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Editorial

Filariasis (or **philariasis**) is a parasitic disease caused by an infection with roundworms of the Filarioidea type. These are spread by blood-feeding black flies and mosquitoes. This disease belongs to the group of diseases called helminthiasis.

Eight known filarial nematodes use humans as their definitive hosts. These are divided into three groups according to the niche within the body they occupy:

- Lymphatic filariasis is caused by the worms *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. These worms occupy the lymphatic system, including the lymph nodes; in chronic cases, these worms lead to the disease elephantiasis.
- Subcutaneous filariasis is caused by *Loa loa* (the eye worm), *Mansonella streptocerca*, and *Onchocerca volvulus*. These worms occupy the subcutaneous layer of the skin, in the fat layer. *L. loa* causes *Loa loa* filariasis, while *O. volvulus* causes river blindness.
- Serous cavity filariasis is caused by the worms *Mansonella perstans* and *Mansonella ozzardi*, which occupy the serous cavity of the abdomen.

The adult worms, which usually stay in one tissue, release early larval forms known as microfilariae into the host's bloodstream. These circulating microfilariae can be taken up with a blood meal by the arthropod vector; in the vector, they develop into infective larvae that can be transmitted to a new host.

Individuals infected by filarial worms may be described as either "microfilaraemic" or "amicrofilaraemic", depending on whether microfilariae can be found in their peripheral blood. Filariasis is diagnosed in microfilaraemic cases primarily through direct observation of microfilariae in the peripheral blood. Occult filariasis is diagnosed in amicrofilaraemic cases based on clinical observations and, in some cases, by finding a circulating antigen in the blood. To get to the complete clinico-diagnostic aspects of filariasis flip this page. "**DISEASE DIAGNOSIS**" amply outlines the complete gamut of Filarial diseases.

"**INTERPRETATION**" details the whole approach to Liver Function Tests (including the viral hepatitis). Lastly, "**TROUBLE SHOOTING**" highlights the simple yet very important test, viz., STOOL ANALYSIS. Rectify what can go wrong and help the patients.

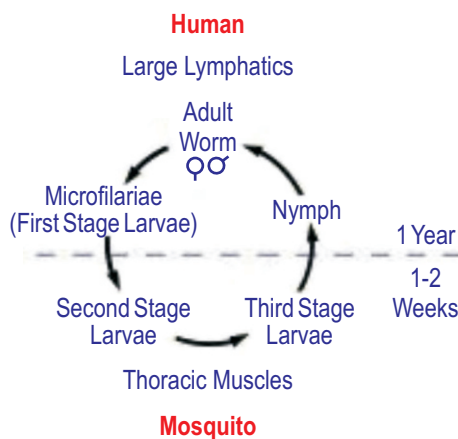
DISEASE DIAGNOSIS

FILARIASIS

Background

Filariasis is a disease group affecting humans and animals, caused by filariae; ie. nematode parasites of the order Filariidae. Filarial parasites can be classified according to the habitat of the adult worms in the vertebral host, as follows: **Cutaneous group** - Includes *Loa loa*, *Onchocerca volvulus*, and *Mansonella streptocerca*, **Lymphatic group** - Includes *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, **Body-cavity group** - Includes *Mansonella perstans* and *Mansonella ozzardi*. Of the hundreds of described filarial parasites, only 8 species cause natural infections in humans. The parasites of the cutaneous and lymphatic groups are the most clinically significant. Other species of filariae may cause incomplete infections, because they are unable to reach adult maturity in human hosts and therefore cannot produce first-stage larvae, known as microfilariae (eg. *Dirofilaria immitis* [dog heartworm], *D. [Nochtiella] repens*, and *D. tenuis* [raccoon heartworm]).

Life cycle of *Wuchereria bancrofti*



Filariasis. This figure displays the life cycle of *Wuchereria bancrofti* in humans and mosquito vectors (ie. *Aedes*, *Anopheles*, *Culex*, *Mansonia* species). Life cycles of other lymphatic nematodes (ie. *Brugia malayi*, *Brugia timori*) are identical, while the life cycles for other filariae differ in the body location of adult worms, the microfilariae present, and the arthropod intermediate hosts and vectors.

Filariasis has a significant economic and psychosocial impact in endemic areas, disfiguring and/or incapacitating more than 40 million individuals. Studies from the Indian subcontinent have shown that infected patients lose significant time from work because of the disease, costing the national treasury a minimum of \$842 million per year. Filariae have a specific geographic distribution. For example, *W. bancrofti* is found in sub-Saharan Africa, Southeast Asia, India, and the Pacific Islands. *B. malayi* is found in similar locations but not in sub-Saharan Africa. *B. timori* occurs on Timor island, in Indonesia. It has been observed (especially in endemic areas), that the prevalence of microfilaremia increases with age, as adult worms are gradually acquired over years. Lymphatic filariasis is first contracted in childhood, and most individuals in endemic areas have been exposed by the third or fourth decade of life. The proportion of infected individuals remains

constant. As with most helminths, adult filarial parasites replicate in a secondary host. The adult worm burden in an individual cannot increase unless the host is exposed to additional microfilaria. Infected individuals cannot sustain higher levels of parasitemia once they leave the endemic area. Because the mosquito vector is inefficient, a relatively prolonged stay in an endemic area is usually required to acquire the infection. Disorganized urbanization is adding to the vector population and hence to the increased incidence and prevalence of such diseases in developing countries.

Patient education

Patients should learn to protect against insect vectors and to refrain from self-treatment regimens, especially with diethylcarbamazine (DEC), since this drug can lead to meningoencephalopathy. Filariasis is a disease group affecting humans and animals, caused by filariae; ie. nematode parasites of the order Filariidae. Of the hundreds of described filarial parasites, only 8 species cause natural infections in humans. The World Health Organization (WHO) has identified lymphatic filariasis as the second leading cause of permanent and long-term disability in the world, after leprosy.

Signs and symptoms

Lymphatic filariasis: Fever, Inguinal or axillary lymphadenopathy, Testicular and/or inguinal pain, Skin exfoliation, Limb or genital swelling - Repeated episodes of inflammation and lymphedema lead to lymphatic damage, chronic swelling and elephantiasis of the legs, arms, scrotum, vulva and breasts.

The following acute syndromes have been described in filariasis: Acute adenolymphangitis (ADL), Filarial fever - Characterized by fever without associated adenitis, Tropical pulmonary eosinophilia (TPE).

Onchocerciasis: The clinical triad of infection in onchocerciasis is as follows: Dermatitis - Skin lesions include edema, pruritus, erythema, papules, scablike eruptions, altered pigmentation, and lichenification. Skin nodules (ie, onchocercomas) - Skin nodules tend to be common over bony prominences. Ocular lesions - Eye lesions are usually related to the duration and severity of infection and are caused by an abnormal host immune response to microfilariae; loss of visual acuity may occur.

Loiasis: The diagnostic feature of loiasis is a Calabar swelling, ie, a large, transient area of localized, nonerythematous subcutaneous edema. This is most common around the joints.

Mansonella infections: These are usually asymptomatic. If symptoms are present, they may include fever, pruritus, skin lumps, lymphadenitis, and abdominal pain.

Diagnosis

Microfilariae can be detected through examination of the following: **Blood** - The microfilariae of all species that cause lymphatic filariasis and the microfilariae of *Loa loa*, *Mansonella ozzardi*, and *M. perstans* are detected in blood. **Urine** - If lymphatic filariasis is suspected, urine should be examined macroscopically for chyluria and then concentrated to examine for microfilariae. **Skin** - *Onchocerca volvulus* and *M. streptocerca* infections are diagnosed when microfilariae are detected in multiple skin-snip specimens from different sites located on both sides of the body; the Mazzotti test allows a presumptive diagnosis of cutaneous filariasis to be made when skin snips are negative for microfilariae. **Eye** - Microfilariae of *O. volvulus* may be detected in the cornea or anterior chamber of the eye using slit-lamp examination.

The following imaging studies can be used in the evaluation of filariasis: **Chest radiography** - Diffuse pulmonary infiltrates are visible in patients with TPE. **Ultrasonography** - Can be used to demonstrate and monitor lymphatic obstruction of the inguinal and scrotal lymphatics; has also been used to demonstrate the presence of viable worms.

Lymphoscintigraphy.

Histologic findings include the following: **Lymphatic filariasis** - Affected lymph nodes demonstrate fibrosis and lymphatic obstruction with the creation of collateral channels. **Elephantiasis** - The skin is characterized by hyperkeratosis, acanthosis, lymph and fatty tissue, loss of elastin fibers, and fibrosis. **Onchocerciasis** - Onchocercomas have a central stromal and granulomatous, inflammatory region where the adult worms are found and a peripheral, fibrous section; microfilariae in the skin incite a low-grade inflammatory reaction with loss of elasticity and fibrotic scarring.

Management

Anthelmintics used in the treatment of filariasis include the following: **Diethylcarbamazine (DEC)**, **Ivermectin** - Drug of choice for *Wuchereria bancrofti*, **Suramin** - Only drug in clinical use for onchocerciasis that is effective against adult worms, **Mebendazole**, **Flubendazole**, **Albendazole**.

Surgery: In lymphatic filariasis, large hydroceles and scrotal elephantiasis can be managed with surgical excision. Correcting gross limb elephantiasis with surgery is less successful and may necessitate multiple procedures and skin grafting. In **onchocerciasis**, nodulectomy with local anesthetic is a common treatment to reduce skin and eye complications.

Pathophysiology

The filarial life cycle, like that of all nematodes, consists of 5 developmental (larval) stages in a vertebral host and an arthropod intermediate host and vector. Adult female worms produce thousands of first-stage larvae, or microfilariae, which are ingested by a feeding insect vector. Some microfilariae have a unique daily circadian periodicity in the peripheral circulation. The arthropod vectors (mosquitoes and flies) also have a circadian rhythm in which they obtain blood meals. The highest concentration of microfilariae usually occurs when the local vector is feeding most actively. **Microfilariae undergo** 2 developmental changes in the insect. Third-stage larvae then are inoculated back into the vertebral host during the act of feeding for the final 2 stages of development. These larvae travel through the dermis and enter regional lymphatic vessels. During the next 9 months, the larvae develop into mature worms (20-100 mm in length). An average parasite can survive for about 5 years. **The prepatent period** is defined as the interval between a vector bite and the appearance of microfilariae in blood, with an estimated duration of about 12 months. **The following factors affect** the pathogenesis of filariasis: **The quantity of accumulating** adult worm antigen in the lymphatics. **The duration and level of exposure** to infective insect bites. **The number of secondary bacterial** and fungal infections. **The degree** of host immune response. **Filarial infection generates** significant inflammatory immune responses that participate in the development of symptomatic lymphatic obstruction. Increased levels of immunoglobulin E (IgE) and immunoglobulin G4 (IgG4) secondary to antigenic (from dead worms) stimulation of Th2-type immune response have been demonstrated. **Studies have shown** that there is a familial tendency to lymphatic obstruction, providing support for the hypothesis that host genes influence lymphedema susceptibility. Studies also suggest that microfilaremia may be increased in individuals with low levels of mannose-binding lectin, suggesting a genetic predisposition. Further, a propensity to develop chronic disease has been demonstrated in patients with polymorphisms of endothelin-1 and tumor necrosis factor receptor II. **Prenatal exposure** seems to be an important determinant in conferring greater immune tolerance to parasite antigen. Thus, individuals from endemic areas are often asymptomatic until late in the disease when they have high worm burden, whereas nonimmune

expatriates tend to have brisk immune responses and more severe early clinical symptoms, even in light infections. **Studies have shown** that lymphatic filarial parasites contain rickettsialike *Wolbachia* endosymbiotic bacteria. This association has been recognized as contributing to the inflammatory reaction seen in filariasis.

Etiology

Lymphatic filariasis: Mosquitoes of the genera *Aedes*, *Anopheles*, *Culex*, or *Mansonia* are the intermediate hosts and vectors of all species that cause lymphatic filariasis. **Acute lymphatic filariasis** is related to larval molting and adult maturation to fifth-stage larvae. Adult worms are found in lymph nodes and lymphatic vessels distal to the nodes. Females measure 80-100 mm in length and males are 40 mm. **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 *B. timori* appears to result in more abscesses than infection with *B. malayi* or *W. bancrofti*.



Filarial abscess scar on the left upper thigh in a young male who is positive for *Wuchereria bancrofti* microfilariae

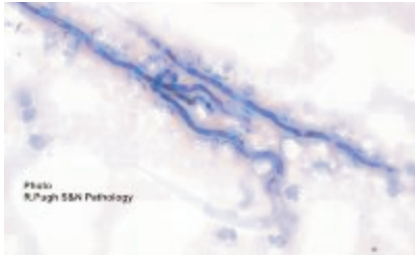
Cellular invasion with plasma cells, eosinophils, and macrophages, together with hyperplasia of the lymphatic endothelium, occurs with repeated inflammatory episodes. The consequence is lymphatic damage and chronic leakage of protein-rich lymph in the tissues, thickening and verrucous changes of the skin, and chronic streptococcal and fungal infections, which all contribute to the appearance of elephantiasis. (The skin of individuals with elephantiasis is characterized by hyperkeratosis, acanthosis, lymph and fatty tissue, loss of elastin fibers, and fibrosis.) ***B. malayi* elephantiasis** is more likely to affect the upper and lower limbs, with genital pathology and chyluria being rare. Secondary bacterial infection in elephantiasis can result in blindness.

Occult filariasis: Occult filariasis denotes filarial infection in which microfilariae are not observed in the blood but may be found in other body fluids and/or tissues. The occult syndromes are as follows: **Tropical pulmonary eosinophilia (TPE)** - Most likely results from a hyperresponsiveness to *W. bancrofti* or *B. malayi* antigen; symptoms result from allergic and inflammatory reactions elicited by the microfilariae and parasite antigens that the lungs clear from the bloodstream. ***D. immitis* or *D. repens* infection** - Human infection with *D. immitis* may result in pulmonary lesions of immature *Dirofilaria* worms in the lung periphery; if *D. immitis* larvae lodge in branches of the pulmonary arteries, they can cause pulmonary infarcts. **Filarial arthritis**, **Filarial breast abscess**, **Filaria - associated immune - complex glomerulonephritis**.

Onchocerciasis: *O. volvulus* microfilariae from the skin are ingested by the *Simulium* species of blackflies. Chronic onchocerciasis cases are hyperresponsive to parasite antigen, have increased eosinophilia, and result in the presence of high levels of serum IgE. Patterns of

onchocercal eye disease also are associated with parasite strain differences at the DNA level.

Loiasis: Mango flies or deerflies of *Chrysops* transmit loiasis. Response to *L. loa* infection appears to differ between residents and nonresidents in endemic areas. Nonresidents with infection appear to be more prone to symptoms than residents, despite lower levels of microfilaremia. Eosinophil, serum IgE, and antibody levels are also higher in nonresidents with infection.



Filariasis. Microfilariae of *Loa loa* detected in skin snips.

***L. loa* meningoencephalopathy:** Meningoencephalopathy is a severe and often fatal complication of infection. This syndrome is usually related to diethylcarbamazine (DEC) administration in individuals with high-density microfilaremia but it may occur without drug therapy. DEC causes a large influx of microfilariae into the cerebrospinal fluid, leading to capillary obstruction, cerebral edema, hypoxia, and coma. Localized necrotizing granulomas are also present, in response to microfilariae. Endomyocardial fibrosis, nephritic syndrome, and venous thrombosis may also be observed.

Epidemiology

International occurrence: Lymphatic filariasis affects more than 90 million people worldwide and is found throughout the tropics and subtropics. At least 21 million people are infected with *O. volvulus* in equatorial Africa and foci in Central and South America. Approximately 3 million people in Central Africa are infected with *L. loa*. In 1997, the World Health Organization (WHO) initiated a program to globally eliminate lymphatic filariasis as a public health problem.

Sex- and age-related demographics: Both sexes are equally susceptible to filariasis. Because of different local and cultural practices, however, as well as differences in exposure to insect vectors, one sex or the other may be exposed to infection more often. **Individuals of all ages** are susceptible to infection and are potentially microfilaremic. Microfilaremia rates increase with age through childhood and early adulthood, although clinical infection may not be apparent. The manifestation of acute and chronic filariasis usually occurs only after years of repeated and intense exposure to infected vectors in endemic areas.

Prognosis

The prognosis in filariasis is good if infection is recognized and treated early. Filarial diseases are rarely fatal, but the consequences of infection can cause significant personal and socioeconomic hardship for those who are affected. **The morbidity of human filariasis** results mainly from the host reaction to microfilariae or developing adult worms in different areas of the body. The WHO has identified lymphatic filariasis as the second leading cause of permanent and long-term disability in the world, after leprosy.

History

Symptoms of filariasis are dependent on species and body type and can be acute or chronic in nature. Up to 70% of infected individuals remain asymptomatic. Symptoms usually do not manifest until adolescence or

adulthood, when worm burden is usually the highest. Several variations have been observed. **Because cases of filariasis** in the industrialized world and the Western Hemisphere are uncommon, the diagnosis may initially be missed. To avoid this pitfall, obtain and document a travel history from patients with suspicious lesions.

Lymphatic filariasis: The clinical course of lymphatic filariasis is broadly divided into the following: **Asymptomatic microfilaremia** - Patients with microfilaremia are generally asymptomatic, although those with heavy microfilarial loads may develop acute and chronic inflammatory granulomas secondary to splenic destruction; passage of cloudy, milklike urine may denote chyluria. **Acute phases of adenolymphangitis (ADL).** **Chronic,** irreversible lymphedema.

Lymphatic filariasis symptoms predominantly result from the presence of adult worms residing in the lymphatics. They include the following: **Fever, Inguinal or axillary lymphadenopathy, Testicular** and/or inguinal pain, **Skin** exfoliation, **Limb or genital** swelling.

The following acute syndromes have been described in filariasis: **Acute ADL, Filarial fever** - Characterized by fever without associated adenitis, **Tropical pulmonary eosinophilia (TPE).**

Acute ADL: This refers to the sudden onset of febrile, painful lymphadenopathy. Pathologically, the lymph node is characterized by a retrograde lymphangitis, distinguishing it from bacterial lymphadenitis. Symptoms usually abate within 1 week, but recurrences are possible.

Signs and symptoms of ADL include episodic attacks of fever associated with inflammation of the inguinal lymph nodes, testis, and spermatic cord, as well as with lymphedema. Skin exfoliation of the affected body part usually occurs with resolution of an episode.

Tropical pulmonary eosinophilia: TPE is a form of occult filariasis. Presenting symptoms include a dry, paroxysmal cough, wheezing, dyspnea, anorexia, malaise and weight loss. **Symptoms of TPE** are usually due to the inflammatory response to the infection. Characteristically, peripheral blood eosinophilia and abnormal findings on chest radiography are observed. TPE is usually related to *W. bancrofti* or *B. malayi* infection.

Onchocerciasis: This also is known as hanging groins, leopard skin, river blindness, or sowda. Symptoms result from the presence of microfilariae in the skin and include pruritus, subcutaneous lumps, lymphadenitis, and blindness. **Patients with onchocerciasis** may report impaired visual acuity due to corneal fibrosis. Epilepsy has been associated with onchocerciasis in some studies.

Loiasis: The symptoms of *L. loa* infection are usually confined to subcutaneous swellings on the extremities, localized pain, pruritus, and urticaria. **Rare manifestations** of infection include the following: **Arthritis, Breast calcification, Meningoencephalopathy, Endomyocardial fibrosis, Peripheral neuropathy, Pleural effusions, Retinopathy.**

***M. ozzardi, M. perstans* and *M. streptocerca* infection:** *Mansonella* infections are usually asymptomatic. If symptoms are present, they may include fever, pruritus, skin lumps, lymphadenitis, and abdominal pain.

Dirofilaria infection: Symptoms of *D. immitis* infection involve the respiratory system and include chest discomfort, cough, fever, and hemoptysis. **Symptoms of *D. repens* infection** usually include a lump in the subcutaneous tissue, submucosa, or eyelid.

Physical Examination

Signs of filariasis present on examination are species-dependent and may be acute or chronic in nature.

Lymphatic filariasis

In lymphatic filariasis, repeated episodes of inflammation and lymphedema lead to lymphatic damage, chronic swelling, and elephantiasis of the legs, arms, scrotum, vulva, and breasts.

Lymphatic filariasis resulting from *Wuchereria bancrofti* infection, which is causing limb lymphoedema, inguinal lymphadenopathy, and hydrocele.



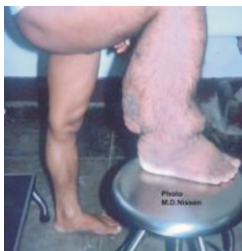
Unilateral left lower leg elephantiasis secondary to *Wuchereria bancrofti* infection in a boy.



This is a close-up view of the unilateral lower leg elephantiasis shown in previous image. Note the lymphoedema and typical skin appearance of depigmentation and verrucosities (warty changes).



Lateral view of the right outer aspect of a leg affected by gross elephantiasis secondary to *Wuchereria bancrofti* infection.



Inner aspect of the lower leg of the male patient in previous image, showing gross elephantiasis secondary to *Wuchereria bancrofti* infection.



Unilateral left hydrocele and testicular enlargement secondary to *Wuchereria bancrofti* infection in a man who also was positive for microfilariae.



Bilateral hydrocele, testicular enlargement, and inguinal lymphadenopathy secondary to *Wuchereria bancrofti* infection in a man who also was microfilaremic.

The WHO has developed a system to grade the severity of edema, as follows: **Grade 1** - Pitting edema reversible with limb elevation, **Grade 2** - Nonpitting edema irreversible with limb elevation, **Grade 3** - Severe swelling with sclerosis and skin changes. **Hydrocele** is the most common manifestation of chronic *W. bancrofti* infection in males in endemic areas but is rare with *B. malayi* and *B. timori* infection. **Chyluria** also may be present in chronically infected persons. Since large amounts of fat and protein are lost in the urine, these conditions can lead to nutritional deficiencies.

Tropical pulmonary eosinophilia

Scattered wheezes and crackles are heard in both lung fields. Lymphadenopathy and hepatomegaly may be present.

Onchocerciasis

The clinical triad of infection is as follows: **Dermatitis** - Skin lesions include edema, pruritus, erythema, papules, scablike eruptions, altered pigmentation, and lichenification. **Skin nodules** (ie. onchocercomas) - Skin nodules tend to be common over bony prominences.



Onchocercomas of the forearm skin (sowda) in a Sudanese man.

Ocular lesions - Eye lesions are usually related to the duration and severity of infection and are caused by an abnormal host immune response to microfilariae; loss of visual acuity may occur.

Common eye findings in onchocerciasis include the following: **Punctate keratitis**, **Pannus** formation, **Corneal** fibrosis, **Iridocyclitis**, **Glaucoma**, **Choroiditis**, **Optic** atrophy.

Loiasis: The diagnostic feature of loiasis is a Calabar swelling, ie, a large, transient area of localized, nonerythematous subcutaneous

edema. This is most common around the joints. **Peripheral nerve involvement** in loiasis has been described. Microfilaremia tends to be asymptomatic. Occasionally, the worm is observed migrating through subconjunctival or other tissues.

***M. ozzardi*, *M. perstans*, and *M. streptocerca* infection:** Subcutaneous or conjunctival nodules and lymphadenopathy may be detected in symptomatic persons.

Dirofilaria infection: These infections are characterized as follows: ***D. repens* infection** - May result in painless subcutaneous, submucosal, or eyelid lumps, ***D. immitis* infection** - Reduced localized air entry on chest auscultation may be detected.

Diagnostic Considerations

Differentials in the diagnosis of filariasis include the following: **Allergic bronchopulmonary aspergillosis**, **Systemic vasculitides**, **Chronic eosinophilic pneumonia**, **Idiopathic hypereosinophilic syndrome**, **Acute poststreptococcal glomerulonephritis**.

Lymphatic filariasis: Differentials in the diagnosis of lymphatic filariasis include the following : **Bacterial or fungal lymphadenitis** - eg. sporotrichosis resulting from *Sporothrix schenckii* infection, **Recurrent streptococcal lymphadenitis** - ie. relapsing erysipelas, **Congenital or hereditary lymphedema** - eg. Milroy syndrome, **Nonfilarial elephantiasis** - Highlands of East Africa, **Congenital hydrocele**, **Epididymal cysts**, **Carcinoma of testis** and/or scrotum, **Lymphosarcoma**.

Occult filariasis: Differentials in the diagnosis of occult filariasis include the following: **Asthma**, **Bacterial monoarthritis**, **Bacterial breast abscess**, **Idiopathic** or poststreptococcal glomerulonephritis.

Other: Differentials also include the following: **Onchocerciasis** - Vitiligo, trachoma, lepromatous leprosy, **Loiasis** - Hereditary and/or localized idiopathic angioedema.

Differential Diagnoses: **Angioedema**, **Asthma**, **Hodgkin Disease**, **Hydrocele**, **Leprosy**, **Lymphedema**, **Lymphoma**, **Non-Hodgkin**, **Scrotal Trauma**, **Testicular Trauma**.

Approach Considerations

The traditional diagnostic method for filariasis is to demonstrate microfilariae in the peripheral blood or skin. For example, the microfilariae of all species that cause lymphatic filariasis and the microfilariae of *L. loa*, *M. ozzardi*, and *M. perstans* are detected in blood.

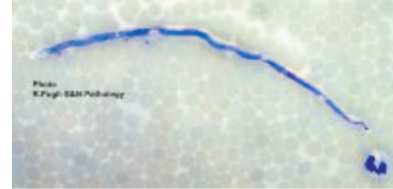
O. volvulus* and *M. streptocerca infections are diagnosed when microfilariae are detected in multiple skin snip specimens from different sites located on both sides of the body. In addition, microfilariae of *O. volvulus* may be detected in the cornea or anterior chamber of the eye, using slit-lamp examination.

Urine examination and microscopy: Microfilariae may also be observed in chylous urine and hydrocele fluid. If lymphatic filariasis is suspected, urine should be examined macroscopically for chyluria and then concentrated to examine for microfilariae.

Detection of Microfilariae in the Skin and Eye: Skin: *O. volvulus* and *M. streptocerca* infections are diagnosed when microfilariae are detected in multiple skin-snip specimens from different sites located on both sides of the body. **In suspected cases** of African onchocerciasis, the recommended sites for skin snips are the gluteus and calf. For American onchocerciasis, the scapula and deltoid skin are preferred. **Mazzotti test:** The Mazzotti test allows a presumptive diagnosis of cutaneous filariasis to be made when skin snips are negative for microfilariae. An intense pruritus is elicited within hours after a single small dose of DEC (50-100 mg). Steroids may be necessary to control this inflammatory reaction. The test must be used with caution in individuals who may be heavily infected, because a severe systemic reaction can be provoked. A DEC patch test that causes a localized skin reaction may be used in such

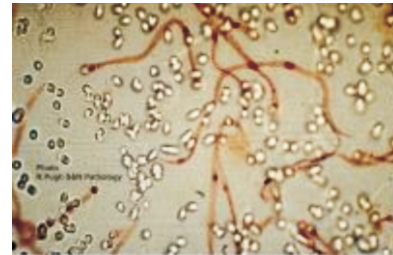
patients. **Eye:** Microfilariae of *O. volvulus* may be detected in the cornea or anterior chamber of the eye using slit-lamp examination.

Detection of Microfilariae in Blood: As mentioned, the microfilariae of all species that cause lymphatic filariasis and the microfilariae of *L. loa*, *M. ozzardi*, and *M. perstans* are detected in blood. (See the image below.)



Microfilariae of Mansonella perstans in peripheral blood.

Capillary finger-prick or venous blood is used for thick blood films. Venous blood also can be concentrated or passed through a Nuclepore filter before being examined microscopically. The species of infection then can be determined by the microscopic appearance. *W. bancrofti* and *Brugia* species have an acellular sheath. *W. bancrofti* has no nuclei in its tail, whereas *B. malayi* has terminal and subterminal nuclei. (See image.)



Appearance of microfilariae after concentration of venous blood with a Nuclepore filter.

Microfilariae may periodically appear in the peripheral circulation. For the best chance of detection, the blood should be examined at different intervals over a 24-hour period.



Microfilaria of Wuchereria bancrofti in a peripheral blood smear.

Bancroftian and brugian filariasis tend to show nocturnal periodicity, so it is recommended that samples be collected between 10:00 pm and 2:00 am. Provocation of nocturnally periodic microfilariae may be achieved with a daytime dose of DEC at 1-2 mg/kg.

Microfilariae may be absent in the following cases: **Patients with ADL** or late chronic lymphatic disease, **Typically, patients** with loiasis, unless the infection has been present for many years.

Complete blood count: Eosinophilia is marked in all forms of patent filarial infection.

Serum immunoglobulin concentrations: Elevated serum IgE and IgG4 may be observed with active filarial disease. Testing based on polymerase chain reaction assay has been described. **A multiplex bead assay** to monitor serial levels of serum antibody during treatment has been proposed.

Detection of filarial antigen: The presence of circulating filarial antigen in the peripheral blood, with or without microfilariae, is considered diagnostic of patent filarial infection and is also used to monitor the effectiveness of therapy. Commercial kits are available to test venous blood and can be quantitative (enzyme-linked immunoassay [ELISA] Og4C3 monoclonal antibody-based assay) or qualitative (immunochromatographic). The ELISA is one of the best predictors of worm burden; the other, although not as sensitive, was once considered the test of choice in field surveys. However, results from this test remain positive for 3 years posttreatment; hence, immunochromatographic testing has been shown to be ineffective.

Detection of filarial antibodies: The use of recombinant antigens for the diagnosis of onchocerciasis IgG4 antibodies (which are a marker of active infection) has improved the sensitivity and specificity of serologic assays. The usual IgG and IgE lack specificity (species differentiation) and usually crossreact with antigens of *Strongyloides*. In addition, they do not differentiate between past and recent infections. Thus, diagnosis based on recombinant antigens is useful in expatriates but not in persons living in endemic regions.

Imaging Studies

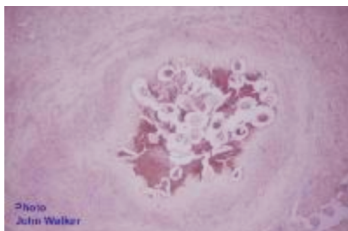
The following imaging studies can be used in the evaluation of filariasis: **Chest radiography** - Diffuse pulmonary infiltrates are visible in patients with tropical pulmonary eosinophilia (TPE), **Ultrasonography** - Can be used to demonstrate and monitor lymphatic obstruction of the inguinal and scrotal lymphatics, **Lymphoscintigraphy**. **Ultrasonography** has also been used to demonstrate the presence of viable worms, which are seen to be in continuous motion (ie. "filarial dance" sign). This imaging characteristic has been used to monitor the effectiveness of treatment. In addition, deep onchocercomas and vitreous changes in the eye can sometimes be detected with ultrasonography.

Biopsy

It is recommended that biopsy specimens be obtained only in patients with cutaneous filariasis, as excising nodes may further impede lymphatic drainage in patients with lymphatic filariasis. Adult worms of *O. volvulus* and *L. loa* are found in the nodules and fibrotic tissue of the skin. *L. loa* worms occasionally can be dissected from the conjunctiva of the eye or bridge of the nose as they migrate through subcutaneous tissue.

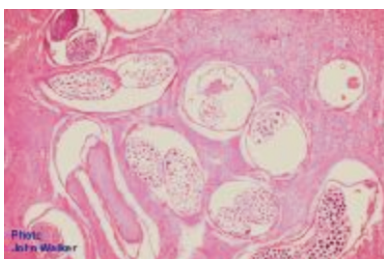
Lymphatic filariasis: Affected lymph nodes demonstrate fibrosis and lymphatic obstruction with the creation of collateral channels. The skin of individuals with elephantiasis is characterized by hyperkeratosis, acanthosis, lymph and fatty tissue, loss of elastin fibers, and fibrosis. (See the image below.)

Adult worms of *Wuchereria bancrofti* in cross section isolated from a testicular lump.



Onchocerciasis: Two areas are evident in onchocercomas: (1) a central stromal and granulomatous, inflammatory region where the adult worms are found and (2) a peripheral, fibrous section. Microfilariae in the skin incite a low-grade inflammatory reaction with loss of elasticity and fibrotic scarring. (See image.)

Adult *Onchocerca volvulus* contained within onchocercomas of the skin.



Approach Considerations

The medical management of a filarial infection should be specific and based on the microfilariae isolated or antigenemia detected. **Mass drug administration** reduces the transmission of filarial infection and disease morbidity by decreasing the burden of microfilaremia, resulting in suboptimal levels for transmission by disease vectors. For example, annual mass treatment with albendazole and ivermectin is employed to interrupt the transmission of *W. bancrofti*. Since this species has no alternative hosts, this approach could theoretically result in eventual eradication of bancroftian filariasis. **One study evaluated** the effect of higher dose and increased frequency (twice yearly) of albendazole-ivermectin therapy for *W. bancrofti* and found that it resulted in complete microfilarial clearance, as well as a more sustained clearance than that resulting from standard-dose albendazole-ivermectin treatment. **The effects of mass treatment** on filariasis have reportedly been sustained for up to 6 years. No filariasis vaccine is currently available, but efforts to develop an effective one are under way.

Surgery: Lymphatic filariasis: Large hydroceles and scrotal elephantiasis can be managed with surgical excision. Correcting gross limb elephantiasis with surgery is less successful and may necessitate multiple procedures and skin grafting. **Onchocerciasis:** Nodules with local anesthetic is a common treatment to reduce skin and eye complications.

Diet and activity: Fatty foods are restricted in individuals with proven chyluria that is associated with lymphatic filariasis. **Individuals** with chronic lymphatic filariasis are encouraged to mobilize (with compression bandage support) the affected limb.

Prevention: Avoidance of bites from insect vectors is usually not feasible for residents of endemic areas, but visitors to these regions should use insect repellent and mosquito nets.

Pharmacologic Therapy

Lymphatic filariasis: Patients with asymptomatic microfilaremia can be treated on an outpatient basis. Supervision of oral DEC therapy and provocation with postadministration observation is recommended for patient compliance with therapy and for the management of febrile reactions in heavily infected patients. **Inpatient care** may initially be required for adenolymphangitis (ADL) and chronic filariasis. Such care includes the use of antihistamines, steroids, pain relief, and intravenous antibiotics for secondary infections.

Lymphedema: Steroids can be used to soften and reduce the swelling of lymphedematous tissues. Mild to moderate filarial lymphedema has been shown to improve with a 6-week course of doxycycline, independent of ongoing infection. **Bed rest, limb elevation**, and compression bandages traditionally have been used for the management of chronic lymphedema.

Chronic filariasis: Treatment of chronic filariasis does not change the prognosis, as irreversible fibrosis usually destroys lymphatic tissue. However, asymptomatic patients, hoping to diminish progression of the disease, still typically undergo treatment, although the benefit of this is unclear.

Chyluria: In the treatment of chyluria, a special low-fat, high-protein diet supplemented with medium-chain triglycerides may prove beneficial. In addition, the sclerosing action conferred by diagnostic lymphangiography may plug the leak.

Secondary infection: Supportive care should include the prevention of secondary infection, especially in patients with advanced disease. Individuals with chronic infections should wash the affected area frequently, apply antiseptic creams to abrasions, keep their nails clean,

wear comfortable footwear, and exercise the affected limb to aid lymphatic flow.

Onchocerciasis: If DEC and suramin (currently the only drug in clinical use for onchocerciasis that is effective against adult worms) are used, inpatient care is recommended to monitor for reactions and complications of therapy. **Moxidectin** is being investigated as an alternative to ivermectin for the treatment of river blindness. This agent may shorten the number of annual treatments to 6.

Bancroftian filariasis: Ivermectin is now considered the drug of choice for the treatment of bancroftian filariasis. In the United States, it can be obtained from the Centers for Disease Control and Prevention (CDC) in endemic areas of the world, it is provided free by the Mectizan Donation Program. The addition of albendazole seems to improve response. **Six-week and 8-week courses** of doxycycline have compared favorably with ivermectin plus albendazole. Doxycycline therapy may be more readily available and may be better tolerated by some patients. It may also be capable of preventing or reversing lymphatic pathology. **In one study**, a 3-week course of doxycycline followed by a single dose of DEC was shown to be microfilaricidal. **Findings have validated** the use of single-dose regimens of ivermectin and DEC or albendazole for large-scale control and eradication programs aimed at reducing *Wuchereria bancrofti* microfilaremia, antigenemia, and clinical manifestations.

***M. perstans* infection:** Because *M. perstans* is resistant to standard antiparasitic treatment, doxycycline is sometimes used to eradicate *Wolbachia*, an endosymbiont found in most filarial species. **Doxycycline treatment** typically kills or sterilizes the filarial nematode. In an open-label, randomized trial, Coulibaly et al recruited patients with *M. perstans* infection from 4 African villages in Mali. Patients were randomly assigned to receive 200 mg of doxycycline orally every day for 6 weeks or no treatment. **At 12 months**, 97% of patients who received doxycycline had no detectable blood levels of *M. perstans*, compared with 16% of patients in the group that did not receive treatment. At 36 months, *M. perstans* remained suppressed in 75% of patients who had received doxycycline.

Long-Term Monitoring: Patient monitoring includes posttreatment follow-up for 12 months, with examination of peripheral blood and skin snips for microfilariae. **Observe and monitor** oral therapeutic plans with DEC because compliance with therapy is poor and usually incomplete. **Patients with filariasis** are, by default, at risk for other parasitic infections because areas endemic for bancroftian filariasis are also endemic for other parasites. After treatment, patients should be monitored for symptoms that are characteristic of parasitic infections.

Medication Summary

Patients with asymptomatic microfilaremia in lymphatic filariasis can be treated on an outpatient basis. Supervision of oral DEC therapy and provocation with postadministration observation is recommended for patient compliance with therapy and for the management of febrile reactions in heavily infected patients. Inpatient care may initially be required for adenolymphangitis (ADL) and chronic filariasis. **Mass drug administration** in filariasis reduces the transmission of filarial infection and disease morbidity by decreasing the burden of microfilaremia, resulting in suboptimal levels for transmission by disease vectors.

Class Summary: Anthelmintic agents include macrocyclic lactone derivatives of avermectin, piperazine derivatives, and benzimidazole derivatives. **The biochemical pathways** of parasites differ from those of their human host. Thus, the toxicity of anthelmintic agents can be directed at the parasite or its egg or larvae. The antiparasitic actions of these drugs vary; they include the following: **Inhibition of microtubules**,

causing irreversible block of glucose uptake, **Tubulin** polymerization inhibition, **Depolarization** of neuromuscular blockade, **Cholinesterase** inhibition, **Increased cell membrane** permeability, resulting in intracellular calcium loss, **Vacuolization** of the schistosome tegument, **Increased cell membrane** permeability to chloride ions via alteration of chloride channels. **Ivermectin (Mectizan):** Ivermectin is a potent microfilaricide and macrofilaricide for *W. bancrofti* in multiple doses. It is used alone or in combination with DEC. It is the drug of choice for the treatment of bancroftian filariasis. **Ivermectin exerts** its antiparasitic action by acting as a potent agonist at gamma-aminobutyric acid (GABA) receptors and potentiating the inhibitory signals sent to motor neurons, thus paralyzing the parasite. Because GABA is confined to the CNS in humans and ivermectin does not cross the blood-brain barrier, the drug has no paralytic action in humans. **Diethylcarbamazine (Hetrazan):** Diethylcarbamazine (DEC) is a microfilaricide. Its precise mechanism of action is not understood, but it has been shown to induce immobilization of microfilariae by using hyperpolarization effects to decrease muscle activity. Alteration of the surface membrane also occurs, with enhanced destruction by the host's immune system. Evidence exists that DEC may enhance adhesion of granulocytes via antibody-dependent and -independent mechanisms. Hypotheses also include interference by microfilarial intracellular processing and transport of specific macromolecules by DEC. **Concurrent administration** of corticosteroids should be considered with DEC treatment to minimize the allergic manifestations secondary to the disintegration of microfilariae, particularly in *O. volvulus* and *L. loa* infections. **Suramin:** Suramin is an antitrypanosome and an anthelmintic. It is currently the only drug in clinical use for onchocerciasis that is effective against adult worms, but its use is restricted because of its intrinsic toxicity and the frequency with which associated complications occur. The WHO has advised that it only be considered for the curative treatment of individuals in areas without transmission of onchocerciasis, in individuals leaving an endemic area, and in individuals with severe hyperreactive onchodermatitis if their symptoms are not adequately controlled with ivermectin. **The WHO** has also recommended that suramin not be used to treat onchocerciasis in individuals who are elderly or infirm, in patients with severe liver or renal disease, in children younger than 10 years, in totally blind persons (unless they require relief from intensely itchy lesions), in lightly to moderately infected people with no symptoms and whose eyes are not at risk, or in pregnant women (who should be treated after delivery). **Mebendazole:** Mebendazole causes worm death by selectively and irreversibly blocking uptake of glucose and other nutrients in a susceptible adult intestine where helminths dwell. **Albendazole:** Albendazole is a broad-spectrum anthelmintic. It decreases adenosine triphosphate (ATP) production in worms, causing energy depletion, immobilization, and, finally, death.

Antibiotics

Class Summary: These agents may provide an alternative to anthelmintics.

Doxycycline: Doxycycline is a broad-spectrum, synthetically derived, bacteriostatic antibiotic in the tetracycline class. This agent is almost completely absorbed, concentrates in bile, and is excreted in urine and feces as a biologically active metabolite in high concentrations. **Doxycycline inhibits** protein synthesis and, thus, bacterial growth by binding to 30S and possibly 50S ribosomal subunits of susceptible bacteria. It may block dissociation of peptidyl transfer RNA (t-RNA) from ribosomes, causing RNA-dependent protein synthesis to arrest.

INTERPRETATION

Liver Test Interpretation - Approach to the Patient with Liver Disease:

A Guide to Commonly Used Liver Tests

Laboratory assessment of the patient with suspected or clinically obvious liver disease is context dependent. For example, the acutely ill jaundiced patient with a history of prolonged alcohol ingestion requires a different laboratory assessment than the well patient in whom one or more standard liver test results are discovered to be abnormal during routine testing. Additionally, the sequence of liver tests depends heavily on the questions being asked. If it is to determine whether this well person whose brother was recently diagnosed with hemochromatosis also has this genetic disease, then a series of tests will be initiated to detect the possibility of iron overload. If it is to determine whether this spouse has been infected with hepatitis B, then blood tests related to hepatitis B will be required. Thus generic algorithms for the evaluation of liver disease need to be considered skeptically. **This article** is intended to discuss a useful way of thinking about liver tests. It emphasizes limitations of and alternative explanations for isolated abnormalities of common liver test results. It also provides information on the initial screening test to be chosen, their interpretation, and the tests needed to confirm the diagnosis of common liver disorders based on current recommendations. Information in this chapter should be combined with discussions of specific liver diseases in the disease management project. A final caveat relates to terminology. Tests done in clinical laboratories do not measure any functional capacity of the liver. Hence, the commonly used term liver function test is inaccurate, and the term liver tests is used in this article. Guidelines on the interpretation and evaluation of abnormal liver test results have been published. Useful algorithms are presented that parallel the recommendations in this chapter.

Isolated Abnormalities in Liver Test Results

A common clinical scenario is the unanticipated discovery of an abnormal liver test result, obtained when a bundle of tests has been done for other reasons. Most clinical laboratories offer bundled blood tests, which often contain all or most of the following: **Bilirubin**, **Aspartate transaminase** (AST, formerly referred to as serum glutamic-oxaloacetic transaminase, SGOT), **Alanine transaminase** (ALT, formerly called serum glutamic-pyruvic transaminase, SGPT), **Gamma-glutamyl-transpeptidase** (GGTP), **Alkaline phosphatase**, **Lactate dehydrogenase** (LDH). **Of these tests only the GGTP** is liver specific. An isolated elevation of just one of the other test values should raise suspicion that a source other than the liver is the cause (Table 1). When several liver test results are simultaneously out of the normal range, consideration of non-hepatic sources becomes irrelevant.

Table 1: Nonhepatic Sources of Abnormalities for Select Laboratory Tests

Test	Nonhepatic Source
Bilirubin	Red blood cells (e.g., hemolysis, intra-abdominal bleed, hematoma)
AST	Skeletal muscle, cardiac muscle, red blood cells
ALT	Skeletal muscle, cardiac muscle, kidneys
LDH	Heart, red blood cells (e.g., hemolysis)
Alkaline phosphatase	Bone, first trimester placenta, kidneys, intestines

ALT - alanine aminotransaminase; AST - aspartate transaminase; LDH - lactate dehydrogenase.

Additional note should be made of the GGTP and LDH as liver tests. The GGTP level is too sensitive, frequently elevated when no liver disease is apparent. A GGTP test is useful in only two instances: (1) It confers liver specificity to an elevated alkaline phosphatase level; (2) In aminotransferase level elevations with AST/ALT ratio greater than 2, elevation of GGTP further supports alcoholic liver disease. In addition, it can be used to monitor abstinence from alcohol. An isolated elevation of the GGTP level does not need to be further evaluated unless there are additional clinical risk factors for liver disease. The LDH assay is insensitive and nonspecific because LDH is present in tissues throughout the body.

Evaluation of Liver Disease Based on Enzyme Levels

It is customary and useful to categorize liver diseases into three broad categories: Hepatocellular, in which primary injury is to the hepatocytes; cholestatic, in which primary injury is to the bile ducts; and infiltrative, in which the liver is invaded or replaced by non-hepatic substances, such as neoplasm or amyloid. Although there is a great deal of overlap in liver test result abnormalities seen in these three categories, particularly in cholestatic and infiltrative disorders, an attempt to characterize an otherwise undifferentiated clinical case as hepatocellular, cholestatic, or infiltrative often makes subsequent evaluation faster and more efficient. The AST, ALT, and alkaline phosphatase tests are most useful to make the distinction between hepatocellular and cholestatic disease. **The normal range** for aminotransferase levels in most clinical laboratories is much lower than that for the alkaline phosphatase level. Accordingly, when considering levels of elevations, it is necessary to consider them relative to the respective upper limit of normal for each test compared. Consider a patient with an AST level of 120 IU/mL (normal, 40 IU/mL) and an alkaline phosphatase of 130 IU/mL (normal, 120 IU/mL). This represents a hepatocellular pattern of liver injury because the AST level is three times the upper limit of normal, whereas the alkaline phosphatase level is only marginally higher than its upper limit of normal. Serum aminotransferase levels ALT and AST are two of the most useful measures of liver cell injury, although the AST is less liver specific than is ALT level. Elevations of the AST level may also be seen in acute injury to cardiac or skeletal muscle. Lesser degrees of ALT level elevation may occasionally be seen in skeletal muscle injury or even after vigorous exercise. Thus in clinical practice, it is not uncommon to see elevations of AST, ALT or both in common non-hepatic conditions such as myocardial infarction and rhabdomyolysis. Diseases that primarily affect hepatocytes, such as viral hepatitis, will cause disproportionate elevations of the AST and ALT levels compared with the alkaline phosphatase level. The ratio of AST/ALT is of little benefit in sorting out the cause of liver injury except in acute alcoholic hepatitis, in which the ratio is usually greater than 2. **The current upper limit** of serum ALT, though varied among laboratories, is generally around 40 IU/L. However, recent studies have shown that the upper limit threshold of ALT level should be lowered because people who have slightly raised ALT levels that are within the upper limit of normal (35-40 IU/L) are at an increased risk of mortality from liver disease. In addition, it has been suggested that gender-specific thresholds be applied because women have slightly lower normal ALT levels than men. One such study conducted in the U.S. identified an ALT upper limit of 29 IU/L for men and

22 IU/L for women. In asymptomatic patients with minimal elevations of aminotransferases, it is reasonable to repeat the test in a few weeks to confirm elevation. Common causes of mild increases in AST and ALT levels include non-alcoholic fatty liver disease (NAFLD), hepatitis C, alcoholic fatty liver disease, and medication effect (e.g., due to statins). **Serum alkaline phosphatase** comprises a heterogeneous group of enzymes. Hepatic alkaline phosphatase is most densely represented near the canalicular membrane of the hepatocyte. Accordingly, diseases that predominately affect hepatocyte secretion (e.g., obstructive diseases) will be accompanied by elevations of alkaline phosphatase levels. Bile-duct obstruction, primary sclerosing cholangitis, and primary biliary cirrhosis (PBC) are some examples of diseases in which elevated alkaline phosphatase levels are often predominant over transaminase level elevations (Table 2).

Table 2: Category of Liver Disease by Predominant Serum Enzyme Abnormality

Test	Liver Disease Category		
	Hepatocellular	Cholestatic	Infiltrative
AST,ALT higher than alkaline phosphatase level	Typical	—	—
Alkaline phosphatase higher than AST,ALT levels	—	Typical	—
Elevation of alkaline phosphatase with near-normal AST,ALT levels	—	Typical	Typical

ALT - alanine aminotransaminase; AST - aspartate transaminase.

Infiltrative liver diseases most often result in a pattern of liver test result abnormalities similar to those of cholestatic liver disease. Differentiation often requires liver imaging studies. Liver imaging by ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) most often identify infiltration of the liver by mass lesions such as tumors. Imaging by cholangiography—endoscopic retrograde cholangiography, transhepatic cholangiography, or magnetic resonance cholangiography—identifies many bile duct lesions that cause cholestatic liver disease. Liver biopsy is often needed to confirm certain infiltrative disorders (e.g., amyloidosis) and microscopic biliary disorders such as PBC.

Bilirubin Level Elevations

Bilirubin is produced by the normal breakdown of pigment-containing proteins, especially hemoglobin from senescent red blood cells and myoglobin from muscle breakdown. Bilirubin released from such sources, tightly albumin bound, is delivered to the liver, where it is efficiently extracted and conjugated by hepatic glucuronidation and sulfation. Conjugated bilirubin is rapidly excreted into bile and removed from the body through the gut. Therefore, the amount of conjugated bilirubin present in serum in healthy subjects is trivial (<10% of measured total bilirubin). An elevated level of conjugated serum bilirubin implies liver disease. Also, it is important to note that only conjugated bilirubin appears in urine (unconjugated bilirubin is albumin bound and water insoluble). The presence of bilirubin in urine almost always implies liver disease. **Many laboratories** report only the total bilirubin level, the sum of the conjugated and unconjugated portions. It is sometimes useful to determine the fraction of total serum bilirubin that is unconjugated versus

that which is conjugated, usually referred to as fractionation of bilirubin. This is most useful when all the standard liver test results are normal, except the total bilirubin. To make matters more confusing, the conjugated bilirubin is sometimes referred to as the direct-reacting bilirubin and the unconjugated as the indirect-reacting bilirubin (Table 3).

Table 3: Bilirubin Fractions Present in Blood and Urine

Fraction	In Serum As	Measured As	Present in Urine
Unconjugated	Albumin-bound	Indirect-reacting bilirubin	Never
Conjugated	Unbound	Direct-reacting bilirubin	Yes, when serum bilirubin level is elevated

Normally, 90% or more of measured serum bilirubin is unconjugated (indirect-reacting). When the total bilirubin level is elevated and fractionation shows that the major portion (90%) is unconjugated, liver disease is never the explanation. Instead, the clinician should suspect one of two explanations: Gilbert disease or hemolysis. If the patient is young and healthy, an inherited decrease in the inability to conjugate bilirubin is likely and is referred to as Gilbert syndrome. It is seen in about 5% of the general population and causes only mild hyperbilirubinemia without symptoms. It is not associated with liver disease. Interestingly, fasting and intercurrent illnesses such as influenza often make the level of unconjugated bilirubin even higher in those with Gilbert syndrome. This syndrome is easily diagnosed when all standard liver-test results are normal and 90% or more of the total bilirubin is unconjugated. There is no need for an imaging study or liver biopsy in cases of suspected Gilbert syndrome. **Elevations of the unconjugated** bilirubin level when the conjugated bilirubin level remains normal may also indicate an increased load of bilirubin caused by hemolysis. Anemia and an elevated reticulocyte count are usually present in such cases (Table 4).

Table 4: Common Causes of Isolated Bilirubin Elevation

Cause	Direct-Reacting Bilirubin	Indirect-Reacting Bilirubin	Associated Features
Liver disease (many types)	Elevated	Elevated or normal	Liver enzyme levels often elevated
Hemolysis	Normal	Elevation represents more than 90% of total bilirubin	Anemia usual; increased reticulocyte count; normal liver enzyme levels (although LDH may be elevated)
Gilbert's syndrome	Normal	Elevation represents more than 90% of total bilirubin (common)	No abnormal liver tests; no anemia; onset in late adolescence; fasting makes bilirubin rise

LDH - lactate dehydrogenase.

Many clinicians mistakenly interpret elevations of direct-reacting bilirubin to indicate that cholestatic (obstructive) liver disease is present. It is apparent from Table 2 that the serum bilirubin level plays no useful

role in categorizing a case as hepatocellular, cholestatic, or infiltrative. The bilirubin level may be normal or elevated in each type of disorder. Viral hepatitis A, a prototypic hepatocellular disease, may frequently be associated with bilirubin levels that are high, whereas PBC, a prototypic cholestatic disorder, is associated with a normal serum bilirubin level except in later stage disease. Serum bilirubin levels should be disregarded when trying to decide whether the liver-test pattern is more suggestive of hepatocellular or cholestatic disease.

Determination of Specific Liver Disorders

Acute Alcoholic Hepatitis: Acute alcoholic hepatitis may be mild or life threatening. The pattern of liver test abnormality is hepatocellular. The AST is typically in the 100 to 200 IU/L range, even in severe disease, and the ALT level may be normal, even in severe cases. The AST level is higher than the ALT level, and the ratio is greater than 2:1 in 70% of patients. A ratio greater than 3 is strongly indicative of alcoholic hepatitis. An important corollary is that an AST greater than 500 IU/L or an ALT greater than 200 IU/L is not likely to be explained by acute alcoholic hepatitis - even in an alcoholic patient and should suggest another etiology. **The degrees of bilirubin level** increase and prothrombin time elevation are better indicators of severity of disease. In alcoholic hepatitis, the Maddrey discriminant function (MDF), a disease-specific prognostic score which indicates the severity of liver injury, has been developed. The formula to calculate the score is as follows: **MDF = 4.6 (patient's prothrombin time – control prothrombin time) + total bilirubin (mg/dL)**. Patients who have a score of 32 or greater have an increased risk of death, with a 1-month mortality rate of 30% to 50%.

Viral Hepatitis: Viral hepatitis most often produces a hepatocellular pattern of injury (AST and ALT level elevations predominate). Patients who have no symptoms and in whom aminotransferase levels are normal may still be infected. In addition, a great deal of confusion is caused by abnormal viral markers, many of which do not indicate active infection but rather immunity. These concepts are more fully developed elsewhere in the Cleveland Clinic Disease Management Project.

Hepatitis A: Hepatitis A virus (HAV) infection is an acute, self-limited disease in most cases, although it may rarely be fatal. Diagnosis is made through the use of antibody tests (anti-HAV). Positive anti-HAV IgM antibody is diagnostic of acute hepatitis A infection and has a very good sensitivity and specificity. The IgM antibodies are usually positive at the time of the onset of symptoms and they remain positive for about 3 to 6 months after, and in some cases as long as 1 year. Anti-HAV immunoglobulin G (IgG) antibodies develop later than anti-HAV immunoglobulin M (IgM) but they persist for many years and offer immunity. Anti-HAV IgG antibodies are also seen following vaccination.

The presence of anti-HAV IgM irrespective of the presence of anti-HAV IgG suggests acute infection. The presence of anti-HAV IgG in the absence of IgM suggests previous infection or post-vaccination antibodies. **When an acute hepatitis A** panel is ordered, the test result that is obtained from the laboratory must be interpreted with caution before making the diagnosis. This is because the standard screening tests performed by most laboratories measure the level of total anti-HAV antibodies. Total anti-HAV antibody tests will be positive in the presence of either anti-HAV IgG or IgM, as the reagents used in this test will react to both anti-HAV IgG and IgM. Therefore, a positive total anti-HAV antibody test alone does not provide the diagnosis of acute hepatitis A. Selective testing of serum IgM anti-HAV is required to establish such a diagnosis (Table 5).

Table 5: Hepatitis A Antibody Testing In Different Clinical States

State	Total Anti-HAV (IgG, IgM)	Anti-HAV IgM
Acute hepatitis A	Positive	Positive
Resolved hepatitis A	Positive	Negative
Immunization	Positive	Negative

HAV - hepatitis A virus; IgG - immunoglobulin G; IgM - immunoglobulin M.

Hepatitis B: Like hepatitis A, hepatitis B in adults produces hepatocellular enzyme level elevations (AST and ALT predominate). In adults who acquire hepatitis B, the infection almost always clears, but antibodies persist. In a few, the disease does not resolve but becomes chronic. These patients retain serum markers of viral infection. Many blood tests are available for hepatitis B antigenic determinants and their antibodies. It is best to separate testing appropriate for the acute hepatitis situation from testing for chronic liver disease caused by hepatitis B. Only a few tests need to be considered by the generalist to determine the status of a patient with possible hepatitis B. A full discussion of hepatitis B can be seen in the Disease Management Project chapter on Hepatitis B. **Acute Hepatitis B:** Hepatitis B surface antigen (HBsAg) emerges within 2 weeks of exposure but can often be delayed for weeks or months. This antigen is present in the blood for a variable period, usually encompassing the time during which the patient is clinically ill and most likely to seek medical attention. In patients with mild symptoms whose testing may be delayed, the HBsAg level may have already declined. In this case, a second chance to make the diagnosis comes from detection of the IgM antibody directed against the hepatitis B core (HBc) antigen, anti HBc-IgM (Table 6). Similar to the testing for acute hepatitis A, selective testing of serum IgM anti-HBc is required to establish a diagnosis of acute hepatitis B in patients whose HBsAg levels have already declined. The total anti-HBc antibody test will be positive in the presence of either anti-HBc IgG or IgM.

Table 6. Common Hepatitis B Testing Results

Test	Result	Interpretation
HBsAg	Negative	Susceptible
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune due to natural infection
Anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronically infected
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Interpretation unclear 4 possibilities: 1. Resolved infection (most common) 2. False positive 3. "Low level" chronic infection 4. Resolving acute infection
Anti-HBc	Positive	
Anti-HBs	Negative	

From: *Interpretation of hepatitis B serologic test results*. Centers for Disease Control and Prevention website. www.cdc.gov. Accessed June 27, 2013.

In acute hepatitis B, medical attention is not sought early. In such cases the HBsAg may have already disappeared. The anti-HBs will not yet have emerged. Thus the sole viral marker may be anti-HBc. This same serologic pattern may be seen years after infection when the titer of anti-HBs is low. Sorting out the difference between late resolved hepatitis B and the period in acute hepatitis B described above can be achieved by testing for anti-HBc IgM which will be positive during this so-called "window period" of acute hepatitis B. **Chronic Hepatitis B:** Chronic hepatitis B is characterized by persistence of HBsAg for a period longer than 6 months with positive anti-HBc (IgG), and negative anti-HBs. An additional antigen-antibody system plays a role in patients with chronic hepatitis B and requires mention: the hepatitis B e antigen (HBeAg) and its antibody (anti-HBe). HBeAg positivity in chronic hepatitis B usually indicates active viral replication and significant liver injury. In time, HBeAg may be lost, replaced by its antibody, anti-HBe. This transformation is often associated with lower level infection (less viral replication) or HBV DNA, lower AST and ALT values, and less (or no) hepatic inflammation. **Reactivation Hepatitis B:** Hepatitis B reactivation is a sudden increase in hepatitis B virus (HBV) replication or the reappearance of active inflammatory disease of the liver in a patient with previously documented resolved HBV, or with the inactive HBsAg carrier state. Reactivation is usually triggered by immunosuppression in the host, which can occur following the use of chemotherapeutic agents for malignancy and following therapy for autoimmune diseases or organ transplantation. **Reactivation** can also occur spontaneously. The extent of clinical manifestation from reactivation HBV can vary from a transient, clinically silent disease to severe or acute liver failure. A chronic infectious state can also be seen following HBV reactivation. Diagnosis of HBV reactivation depends on the HBV disease state before activation. In a patient with resolved infection (negative HBsAg and positive anti-HBs), reactivation is indicated by the decline in anti-HBs and the reappearance of HBsAg. In patients with quiescent HBV with positive HBsAg, reactivation is diagnosed by a rise in the serum HBV DNA (>1 log₁₀ IU/mL) or a rise in the serum ALT levels (>3 times baseline). Reappearance of HBeAg in a patient with previous negative HBeAg also indicates HBV reactivation. **Role of HBV DNA Assays, HBV Genotypes and Liver Biopsy in Chronic Hepatitis B:** HBV DNA level plays several important roles in chronic hepatitis B. It is the most important factor for predicting the progression to cirrhosis, helps to determine the need for treatment in HBeAg negative patients, and also plays a crucial role in estimating the response to treatment. Up to 8 HBV genotypes, labeled from A to H, have been identified. Recent studies have shown that some genotypes are associated with early HBeAg seroconversion, less progression to cirrhosis and hepatocellular carcinoma, and may also predict the response to treatment with interferon. These concepts and exceptions are discussed more fully in the Hepatitis B chapter. **Resolved Hepatitis B and Immunization Status:** As indicated in Table 6, an individual with resolved hepatitis B infection almost always has anti-HBc and anti-HBs. An individual successfully immunized against hepatitis B expresses only anti-HBs. Confusion may occasionally arise in the interpretation of hepatitis B tests in a patient who has recovered from hepatitis B many years ago and who has a low or absent level of

measurable anti-HBc.

Hepatitis C: Because hepatitis C infection usually produces no symptoms, or only mild, nonspecific, flu-like symptoms, it is infrequently diagnosed in the acute phase. The virus clears spontaneously in about 15% of infected patients. Although generally helpful for the diagnosis of chronic infection, antibody tests are often not useful for diagnosis of acute hepatitis C virus (HCV) infection because the emergence of the antibody is delayed for several months after infection. To test for possible acute HCV infection, measurement of HCV RNA should be performed (Table 7). See the Disease Management Project chapter on Hepatitis C for further details.

Table 7: Hepatitis C Testing

Test	Source	When To Order
Anti-HCV EIA	Patient immune system	Suspect HCV
HCV RNA PCR	HCV virus	Confirm current infection - If anti-HCV positive Or if acute HCV suspected Or in immunocompromised HCV suspect
HCV genotype	HCV virus	If HCV RNA positive and treatment contemplated
IL28B	Patient DNA	If genotype I HCV and treatment contemplated

HCV - hepatitis C virus; EIA - enzyme immunoassay; PCR - polymerase chain reaction.

To test for chronic HCV infection, immunologic response to infection (antibodies) and viral assays are used. The most commonly used anti-HCV antibody test is an enzyme immunoassay with a specificity of greater than 99%. An individual with risk factors, elevated liver tests, and a positive anti-HCV has an overwhelming chance of HCV infection. **False-positive anti-HCV antibodies** are occasionally encountered. Confirmation of chronic hepatitis C infection is obtained by the direct measurement of viral products in serum (HCV RNA). HCV RNA in serum definitively establishes the presence of HCV infection and is recommended in all patients with a positive anti-HCV test. Some clinicians have questioned whether the initial screening test for HCV should be an HCV RNA test or an antibody test. Currently, however, because of cost considerations, the initial test for HCV remains an anti-HCV antibody test.

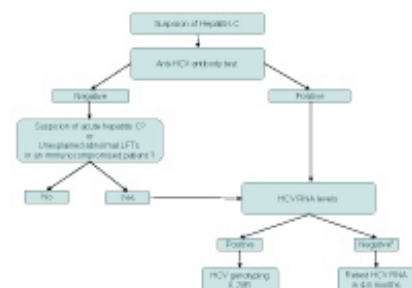


Figure 1

False-negative anti-HCV tests can occur in two clinical contexts: in a patient with a recent infection, in an immunocompromised individual, or

an individual receiving hemodialysis. HCV RNA testing is recommended in patients with negative anti-HCV antibody tests but who have liver disease of unknown etiology and are also immunocompromised. In addition, all potential organ donors should be tested for HCV RNA. Figure 1 gives a simplified diagnostic algorithm for hepatitis C. **Once the presence of HCV** is established, the genotype should be determined. There are 6 major HCV genotypes (1-6). Genotyping continues to gain importance for treatment determinations. This is discussed more fully elsewhere in the Hepatitis C chapter. **Role of IL28B Genotype in Hepatitis C:** Current guidelines do not routinely recommend interleukin 28B (IL28B) genotype testing. Nevertheless, it is commonly ordered to obtain information about the probability of treatment response and the duration of treatment. We recommend one-time testing of IL28B in every patient who is infected with genotype-1 hepatitis C who is also a candidate for treatment. **IL28 is a cytokine** that plays an important role in the defense against viral infection. It belongs to the IL10 interferon family and, in response to a virus, helps to upregulate the inflammatory potential and the innate immunity. IL28 has two isoforms, namely IL28A and IL28B. The gene for IL28B resides on chromosome 19. Recent studies have identified a single nucleotide pleomorphism near the IL28B gene that can predict the response to treatment in hepatitis C. Three genotypes exist as a result of the nucleotide pleomorphism. They are the CC, CT, and TT genotypes. Among patients who spontaneously clear HCV virus, the CC genotype has been shown to be present more than twice as frequently than the other genotypes. In addition, patients with the CC genotype also show a much better response to treatment with anti-viral therapy as compared with the CT or TT genotype. Those with TT have the least response to treatment. This pattern has been observed among all ethnic groups.

Iron and Copper Overload Diseases: Diseases characterized by iron overload and copper overload are discussed in detail in the *Disease Management Project* (Inherited Metabolic Liver Diseases: Hemochromatosis, Wilson Disease). A practice guideline has been published. **Iron Tests:** Excess iron may accumulate in the liver and other organs for a variety of reasons. Some individuals have a genetic disorder while others may accumulate too much iron for other reasons. Among the genetic iron-overload conditions, the most common in individuals of Northern European ancestry is related to an autosomal recessive disorder, hereditary hemochromatosis. Before ordering tests it is important to be clear about what question is being asked. Most of the time the question is: *Does my patient have iron overload?* **This question** should be entertained in the following situations: **Any adult with liver disease**, especially men and post-menopausal women. **Patients with symptoms** suggestive of or having a family history of HH. **The initial evaluation** for iron overload includes measurement of serum ferritin, iron, iron-binding capacity, and transferrin saturation levels. Transferrin saturation less than 45%, in addition to normal serum ferritin level usually rules out iron overload (negative predictive value of 97%), and no further testing is necessary. Transferrin saturation greater than 45% and/or a serum ferritin above normal level warrants further investigation. However, these thresholds are low, and most patients who exceed these limits will not prove to have iron overload as explained below. **Limitations of Serum-Based Tests of Iron Overload:** Because both iron and ferritin are stored in liver cells, any condition that results in hepatocyte injury and release of intracellular contents into the blood will falsely raise iron, transferrin saturation, and ferritin levels. Therefore, in

acute hepatic injury these tests will falsely suggest iron overload. Acute inflammation outside the liver may also falsely elevate the results of serum-based iron tests. Tests of serum ferritin levels, iron, iron-binding capacity and percentage saturation determined in the setting of markedly elevated aminotransferase levels (AST and ALT), such as those seen in acute viral hepatitis or massive hepatic necrosis, will be identical to those seen in hemochromatosis. Iron studies cannot be interpreted in the face of major elevations of transaminase levels. **Normal serum iron** studies do not preclude future iron overload in the genetically susceptible individual. In a young patient with this condition who has not yet had enough time to accumulate iron (especially the premenopausal woman), screening tests for iron overload may be normal, even though the individual is at risk for the subsequent development of iron overload. **When iron overload** is found or suspected, the question may become: *Does my patient have hereditary hemochromatosis?* This question should be entertained in: **Any patient** with elevated iron/total iron-binding capacity ferritin values. **Those with a family history** of liver disease or of hemochromatosis. **It has been known for years** that many cases of hemochromatosis are inherited as an autosomal recessive trait. In many cases, a defective gene called the *HFE* gene is implicated. The presence of this inherited gene results in the production of a protein in which a tyrosine amino acid rather than a cysteine amino acid is present at position 282 of the HFE protein. A second missense gene that results in an aspartic acid (instead of histidine) at position 63 of the same protein may increase iron absorption in some patients. The abnormalities are called *C282Y* and *H63D* mutations respectively. Most individuals of Northern European descent with hereditary hemochromatosis usually have two abnormal genes (homozygosity). Most often, two *C282Y* genes are present, but occasionally a compound heterozygote (*C282Y-H63D*) will also have excess iron. Homozygosity for *H63D* does not usually result in excess iron absorption (Table 8).

Table 8: Guidance for the Likelihood of Iron Accumulation with Various HFE Patterns

HFE Finding	Likelihood of Iron Overload
Wild type/wild type (no abnormal genes)	Nil
Wild type/C282Y	Nil
C282Y/C282Y (C282Y homozygote)	High
Wild type/H63D	Nil
H63D/H63D (H63D homozygote)	Low
C282Y/H63D (compound heterozygote)	Moderate

Confirming a Diagnosis of Hemochromatosis and the Role of Liver Biopsy: Homozygosity for *C282Y* and compound heterozygosity for *C282Y/H63D* are diagnostic of HH and a liver biopsy with hepatic iron index (HII) estimation, which was previously the criteria for diagnosis, is no longer needed to confirm the diagnosis of HH in these patients. In addition, HFE gene mutation testing is indicated in all first-degree relatives of patients with hemochromatosis. However, it must be remembered that many individuals have iron overload with normal HFE protein. Pre-menopausal women with *C282Y* homozygosity most often have no iron accumulation. Finally, there is incomplete penetrance of iron overload in many *C282Y* homozygotes. In other words, expression of disease may not occur despite having the genetic susceptibility. **HFE gene mutation analysis** does not establish either the presence or the

degree of liver fibrosis or cirrhosis. Studies have shown that patients with serum ferritin less than 1,000 ng/mL are less likely to have cirrhosis in HH. A liver biopsy is thus indicated in patients with elevated ferritin greater than 1,000 ng/mL or having abnormal liver enzymes. This serves two purposes, determining fibrosis and providing an assessment of iron stores. Because there is an age-dependent increase in hepatic iron in normal individuals, it is necessary to create an index that takes this into account. HII is calculated as follows: $HII = \text{hepatic iron concentration (mcg/g dry weight)} \div \text{patient age (years)}$. HII less than 1.9 is normal; values greater than 1.9 are seen in hemochromatosis. A caveat to this would be in cirrhotic livers, which have the tendency to rapidly accumulate iron in liver disease of other etiologies and cause elevation of HII to a level greater than 1.9. Newer techniques, such as the HIC estimation by proton transverse relaxation time determined by MRI, could be an alternative to liver biopsy, and studies have shown good correlation between the tests. It must be remembered that bone marrow iron stores are not adequate to assess total body iron stores. Cases of hemochromatosis with absent stainable bone marrow iron have been reported.

Copper Tests: Although copper may accumulate to moderate excess in the liver in any chronic cholestatic liver condition, it does not appear to be injurious in these conditions. Wilson disease is the main disease in which pathologic copper deposition results in serious liver injury, cirrhosis, and death. In Wilson disease, copper also accumulates in the basal ganglia of the brain, where it produces a wide gamut of neurologic abnormalities. Patients may present with liver disease, brain disease, or both. This disorder is discussed in more detail in the *Disease Management Project* (Inherited Metabolic Liver Diseases: Wilson Disease). **Wilson disease is rare.** Untreated, it is usually fatal before the patient is aged 40 years. Therefore, it is most appropriate to consider this potential cause in a child or young adult with otherwise unexplained liver disease. However, a diagnosis of Wilson disease should not be excluded based on age alone. Laboratory diagnosis is most often based on the finding of a low ceruloplasmin level. Serum ceruloplasmin level of less than 5 mg/dL strongly suggests Wilson disease while any subnormal level warrants further evaluation. Most acute and chronic liver diseases cause the ceruloplasmin level to elevate. There are a few exceptions to this. A patient with acute fulminant liver failure of any sort may no longer have a liver capable of ceruloplasmin synthesis, so that patient may have a low serum level. Similarly, the patient with terminal end-stage liver disease may have a falling ceruloplasmin level. Finally, a few individuals have congenital hypoceruloplasminemia without copper accumulation and are healthy. At the same time, it must also be remembered that a normal serum ceruloplasmin level does not exclude Wilson disease. **In patients** in whom Wilson disease is suspected, in addition to serum ceruloplasmin, 24-hour urinary copper levels and slit lamp examination to look for Kayser-Fleischer (KF) rings should be obtained. A serum ceruloplasmin level less than 20 mg/dL, 24-hour urine copper greater than 40 mcg, and the presence of KF rings confirms the diagnosis of Wilson disease. No further testing such as a liver biopsy is needed in this setting. **Copper is present** in the serum in two forms: copper that is bound to ceruloplasmin, and free copper or the non-ceruloplasmin bound copper. The *total serum copper* level is the sum of the levels of these two forms of copper and is usually low in those with Wilson disease. This is partly explained by the decrease in the ceruloplasmin bound copper level that results from a reduction in the ceruloplasmin level in Wilson

disease. However, the serum free copper level is typically elevated to 25 mcg/dL in patients with Wilson disease and may be approximated as follows: **Serum free copper level = Total serum copper level (ug/dl) – (3 x serum ceruloplasmin level (mg/dL))**. A practical algorithm on the diagnostic tests for Wilson disease is shown in Table 9.

Table 9: Diagnostic Tests for Wilson Disease

Level 1 Tests	Level 2 Tests	Level 3 Tests
Low serum ceruloplasmin level (<20 mg/dL)	Liver histopathology and stainable copper	Ultrastructural study of hepatocytes
Kayser-Fleischer rings	Liver copper concentration (>250 µg/g dry weight)	Mutational gene analysis for Wilson disease
Raised serum-free copper level (non-ceruloplasmin-bound) (>25 µg/dL)	Incorporation of radiocopper into ceruloplasmin	24-hr urinary copper (>100 µg/24 hr)

Autoimmune Liver Diseases: The two most common forms of autoimmune liver disease are autoimmune chronic hepatitis and PBC. Ninety percent of those with each disorder are women. Autoimmune hepatitis (AIH) is characterized by very high serum aminotransferase (ALT and AST) levels, whereas PBC is a cholestatic disorder with predominant elevations of the alkaline phosphatase level. Each is associated with autoantibodies in the serum. The treatment for each is different, so accurate diagnosis is essential. Table 10 contrasts the laboratory findings of these two autoimmune liver disorders.

Table 10: Contrasting Features of Two Autoimmune Liver Diseases

Feature	Autoimmune Chronic Hepatitis	Primary Biliary Cirrhosis
AST, ALT	7-10 times upper limit of normal (ULN)	1-3 times ULN
Alkaline phosphatase	1-3 times ULN	2-10 times ULN
Anti-smooth muscle antibody positive	90% (usually high titer)	10%-20% (usually low titer)
Anti-mitochondrial antibody positive	10%-20% (usually low titer)	90%-100% (usually high titer)
Liver-kidney microsomal	Positive in some cases antibody positive in which smooth muscle antibody is negative (rare in North America)	Negative

ALT - alanine aminotransaminase; AST - aspartate transaminase.

Interpretation of autoimmune markers in a patient with liver disease is highly context-dependent. Autoantibodies are common in low titer in a number of acute and chronic liver conditions, such as viral hepatitis. Therefore, the finding of autoantibodies in low titer is not sufficient evidence with which to make a diagnosis of autoimmune chronic hepatitis or PBC. At the same time, low titers do not exclude the

diagnosis. **Autoimmune Hepatitis:** AIH should be rapidly recognized by its propensity to occur in women (90%) and to be associated with high transaminase levels (200 IU/mL or higher). In this disease, elevations of the gamma globulins (especially IgG) are pronounced. A myriad of autoimmune markers may be positive in autoimmune chronic hepatitis, but only a few serological markers have to be assessed: anti-smooth muscle antibody, antinuclear antibody, liver-kidney microsomal antibody and anti-liver cytosol type 1 antibody. High titers of antibodies are suggestive of but on their own they do not establish a diagnosis of AIH. **The diagnosis of AIH** can be difficult at times and various factors need to be taken into account. Clinical criteria are usually sufficient to make a diagnosis of or to exclude AIH. Scoring systems have been developed to assist in establishing a diagnosis of AIH. Exclusion of other liver diseases should be undertaken as part of the work up. A liver biopsy at presentation is recommended to establish the diagnosis of AIH and to make treatment decisions. **Primary Biliary Cirrhosis:** PBC is an autoimmune liver disease that characteristically involves the intrahepatic small bile ducts. In this condition, serum-based liver tests reveal a predominant elevation of the alkaline phosphatase level. It is associated with the elevation of an autoantibody in high titer known as the anti-mitochondrial antibody (AMA). It has a high sensitivity and a very high specificity. It is reported to be seen in less than 1% of normal people. However AMA has been shown to be present in increased frequency in relatives of patients with PBC. One study showed that the frequency of positive AMA among first-degree relatives of patients with PBC was 13% as compared with 1% in controls. Though positive AMA antibodies may suggest susceptibility to development of PBC, they, on their own even in high titers, do not establish a diagnosis of PBC. Ultrasound or other imaging techniques are necessary in all patients to exclude bile duct obstruction as the cause of cholestasis. Presence of predominant alkaline phosphatase elevation and positive AMA antibody establishes the diagnosis of PBC. Liver biopsy is indicated if the AMA is negative or is in low titers and if associated AIH or NAFLD is suspected. Occasionally, a patient may have features of both autoimmune chronic hepatitis and PBC known as AIH/PBC overlap syndrome. PBC is discussed more in detail elsewhere in the *Disease Management Project* ("Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, and Other Cholestatic Liver Diseases"). **Non-Alcoholic Fatty Liver Disease:** NAFLD is the most common cause of mildly elevated liver enzymes. Please see the chapter on Non-Alcoholic Fatty Liver Disease in *Disease Management Project*. NAFLD is defined as the accumulation of fat in the liver in the absence of conditions that cause secondary fat accumulation such as alcoholic hepatitis, medications, metabolic disorders or viral hepatitis. Two types of NAFLD have been described, non-alcoholic fatty liver and non-alcoholic steatohepatitis. The latter has evidence of hepatocellular injury in addition to fat accumulation. Patients with NAFLD are non-alcoholic, usually obese, and have a high BMI. **Liver tests** are unreliable guides to the presence or absence of fatty liver disease. When elevated, enzymes show hepatocellular pattern, often with an AST/ALT ratio of less than 1. However, they can be normal. Therefore, liver tests are not useful to make a diagnosis of NAFLD. A history of significant alcohol intake can reliably distinguish between alcoholic fatty liver disease and NAFLD.

Imaging is performed to demonstrate the presence of fat in the liver. Liver biopsy is indicated if competing etiologies cannot be ruled out, if a co-existing liver disease is suspected, and for patients at risk of developing cirrhosis. **A scoring system** has been developed to identify patients with liver fibrosis in NAFLD. This scoring system comprises of six variables namely: age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio. The system has been shown to distinguish patients with NAFLD and with or without advanced fibrosis accurately. Certain biomarkers such as serum CK18 have been shown to predict the presence of hepatocellular injury in NAFLD, but further studies are needed to establish their utility. **Noninvasive Tests for Liver Fibrosis and Cirrhosis:** Liver biopsy is the gold standard for determining the stage of liver fibrosis and cirrhosis. However, it is invasive and can cause significant complications and sampling error, the latter due to the non-uniform distribution of fibrosis in the liver. In recent years, a number of noninvasive tests have been developed and are being studied to assess liver fibrosis and cirrhosis. Among these, the most widely studied and promising noninvasive tests are hepatic elastography and the serologic markers of fibrosis. Serologic markers can be further divided into direct markers and indirect markers. Direct serologic markers are those that are associated with the deposition of matrix and include procollagen type III amino-terminal peptide (P3NP), type I and IV collagens and matrix metalloproteinases among others. P3NP is found to be the most promising among these markers. It is elevated in both acute and chronic liver disease. Studies have also shown that the serum levels of P3NP reflect the degree of fibrosis in chronic liver disease. However, the test is currently not readily available in commercial laboratories and has not yet been validated for use. **Hepatic elastography** is a noninvasive imaging technique used to determine the degree of fibrosis of the liver. Most frequently, ultrasound-based elastography is performed. It uses a device called Fibroscan which transmits low-frequency waves into the liver. The waves' velocities are then recorded and are shown to correlate with the liver stiffness. It can be performed either by an ultrasound or MRI. Studies have shown that ultrasound elastography has excellent diagnostic accuracy to diagnosing cirrhosis but does not perform as well to assess fibrosis. Magnetic resonance elastography has been shown to be the most promising noninvasive test as studies have shown that it can assess both the degree of fibrosis in addition to diagnosing cirrhosis. However, its use may be limited by its high cost. In addition, these tests are not yet FDA-approved to be used in the United States. Therefore, liver biopsy still remains the most important tool in the assessment of liver fibrosis and cirrhosis, though the need for it may be significantly decreased in the future with the further development and validation of noninvasive tests.

Conclusion

Laboratory assessment of the patient with suspected or clinically obvious liver disease is context dependent and has to be individualized. It is useful to categorize liver diseases into three broad categories: hepatocellular, cholestatic, and infiltrative. Once the liver disease has been categorized, following appropriate diagnostic algorithms driven by a good history and physical examination are the easiest and the most reliable ways to obtain the correct diagnosis.

BOUQUET

In Lighter Vein

Hymn Titles By Occupation

Dentist's Hymn.....Crown Him with Many Crowns
 Weatherman's Hymn...There Shall Be Showers of Blessings
 Contractor's Hymn.....The Church's One Foundation
 The Tailor's Hymn.....Holy, Holy, Holy
 The Golfer's Hymn.....There's a Green Hill Far Away
 The Politician's Hymn.....Standing on the Promises
 Optometrist's Hymn.....Open My Eyes That I Might See
 The IRS Agent's Hymn.....I Surrender All
 The Gossiper's Hymn.....Pass It On
 The Electrician's Hymn.....Send The Light
 The Shopper's Hymn.....Sweet By and By
 The Realtor's Hymn.....I've Got a Mansion
 The Massage Therapists Hymn.....He Touched Me
 The Doctor's Hymn.....The Great Physician

AND for those who speed on the highway – a few hymns:

45mph..... God Will Take Care of You
 65mph..... Nearer My God To Thee
 85mph..... This World Is Not My Home
 95mph..... Lord, I'm Coming Home
 100mph..... Precious Memories

A University student was in school and now wrote this letter home.

Dear Daddy,

How are you sir?

School is hard and if you don't send money suicide is contemplated.

The reply from the father was:

Dear Son,

I hope every thing is OK. Condition at home is more critical
 Suicide is approved.

A man who says marriage is a 50-50 proposition doesn't understand two things: 1 – Women, 2 – Fractions.

BUMPER STICKER PHILOSOPHY – MARRIAGE

- Marriage is the triumph of imagination over intelligence. Second marriage is the triumph of hope over experience.
- If you want your spouse to listen and pay strict attention to every word you say, talk in your sleep.
- One good turn gets most of the blankets.
- Marriage: A woman marries a man expecting he will change, but he doesn't. A man marries a woman expecting that she won't change and she does.

Wisdom Whispers

Why Invest in Laughter

- It is impossible to worry while you're laughing.
- Humor cuts stress levels in half.
- Laughing helps you to stay happy and healthy and helps you return to good health when ill.
- Laughter increases, by 20%, the activity of killer cells within the body which serve to destroy viruses and tumor cells.
- Train yourself to look for the comedy in your chaos.
- A sense of humor is the number one survival skill.
- George Bernard Shaw once said, "When you find something funny search it for hidden truth."
- "The art of medicine consists of amusing the patient while nature cures the disease." Voltaire
- Humor helps us cope, conquer, and carry on.
- A good laugh is not only the result of humor, it is often also the cause.
- The body heals with play, the mind heals with laughter and the spirit heals with joy.
- The best exercise is jumping for joy.
- "Joy is the serious business of heaven." C.S. Lewis.
- We begin to solve our problems when we begin to see the humor in them.
- "Time spent laughing is time spent with the gods." Japanese proverb.
- When we feel like laughing the least, we need it most.
- If it feels good to laugh, then laugh to feel good.
- A sense of humor is not inherited, it is learned.

Brain Teasers

1. What is the pH for measuring the alkaline phosphatase activity
 A. 10
 B. 5
 C. 15
 D. 8
2. What is the pH for measuring the acid phosphatase activity
 A. 10
 B. 5
 C. 15
 D. 8
3. Increased BSP retention is not seen in
 A. Gilbert's disease
 B. Viral hepatitis
 C. Toxic hepatitis
 D. Dubin Johnson syndrome
4. Prothrombin and albumin concentrations evaluate which liver activity
 A. Excretory
 B. Synthetic
 C. Enzymatic
 D. None of the above
5. Bodansky, King-Armstrong, Bessey-Lowery-Brock are all units of which of the following enzyme/s?
 A. ALP
 B. AST
 C. ALT
 D. HBDH
6. Which of the following enzymes is not related to liver disorders
 A. LAP, Leucine Aminopeptidase
 B. GGTP Gamma-Glutamyl
 C. 5' nucleotidase
 D. CK-MB
 Transpeptidase

ANSWERS: 1.A, 2.B, 3.A, 4.B, 5.A, 6.D

TROUBLESHOOTING

Stool Analysis

A stool analysis is a series of tests done on a stool (feces) sample to help diagnose certain conditions affecting the digestive tract. These conditions can include infection (such as from parasites, viruses, or bacteria), poor nutrient absorption, or cancer.

For a stool analysis, a stool sample is collected in a clean container and then sent to the laboratory. Laboratory analysis includes microscopic examination, chemical tests, and microbiologic tests. The stool will be checked for color, consistency, amount, shape, odor, and the presence of mucus. The stool may be examined for hidden (occult) blood, fat, meat fibers, bile, white blood cells, and sugars called reducing substances. The pH of the stool also may be measured. A stool culture is done to find out if bacteria may be causing an infection.

Why It Is Done

Stool analysis is done to:

- Help identify diseases of the digestive tract, liver, and pancreas. Certain enzymes (such as trypsin or elastase) may be evaluated in the stool to help determine how well the pancreas is functioning.
- Help find the cause of symptoms affecting the digestive tract, including prolonged diarrhea, bloody diarrhea, an increased amount of gas, nausea, vomiting, loss of appetite, bloating, abdominal pain and cramping, and fever.
- Screen for colon cancer by checking for hidden (occult) blood.
- Look for parasites, such as pinworms or Giardia.
- Look for the cause of an infection, such as bacteria, a fungus, or a virus.
- Check for poor absorption of nutrients by the digestive tract (malabsorption syndrome). For this test, all stool is collected over a 72-hour period and then checked for fat (and sometimes for meat fibers). This test is called a 72-hour stool collection or quantitative fecal fat test.

How To Prepare

Many medicines can change the results of this test. You will need to avoid certain medicines depending on which kind of stool analysis you have. You may need to stop taking medicines such as antacids, antidiarrheal medicines, antiparasite medicines, antibiotics, laxatives, or nonsteroidal anti-inflammatory drugs (NSAIDs) for 1 to 2 weeks before you have the test. Be sure to tell your doctor about all the nonprescription and prescription medicines you take.

Be sure to tell your doctor if you have:

- ◆ Recently had an X-ray test using barium contrast material, such as a barium enema or upper gastrointestinal series (barium swallow). Barium can interfere with test results.
- ◆ Traveled in recent weeks or months, especially if you have traveled outside the country. This helps your doctor look for the parasites, fungi, viruses, or bacteria that may be causing a problem.

If your stool is being tested for blood, you may need to avoid certain foods for 2 to 3 days before the test. This depends on what kind of stool test you use. And do not do the test during your menstrual period or if you have active bleeding from hemorrhoids. If you aren't sure about how to prepare, ask your doctor.

Do not use a stool sample for testing that has been in contact with toilet bowl cleaning products that turn the water blue.

How It Is Done

Stool samples can be collected at home, in your doctor's office, at a medical clinic, or at the hospital. If you collect the samples at home, you will be given stool collection kits to use each day. Each kit contains applicator sticks and two sterile containers.

You may need to collect more than one sample over 1 to 3 days. Follow the same procedure for each day.

Collect the samples as follows:

- Urinate before collecting the stool so that you do not get any urine in the stool sample.
- Put on gloves before handling your stool. Stool can contain germs that spread infection. Wash your hands after you remove your gloves.
- Pass stool (but no urine) into a dry container. You may be given a plastic basin that can be placed under the toilet seat to catch the stool.
 - Either solid or liquid stool can be collected.
 - If you have diarrhea, a large plastic bag taped to the toilet seat may make the collection process easier; the bag is then placed in a plastic container.
 - If you are constipated, you may be given a small enema.
 - Do not collect the sample from the toilet bowl.
 - Do not mix toilet paper, water, or soap with the sample.
- Place the lid on the container and label it with your name, your doctor's name, and the date the stool was collected. Use one container for each day's collection, and collect a sample only once a day unless your doctor gives you other directions.

Take the sealed container to your doctor's office or the laboratory as soon as possible. You may need to deliver your sample to the lab within a certain time. Tell your doctor if you think you may have trouble getting the sample to the lab on time.

If the stool is collected in your doctor's office or the hospital, you will pass the stool in a plastic container that is inserted under the toilet seat or in a bedpan. A health professional will package the sample for laboratory analysis.

You will need to collect stool for 3 days in a row if the sample is being tested for quantitative fats. You will begin collecting stool on the morning of the first day. The samples are placed in a large container and then refrigerated.

You may need to collect several stool samples over 7 to 10 days if you have digestive symptoms after traveling outside the country.

Samples from babies and young children may be collected from diapers (if the stool is not contaminated with urine) or from a small-diameter glass tube inserted into the baby's rectum while the baby is held on an adult's lap.

Sometimes a stool sample is collected using a rectal swab that contains a preservative. The swab is inserted into the rectum, rotated gently, and then withdrawn. It is placed in a clean, dry container and sent to the lab right away.

How It Feels

There is no pain while collecting a stool sample. If you are constipated, straining to pass stool may be painful.

If your health professional uses a rectal swab to collect the sample, you may feel some pressure or discomfort as the swab is inserted into your rectum.

Risks

Any stool sample may contain germs that can spread disease. It is important to carefully wash your hands and use careful handling techniques to avoid spreading infection.

Results

A stool analysis is a series of tests done on a stool (feces) sample to help diagnose certain conditions affecting the digestive tract.

The normal values listed here—called a reference range—are just a guide. These ranges vary from lab to lab, and your lab may have a different range for what's normal. Your lab report should contain the range your lab uses. Also, your doctor will evaluate your results based on your health and other factors. This means that a value that falls outside the normal values listed here may still be normal for you or your lab.

Stool analysis test results usually take at least 1 to 3 days.

Stool analysis

Normal:	The stool appears brown, soft, and well-formed in consistency.
	The stool does not contain blood, mucus, pus, undigested meat fibers, harmful bacteria, viruses, fungi, or parasites.
	The stool is shaped like a tube.
	The pH of the stool is 7.0–7.5.
	The stool contains less than 0.25 grams per deciliter (g/dL) [less than 13.9 millimoles per liter (mmol/L)] of sugars called reducing factors. The stool contains 2–7 grams of fat per 24 hours (g/24h).
Abnormal:	The stool is black, red, white, yellow, or green.
	The stool is liquid or very hard.
	There is too much stool.
	The stool contains blood, mucus, pus, undigested meat fibers, harmful bacteria, viruses, fungi, or parasites.
	The stool contains low levels of enzymes, such as trypsin or elastase.
	The pH of the stool is less than 7.0 or greater than 7.5.
	The stool contains 0.25 g/dL (13.9 mmol/L) or more of sugars called reducing factors.
	The stool contains more than 7 g/24h of fat (if your fat intake is about 100 g a day).

Many conditions can change the results of a stool analysis. Your doctor will talk with you about any abnormal results that may be related to your symptoms and past health.

Abnormal values

- High levels of fat in the stool may be caused by diseases such as pancreatitis, sprue (celiac disease), cystic fibrosis, or other disorders that affect the absorption of fats.
- The presence of undigested meat fibers in the stool may be caused by pancreatitis.
- A low pH may be caused by poor absorption of carbohydrate or fat. Stool with a high pH may mean inflammation in the intestine (colitis), cancer, or antibiotic use.
- Blood in the stool may be caused by bleeding in the digestive tract.
- White blood cells in the stool may be caused by inflammation of the intestines, such as ulcerative colitis, or a bacterial infection.
- Rotaviruses are a common cause of diarrhea in young children. If diarrhea is present, testing may be done to look for rotaviruses in the stool.
- High levels of reducing factors in the stool may mean a problem digesting some sugars.
- Low levels of reducing factors may be caused by sprue (celiac disease), cystic fibrosis, or malnutrition. Medicine such as colchicine (for gout) or birth control pills may also cause low levels.

What Affects the Test

- Reasons you may not be able to have the test or why the results may not be helpful include:
- Taking medicines such as antibiotics, antidiarrheal medicines, barium, bismuth, iron, ascorbic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), and magnesium.
- Contaminating a stool sample with urine, blood from a menstrual period or a bleeding hemorrhoid, or chemicals found in toilet paper and paper towels.
- Exposing the stool sample to air or room temperature or failing to send the sample to a laboratory within 1 hour of collection.

What To Think About

- Stool may be checked for hidden (occult) blood. Testing for faecal Occult Blood confirms.
- A stool culture is done to find the cause of an infection, such as bacteria, a virus, a fungus, or a parasite.
- A bowel transit time test is done to help find the cause of abnormal movement of food through the digestive tract.
- The D-xylose absorption test is done to help diagnose problems that prevent the small intestine from absorbing nutrients in food. This test may be done when symptoms of malabsorption syndrome (such as chronic diarrhea, weight loss, and weakness) are present.
- A stool analysis to measure trypsin or elastase is not as reliable as the sweat test to detect cystic fibrosis.

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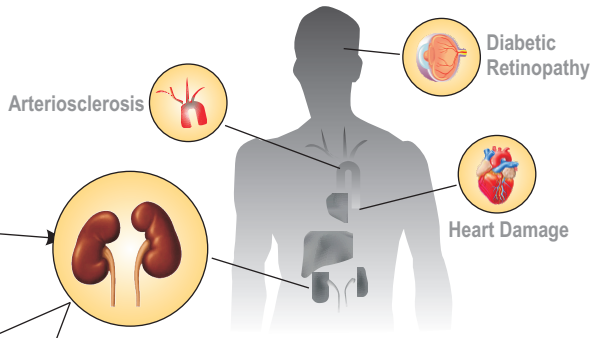
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Printed and published by D.G. Tripathi, Edited by Dr. Ramnik Sood, M.D. (Path.) for and on behalf of Tulip Diagnostics Private Ltd., Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh, Alto Santacruz, Bambolim Complex Post Office, Goa - 403 202, INDIA. Fax: (0832) 2458544. E-mail: sales@tulipgroup.com Website: www.tulipgroup.com

