Recent Updates on Onchocerciasis: Diagnosis and Treatment

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Recent progress in onchocerciasis research has led to improved understanding of the immunopathology of *Onchocerca volvulus*, as well as improvements in diagnosis and treatment of this morbid disease. This article reviews the recent literature, highlighting breakthroughs in sensitive means of antigen testing and an unusual new approach to therapy that targets an endosymbiotic bacterium required for filarial worm fecundity.

**EPIDEMIOLOGY**

Most widely known for causing “river blindness,” *Onchocerca volvulus* infection affects an estimated 17.7 million people worldwide in 34 countries in Africa, the Middle East, South America, and Central America. An estimated 500,000 people and 270,000 people experience secondary visual impairment and blindness, respectively [1]. Nations with the highest historical prevalence of onchocerciasis include 11 sub-Saharan West African nations, such as Ghana, Nigeria, Liberia, and parts of Mali; however, endemicity extends latitudinally across the entire continent of Africa and into Southwest Asia, with patchy foci in Yemen and Oman in the Arabian Peninsula. Small foci are also located in Ecuador, Venezuela, Colombia, Brazil, southern Mexico, and Guatemala [2]. Relationships between infection prevalence and individual infection intensity and between infection prevalence and transmission intensity appear to follow similar patterns in Africa and in Latin America, lending epidemiological support for Mesoamerican *O. volvulus* having a genetically recent relation to African *O. volvulus* [3]. In all, an estimated 123 million people live in areas where the disease is endemic. Onchocerciasis among nonimmigrant North Americans is almost entirely limited to travelers to areas of endemicity.

Onchocerciasis as a human disease has been shown to have more than just an effect on the quality of life; it also appears to shorten it. Little et al. [4] found an association between *O. volvulus* microfilarial load and all-cause mortality, claiming that 5% of the deaths in the study’s temporal and regional boundaries were attributable to *O. volvulus* infection. Blindness per se did not appear to have a significant effect on mortality when adjusted for microfilarial load. Recent data show that patients with glaucoma in Ghana had a higher prevalence of onchocerciasis (i.e., they had positive skin snip test results), even after adjustment for age, region, and sex (OR, 3.50; 95% CI, 1.10–11.18) [5].

**LIFE CYCLE**

*O. volvulus* has a 5-stage life cycle, in which the blackfly (genus *Simulium*) acts as obligate intermediate host (figure 1). Humans are the sole definitive host. Infection occurs when a blackfly introduces an *O. volvulus* stage 3 larva into the host during a blood meal. The female nematode develops to adulthood and permanently incarcerates itself in a fibrous capsule, whereas male adults move freely throughout the skin and subcutaneous spaces. During adulthood, the female worm sheds hundreds of thousands of microfilariae measuring 220–360 \( \mu \)m [6] that migrate through the skin of the human host, with particular affinity for the eyes. The inflammatory response against dying microfilariae over years of repeated infection causes the gradual and eventually blinding scleral opacification of the anterior eye by local inflammation and of the posterior eye by auto-
immune mechanisms [7]. The *O. volvulus* life cycle continues on uptake of microfilariae by the blackfly during a blood meal. Once inside, the microfilariae penetrate the fly’s gut and migrate to the thoracic flight muscles, where they develop to third-stage larvae and then find their way to the blackfly’s feeding apparatus. They then enter another human host during a blood meal, thus completing the cycle. Microfilariae persist in the human host for 3–5 years, in contrast to the adult female worm life span, which is 2–15 years [8, 9]. Filarial reproduction numbers and life spans are listed in table 1.

During the late 1990s, it was discovered that a *Wolbachia* rickettsial bacterium inhabits the endodermis of female *O. volvulus* worms and various stages of its intrauterine embryos, and it appears to have coevolved with *Onchocerca* [10]. This obligate endosymbiont has confused past efforts to characterize worm proteins. Previous studies on “filarial” peptides obtained by homogenizing the entire worm—with only rudimentary purification steps—actually may have been detecting *Wolbachia* proteins and intrinsic worm antigens [13].

**CLINICAL PRESENTATION AND PATHOGENESIS**

Onchocerciasis most commonly presents as a diffuse papular dermatitis, often with intense pruritis. These recently infected patients tend to demonstrate a strong \( T_{h1} \)-type immune response. In patients with chronic disease, however, the cutaneous manifestations can be differentiated across a spectrum, from pruritic lichenification on one end to asymptomatic depigmentation (the “leopard skin” pattern) on the other. Chronic papules and lichenification are associated with strong \( T_{h1} \) helper lymphocyte (\( T_{h2} \)) response, whereas depigmentation has been shown to correlate with a milder \( T_{h2} \) reactivity [11]. A subset of patients with chronic disease have papular disease that is similar in appearance to the acute papular eruption, but it is nevertheless \( T_{h2} \) predominant. Retinal and retinoic acids accumulate in tissues after the death of microfilariae and may be partially responsible for skin and ocular symptoms [14]. Exposure to *Onchocerca* breakdown products induces a strong eosinophilic response as well [15]. In contrast, the ocular pathology has been attributed to an immune reaction to *Wolbachia* antigens released as microfilariae undergo natural attrition over time [10, 16].

Subdermal nodules called “onchocercomata,” which are most easily seen over bony prominences [17], are another commonly reported manifestation of onchocerciasis. The value and reliability of verbal diagnosis by eliciting a history of nodules in areas where the disease is highly endemic have been described elsewhere [18]. In Africa, onchocercomata are often found over the bony prominences of the torso and hips, whereas in South America, where it is sometimes called “Robles disease” [1], the predominant strains typically produce nodules in the head and shoulders [19]. Cases of onchocercoma presenting as a breast mass [20] or as deep nodules in the pelvis [17] have been described. An angiogenic protein produced by the adult female is thought to contribute to the formation of the nodules. Each adult worm is estimated to produce 1600 microfilariae per day [14], and estimates have indicated a total daily turnover of 10,000–300,000 microfilariae at a steady state, with peak total body loads of 150 million [10, 12]. The presence of onchocercoma does not correlate with microfilarial load [17].

Aside from exposure to infected blackfly bites, a dominant risk factor for onchocerciasis infection in children in areas of endemicity may be maternal onchocercal infection during the gestational period [21]. This is not thought to result from vertical transmission but, rather, from stimulation of a fetal shift toward a \( T_{h2} \) response to onchocercal infection that, on exposure later in life, favors tolerance of the presence of *O. volvulus* and, paradoxically, more-severe dermatological symptoms [11]. This conclusion has yet to be independently validated.
Table 1. Illustrative numbers in onchocerciasis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Females per nodule</td>
<td>2–50 worms⁶</td>
</tr>
<tr>
<td>Males per nodule (constantly exchanging)</td>
<td>1–10 worms⁵</td>
</tr>
<tr>
<td>Microfilariae produced per day --- per adult female</td>
<td>1600⁵</td>
</tr>
<tr>
<td>Total body daily microfilariae turnover (steady state)</td>
<td>10,000–300,000³</td>
</tr>
<tr>
<td>Total body loads</td>
<td>As high as 150 million microfilariae³</td>
</tr>
</tbody>
</table>

* Females remain incarcerated in nodules [9].
† Males move in and out of nodules throughout lifespan [9].
⁻ From [10, 12].

ONCHOCERCIASIS AND THE IMMUNE SYSTEM

It has been suggested that people with early *O. volvulus* infection have a significantly increased cell-mediated immune response, compared with patients who have chronic infection, who tend to have a blunted cellular immunity [22]. Prolonged infection promotes physiology more tolerant of the *O. volvulus* presence, although the mechanisms are not clear.

Higher microfilarial loads have been associated with a lower severity of onchodermatitis. The degree of dermatitis is directly correlated with cytoadherence activity and cell proliferation in the host, and it is inversely correlated with microfilarial loads [23]. Thus, as is seen in Hansen disease and leishmaniasis, there appears to be a spectrum of disease with low-level infestations and highly symptomatic host reaction on one side, and concentrated infestation but less severe immune-mediated disease on the other. Whether this variability is inherent in the strains or is associated with host variability is not clear. In addition, the immune response to larval (L3) antigens appears to strengthen with age and duration of patency while developing an immune environment increasingly permissive to the presence of adult worms and microfilariae [24]. In other words, as the infected patient ages and develops a larger total worm load, the body becomes less susceptible to infection with new blackfly-transmitted L3 larvae.

The predominant skin disease is thought to be a reaction to *Onchocerca* antigens, not *Wolbachia* antigens [11]. In contrast, both *Wolbachia* and *Onchocerca* antigens have an effect on the cornea. *Wolbachia* antigens released during microfilarial dying are largely responsible for the corneal inflammation that eventually leads to blindness [25, 26]. *Wolbachia* species do, however, seem to stimulate a systemic neutrophil response, which Brattig et al. [27] suggest may be part of the worm’s adaptation to the competent host’s immune environment and even a necessary condition for proper mating. In addition, a study that documented a cross-reaction between Ov39 antigen from *Onchocerca volvulus* and the human ocular tissue antigen hr44 implicated autoimmunity in the clinical ocular disease [28].

ONCHOCERCIASIS AND HIV INFECTION

If exposed to HIV, especially the macrophage-tropic HIV-1, patients with onchocerciasis have a greater likelihood of converting to HIV positivity than do those without onchocerciasis [29]. The same study also suggests that treatment of onchocerciasis in HIV-1–infected patients decreases viral replication. HIV infection may worsen the severity of onchodermatitis, although this aspect of the relationship has not been well studied [30, 31]. Recent work by Kipp et al. [32] reaffirms that it is safe to include HIV-infected patients in mass-treatment populations.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the diffuse papular dermatitis seen in acute onchocerciasis is extensive and may include food allergies, leprosy, pinta, syphilis, vitamin A deficiency, and yaws [5]. Also, certain parasitic infestations can resemble onchocerciasis. Other *Onchocerca* species—*Onchocerca gutturosa*, in most cases—have been found to infect humans, but only 6 cases of infection have been reported, without evidence of transmission [33]. Rarely, *O. volvulus* infection can mimic dracunculiasis, the subcutaneous filaria emerging at the skin in 3 documented cases [34].

LABORATORY DIAGNOSIS

Perhaps the most important concept to understand when comparing diagnostic modalities is the lack of a reliable gold standard (table 2). Onchoderocomectomy with direct examination can be used to diagnose infestation, but not necessarily the potential to pass on infection (infectivity), which requires microfilaridermia [17]. Historically, the procedure of choice for the definitive diagnosis of onchocerciasis has been to use a sclerocorneal punch to obtain skin-tissue specimens from the iliac crests and search microscopically for microfilariae (skin-snip microscopy). It takes ~1.5 years [39] for the worm to mature and release enough microfilariae to be detectable by skin-snip microscopy, and the sensitivity of skin-snip microscopy is too low to be useful in areas where there is a low prevalence of cases [35]. Testing for cure in treated populations, especially in those with a low prevalence of infection, presents a challenge. In patients repatriated from areas of endemicity, resolution of pruritic papular eruption is a better indicator of cure than is resolution of eosinophilia or IgE levels [40].

Skin snips are becoming increasingly unpopular in communities where disease is endemic [41], and skin-snip microscopy has a lower sensitivity than newer biochemical methods, including skin-snip PCR, ELISAs, EIAs, and antigen
surveys [42]. Several DNA-based methods for detecting *O. volvulus* exist that may be useful specifically for diagnosis of onchocerciasis in low-prevalence or treated human populations [42, 43]. Pischke et al. [44] compared PCR ELISA and PCR DNA Detection Test Strips, but both tests require skin tissue specimens, and sensitivity was not clearly demonstrated.

The recent development of antibody-based rapid diagnostic tests offers a less expensive and more field-friendly approach to diagnosis. Weil et al. [45] presented data on a serum antibody test card that uses recombinant antigen from finger-prick whole-blood specimens to detect *O. volvulus*-specific IgG4. Initial results of a trial of a triple-antigen, indirect, ELISA rapid-format card test also appear to be promising [46], as do trials of a hybrid of 2 well-established sensitive and specific diagnostic antigens to produce a highly sensitive and specific antibody test [47].

A promising antigen detection dipstick assay was recently developed [35]. With an antigen detection threshold of only 25 nanograms per mL, the test not only detected 100% of all patients with positive results of skin snip microscopy, but it also demonstrated positive results for urine filarial antigen in 240 of 288 subjects with negative skin snip microscopy findings in a study area where the disease is highly endemic (prevalence, 52% [48]). A trial conducted among a low-prevalence population revealed 100% specificity and no cross-reaction with any of several coendemic parasites.

## TREATMENT

The standard treatment for onchocerciasis is ivermectin (150–μg/kg given orally every 6 to 12 months). Ivermectin is a highly lipophilic [49], 16-membered macrocyclic lactone from *Streptomyces avermitilis* [50]. Single-dose ivermectin effectively kills microfilariae by blocking postsynaptic, glutamate-gated chloride ion channels, inhibiting transmission, and paralyzing the nematode. It also appears to enhance immune responses against *O. volvulus* in the treated host [23]. Other than a significant oncogenic effect on adult female worms [51], ivermectin has little macrofilaricidal effect; therefore, it controls but does not cure the disease [50, 52]. One year after receipt of ivermectin treatment, skin microfilarial densities regain at least 20% of pretreatment levels, requiring repeated treatments for the lifespan of the adult worm [53]. A 15-month study showed that ivermectin is actually more effective at preventing further reactive onchocercal skin lesions than at clearing extant lesions [54]. Effective ivermectin treatment apparently requires a robust immune response [55]. Administration of single doses of 150 μg/kg every 3 months has been recommended on the basis.

### Table 2. Diagnostic tests described recently in the literature.

<table>
<thead>
<tr>
<th>Study, diagnostic test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayong et al. [35]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine antigen dipstick assay</td>
<td>100</td>
<td>100</td>
<td>Not yet available commercially</td>
</tr>
<tr>
<td>Tear antigen dipstick assay</td>
<td>92</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>Vincent et al. [36]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum antigen immunoblot</td>
<td>100a</td>
<td>100a</td>
<td>...</td>
</tr>
<tr>
<td>Skin-snip PCR ELISA</td>
<td>90a</td>
<td>100a</td>
<td>...</td>
</tr>
<tr>
<td>Serum IgG4 (OC3.6gst) ELISA</td>
<td>78a</td>
<td>100a</td>
<td>...</td>
</tr>
<tr>
<td>Serum IgG4 (OC3.6gst and OC9.3gst) ELISA</td>
<td>97a</td>
<td>100a</td>
<td>...</td>
</tr>
<tr>
<td>Zhang et al. [37]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin-snip PCR PCHA</td>
<td>88</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>Skin-snip PCR AGE</td>
<td>84</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>Skin-snip PCR ELISA</td>
<td>91</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>Weil et al. [45]: serum antibody card test</td>
<td>91a</td>
<td>95–100a</td>
<td>...</td>
</tr>
<tr>
<td>Guzmán et al. [38]: serum antibody dot blot assay</td>
<td>99</td>
<td>90</td>
<td>Field-use friendly</td>
</tr>
<tr>
<td>Nde et al. [47]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum antibody ELISA (hybrid recombinant antigen OvH2)</td>
<td>98.5</td>
<td>97.7</td>
<td>...</td>
</tr>
<tr>
<td>Serum antibody ELISA (hybrid recombinant antigen OvH3)</td>
<td>98.5</td>
<td>95.35</td>
<td>...</td>
</tr>
<tr>
<td>Boatin et al. [42]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin-snip microscopy</td>
<td>19–50a</td>
<td>100b</td>
<td>...</td>
</tr>
<tr>
<td>DEC skin patch test</td>
<td>36–83a</td>
<td>98a</td>
<td>...</td>
</tr>
<tr>
<td>PCR ELISA</td>
<td>50–88a</td>
<td>96a</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** AGE, agarose gel electrophoresis; DEC, diethyl carbamazine; PCHA, paper chromatography hybridization assay

* Interpreted from text.

b Stated as benchmark in text.
of evidence of decreased rates of posttreatment reactions (e.g., edema, pruritis, and backache) over time, compared with yearly dosing [56]. This is thought to be due to decreased numbers of microfilariae dying and releasing their antigens after more frequent treatments.

High-dose ivermectin (800 μg/kg) was shown to be no more effective than administration of the 150 μg/kg dose, and high doses may be harmful [57, 58]. In 2003, Awadzi et al. [59] reported that coadministration of ivermectin and albendazole, although apparently safe, did not lead to prolonged or enhanced amicrofilaridemia.

Presently, the only approved medication with a significant effect against adult worms is suramin, but toxicity, inconvenience (twice-daily injections administered for several weeks), and availability only through the Centers for Disease Control and Prevention (in the United States) virtually eliminates its clinical utility for treatment of onchocerciasis [60]. A promising new drug, moxidectin, has been shown to have significant macrofilaridical activity in animal studies [61], is safe for use in humans [62], and has already undergone phase II trials [63].

**ADVERSE EFFECTS OF IVERMECTIN**

Skin reactions after receipt of ivermectin treatment are commonly reported in persons with high microfilarial densities. After receipt of ivermectin treatment, circulating eosinophil counts decrease, and IL-5 and eosinophil-derived neurotoxin levels increase, showing a statistically significant correlation with clinical reaction scores [64].

The physiologic enzyme tryptase, released from mast cells, can be used as a marker of degranulation. Cooper et al. [65] showed that plasma tryptase levels increase 12 h after microfilarial killing with ivermectin, preceding adverse symptoms, which start 24 h and peak 36 h after receipt of ivermectin treatment. This increase correlated with clinical reaction scores, markers of eosinophilic sequestration (decreased peripheral blood eosinophilia and increased plasma IL-5 levels), and activation of degranulation (increased plasma eosinophil-derived neurotoxin levels). Reactions could be associated with lipopolysaccharide-like endotoxins released by *Wolbachia* symbionts or by hypersensitivity to true parasite antigen.

Burchard et al. [66] found a statistically significant correlation between ivermectin treatment and protein-leaking glomerular disturbances 5 days after administration of treatment. Total urinary protein excretion was significantly higher in patients with high microfilarial densities (>80 microfilariae per mg of skin). However, the change was minor and deemed to be clinically negligible. No statistically significant association between onchocerciasis and autoimmune glomerular or tubular disorders was demonstrated.

Ivermectin is a potent P-glycoprotein inhibitor [67], and as such, it has been shown to be very safe in mammals, whose γ-amino butyric acid (GABA) receptors and neurons lay behind a blood-brain barrier [50]. Care should be taken in patients with active meningoencephalitis or other states associated with a weakened blood-brain barrier. Seizure associated with ivermectin treatment, which was been rarely reported [50, 68], may be due to the drug passing the blood-brain barrier in susceptible individuals, but it should be noted that epilepsy need not be a contraindication to mass treatment programs. Over the course of large-scale, international treatment programs, there have been no reports of worsened epilepsy after receipt of ivermectin treatment [68].

In addition to epilepsy, some experts believe that onchocerciasis can also cause ≥1 of a loosely defined group of growth retardation syndromes [68]. This has not been thoroughly disputed or validated. Because of the rarity of growth retardation syndromes among populations from areas where onchocerciasis is endemic, the safety of ivermectin therapy for patients with growth retardation syndromes cannot be assumed, and such patients are referred to clinics for proper diagnosis and treatment [68].

**IVERMECTIN RESISTANCE**

As ivermectin continues to be used in both animals and humans, resistance presents another challenge to global eradication efforts [69]. Keddie et al. [70] maintained there may not be preexisting resistance genes among *O. volvulus* populations, slowing the development of ivermectin resistance. However, a study by Ardelli et al. [71] suggests that the genetic heterogeneity of *O. volvulus* is higher than previously thought. They believe that resistance alleles do preexist, that mass ivermectin treatment is rapidly transforming the population genetics of *O. volvulus*, and that clinical resistance is imminent. Indeed, parasites from ivermectin-treated patients demonstrate decreased diversity at many genetic loci for P-glycoprotein [72, 73], suggesting changes in allelic patterns that may lead to resistance. Although ivermectin resistance has been reported in 4 species of nematode parasites that generally do not affect humans [71], it has not yet been unequivocally demonstrated in *O. volvulus*.

**NEW DIRECTIONS IN THERAPY**

A new approach to therapy targets endosymbiotic *Wolbachia* bacteria. In 2000, a landmark study first showed [74] that doxycycline cleared *Wolbachia* bacterial endosymbionts from the endodermis and uteri of adult female worms, leading to unusually extensive worm sterility not seen in other antifilarial treatments. In a nonrandomized, placebo-controlled trial involving humans [53], doxycycline (100 mg per day for 6 weeks), followed by a single 150-μg/kg dose of ivermectin, resulted in up to 19 months of amicrofilaridemia, as well as 100% elimination of *Wolbachia* species from worms that were isolated and tested immunohistologically. The effect on microfilarider-
mias is thought to result from a complete block of embryogenesis for at least 18 months. In contrast, ivermectin only works against late-stage developing microfilariae still in the uterus, and it has little or no effect on early-stage embryos. The authors suggest that infected patients who permanently leave areas of endemicity should be offered, in addition to ivermectin, a 4–6-week course of doxycycline (100–200 mg per day) to achieve long-term amicrofilaridermia. PCR-detectable presence of Wolbachia species may remain and could signify the presence of dormant but viable bacteria [75, 76], but these bacteria appear unable to repopulate the worms up to 18 months after treatment [53, 75]. More research is needed to secure this conclusion.

Hoerauf et al. [76] recommend concurrent administration of ivermectin with doxycycline therapy, as well as administration of another ivermectin dose 6–8 months later to eradicate microfilariae too immature to be sensitive to the initial microfilaricidal treatment. However, caution should accompany the concurrent use of ivermectin and doxycycline, because these agents have not been formally studied for interactions [77]. An easy way to circumvent the potential for interactions is to delay doxycycline therapy until several days after administration of an ivermectin dose.

CONCLUSIONS

Onchocerciasis continues to be a problem in Africa and Latin America. With the recent discoveries in doxycycline-mediated eradication of Wolbachia species, health care providers now have another option for treating this historically devastating disease. As research and development in DNA-based and antigen-based means of diagnosis continues, physicians will soon have an array of effective and convenient tests at their disposal to diagnose the disease and test for cure. Still, global efforts and further research are needed to control the disease worldwide.

Acknowledgments

The Medline database was queried for “onchocerciasis.” Articles published in the past 6 years were scanned for relevance. Additional articles were sought on the basis of references in the original set of articles. I read a total of 128 articles to gain background and evaluate relevance.

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Potential conflicts of interest. D.N.U.: no conflicts.

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64. Cooper PJ, Awadzi K, Ottesen EA, Remic D, Nutman TB. Eosinophil sequestration and activation are associated with the onset and severity of systemic adverse reaction following the treatment of onchocerciasis with ivermectin. J Infect Dis 1999; 179:738–42.


