filaricele.

In many filariasis-endemic areas, hydrocoelelectomy is commonly regarded as a simple, uninteresting procedure that is relegated to junior doctors, and current techniques are regarded as adequate. However, patient follow-up is sporadic, and rates for complications following surgery and for hydrocoele recurrence in filariasis-endemic areas are unavailable. Furthermore, anecdotal reports suggest that relapse rates may be unacceptably high using current standard techniques and that the rates of infection and other post-operative complications are also quite high in some settings. To prevent recurrence of filaricele, complete excision of the tunica vaginalis is recommended by some, but this technique has not been adopted globally and multi-center studies have not yet documented its superiority to current techniques. Therefore,

- comparative studies of filaricele surgical techniques should be performed using standardized procedures and state-of-the-art diagnostics to distinguish various causes of filaricele,
- standardized outcome assessment should include
 - 1) relapse rate at specific post-operative intervals,
 - 2) surgery costs and duration,
 - 3) rates of infectious and other post-operative complications.

Because some hydrocoeles appear to reverse spontaneously and surgical morbidity is high in many filariasis-endemic areas, and because non-invasive physiologic measures such as deep breathing have proved useful in the management of non-filarial lymphedema,⁹

- studies should explore the role of such non-invasive measures in the management of scrotal lymphedema and other forms of urogenital disease where surgery is not required to preserve testicular function (i.e., excluding lymphocele, chylocele, and hematochylocele).

Lymph scrotum is a devastating disease of unclear etiology; however, previous hydrocoele surgery that did not involve excision of the tunica vaginalis has been postulated to be a risk factor.¹⁴ Furthermore, techniques for surgical management of lymph scrotum and urogenital elephantiasis are not standardized and follow-up is limited. Therefore,

- clinical research is needed to determine the most effective techniques for surgical management of scrotal and penile elephantiasis and for lymph scrotum.

Lymphedema and elephantiasis.

Maintaining skin barrier function and treatment of entry lesions.

Little is known about current practices for skin care in filariasis-endemic areas, and it is unknown whether such practices serve to maintain or degrade the skin barrier function.⁹ Locally made topical preparations are widely used, but little is known about them. They may be effective and inexpensive, or they may, in some cases, be harmful. Therefore,

- the safety and efficacy of current skin care practices, including the use of local topical preparations, should be determined.

The physical location and pattern of entry lesions (breaks in the skin that can serve as conduits for infection) likely reflect the anatomy of lymphatic dysfunction, and may have implications regarding its etiology (i.e., filarial or non-filarial). Furthermore, the prevalence and severity of entry lesions in various populations and their relationship to LF infection prevalence are unknown. Because prevention and treatment of entry lesions is such an important focus of recommended lymphedema management, this information is very much needed. Therefore,

- the epidemiology of entry lesions in filariasis-endemic areas needs to be described, using standardized definitions.

Although, in general, most entry lesions respond to basic topical agents, treatment failures do occur. The microbial, antimicrobial, and host factors responsible for these treatment failures are not completely understood. Therefore,

- research is needed on the bacteria and fungi involved in entry lesions in different endemic regions and on their susceptibility to topical antimicrobial agents,
- risk factors for clinical treatment failures should be assessed, especially in areas where investigations can include research on the microbial flora.

Acute attacks.

Two distinct clinical syndromes have been described for acute attacks, one putatively associated with a filarial etiology (i.e., adult worm death) and the other with a bacterial etiology.^{14,15} In addition, observations that the frequency of acute attacks has decreased following MDAs, along with some data from animal models, suggest a possible role for filarial larvae in initiating inflammatory events.¹³ A role for *Wolbachia* in acute attacks has also been speculated.¹⁶ However, such events have not been adequately described clinically, thereby limiting our understanding of the etiology and frequency of such events. Therefore,

- acute attacks or inflammatory events not explained by bacterial infection or by adult worm death should be studied and case definitions developed and tested,
- the frequency of acute filarial attacks and associated acute morbidity, such as hydrocoele, following MDAs should be investigated in areas using different mass treatment drug regimens,
- longitudinal studies of patients treated with doxycycline or other drugs that target *Wolbachia* should be designed to include observation and clinical characterization of acute attacks as well as control groups coming from the same endemic area or from areas with equivalent levels of filarial transmission,
- additional placebo-controlled, blinded trials of different acute attack management and prevention strategies (including prophylactic antibiotics or even bacterial vaccines) should be carried out in areas with bancroftian filariasis.

Lymphedema management.

The role of co-morbid conditions and genetic factors in the progression of lymphedema, fibrosis, and acute attacks is not

well defined. Additional knowledge is needed to guide clinical management. Therefore, studies should be undertaken

- to define the role of co-morbid conditions and genetic factors in the progression of lymphedema, fibrosis, and acute attacks.

Sustained patient motivation is essential for continued daily practice of lymphedema self-care. Therefore, operational research should be carried out to evaluate the effectiveness of a variety of interventions to maintain patient motivation and compliance with lymphedema management techniques.

In filariasis-endemic areas, persons with lymphedema currently seek care for lymphedema and acute attacks from a variety of sources, and traditional methods may be more or less effective. Also, engaging traditional healers in lymphedema management can lead to sustainable programs that are integrated into current health systems. Therefore,

- the effectiveness of traditional methods for lymphedema treatment should be evaluated and clinical trials performed for traditional measures that appear promising.

Chyluria.

Little is known about the epidemiology, risk factors, or complications of chyluria. The effect of diet and co-morbidities such as obesity in triggering the initial appearance of chyluria is poorly understood. In some areas, chyluria has been a relatively frequent clinical manifestation of LF, often frustrating and poorly managed.¹⁴ In severely affected individuals, chyluria can present as a serious wasting illness. Little is known about the inflammatory properties of lymph fluid in the extra-lymphatic spaces in the urinary collection system (e.g., inside the bladder). Therefore,

- field-applicable diagnostic criteria for chyluria should be agreed upon,
- studies should be carried out to define the descriptive epidemiology, risk factors, complications, and best management approaches for chyluria,
- the usefulness (or not) of surgical approaches to management of chyluria should be assessed and compared with dietary management techniques,
- clinical studies should assess the effects of chyluria on the endothelium and function of the urinary collecting system.

Benefits and public health impact of LF morbidity control.

The importance of morbidity control activities to GPELF success is strikingly clear, particularly to program managers. To date, however, few data exist to document quantitatively the degree to which morbidity control activities enhance either the general public health and economic well-being of endemic populations or even the effectiveness of LF MDA activities (by increasing drug coverage or population compliance). This information is essential both for cost-benefit assessments and for program advocacy. Therefore, studies should be designed

- to document the impact of morbidity control on MDA drug coverage and on general public health,
- to analyze cost-effectiveness and cost-benefit of LF mor-

idity control to guide programs in maximizing impact and minimizing cost.

2.3.3 References

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