87 Candida and parasitic infection: Helminths, trichomoniasis, lice, scabies, and malaria

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CANDIDIASIS IN PREGNANCY

Yeast infection is an important issue in women's health, even though systemic fungal infection is exceedingly rare in women of childbearing age. The presence of *Candida* organisms is almost universal. Three-fourths of all women have symptomatic *Candida* vulvovaginitis during their lifetime and almost half of those with an initial attack have additional episodes (1). *Candida* organisms are also isolated by culture in 8% of asymptomatic females (2). The dysuria, itching, and inflammation that accompany symptomatic infections may be severe enough to interrupt daily activities and prompt the patient to seek medical attention or use of over-the-counter products to relieve symptoms.

More than 100 species of *Candida* have been identified, with many further classified to the strain level (3). Only seven species of *Candida* are identified frequently in human clinical cultures. *Candida albicans* and *C. tropicalis* form 80% of all clinical isolates (4,5). *C. glabrata* and *C. parapsilosis* comprise an additional 10% to 15%, leaving 5% to 10% distributed among other species (5,6).

The species breakdown in vulvovaginal specimens differs in that *C. albicans* is identified in 80% to 85% of all positive vaginal cultures, *C. glabrata* in 10% to 15%, and *C. tropicalis* in 5%, with minimum identification of other species (7).

Pathophysiology of *Candida* Infection

Candida are dimorphic organisms with blastospore and mycelial forms. The blastospore form (budding yeast) is associated with transmission and colonization, and is the form found in the bloodstream in systemic infection. Germinated yeast with mycelia and pseudohyphae is the tissue-invasive form that causes symptomatic disease. The *Candida* life cycle is one of rapid budding, maturation, and degeneration. Budding occurs as a new cell outgrowth from the mother blastospore. Following mitosis, a septum partitions the two cells and budding resumes in each cell. Mycelium formation begins as a cylindrical outgrowth from the cell wall. Septa are laid down behind the apical tip as the hyphae shoot lengthens. Blastospores are then produced just behind the newly created septa. Pseudohyphae are a morphologic derivative between budding and hyphal growth that is found in all *Candida* species (8).

The attachment of *Candida* to vaginal cells has been reported to be mediated by mannose-containing receptors on the surface of the mucosal epithelial cells (3). The effect of estrogen in increasing vaginal epithelial avidity for candidal adherence may involve these surface receptors (1). Intracellular receptors for estradiol and corticosteroids have been identified in *C. albicans* and *C. glabrata* (9,10). Although the mechanisms of action of these receptors have not yet been elucidated, high levels of estrogens and corticosteroids are associated with increased candidal virulence and tissue invasion.

The human host defense mechanism against candidal vaginitis is primarily based on the natural bacterial flora of the vagina, particularly lactobacilli. Lactobacillus is thought to decrease fungal growth via competition for nutrients, mechanical interference with candidal mucosal adherence, and chemical inhibition by lactobacillus secretions (1). Cell-mediated immunity also plays a role in preventing infection. Monocytes and leukocytes prevent deep tissue invasion and systemic infection. IgG and IgM are elicited systemically and IgA is secreted in cervical mucus in response to acute candidal infection, but infection rates are not increased in patients with isolated immunoglobulin deficiencies (1).

Factors that predispose a patient to *Candida* vulvovaginitis can be categorized as systemic, localized, or exogenous. Systemic conditions associated with genital candidiasis include diabetes, nondiabetic glycosuria, endocrinopathies, debilitating disease, older age, and pregnancy. Local conditions that alter the barrier function of the perineal epithelium allow higher infection rates including tissue maceration (from moisture accumulation, urinary leakage, or abrasion from tight-fitting clothing) and thinning of the skin (from menopause or topical steroid use). Exogenous factors include commonly prescribed medications such as antibiotics (particularly tetracycline, ampicillin, and oral cephalosporins), immunosuppressive agents, and systemic steroids. Oral contraceptives were previously thought to increase infection rates, but recent studies with the low-dose combination pills have shown no effect (1).

Diagnosis of Candidiasis

Although the diagnosis of *Candida* infection is generally suspected on the basis of physical findings, confirmation should be obtained. The use of saline or potassium hydroxide (KOH) wet mounts of the vaginal secretions is the most rapid and least expensive confirmatory test. If a saline preparation is used, dark-field or phase-contrast microscopy may aid in visualization of the fungal elements. Potassium hydroxide (10–20% solution) lyses the epithelial cells, allowing the *Candida* to be seen more easily. Wet-mount analysis is highly specific, but sensitivity is poor (as low as 20%) (11). Other microscopic methods of *Candida* detection include Gram stain of smears or touch preps and Papanicolaou smears. If microscopic analysis is negative despite persistent symptoms following therapy, culture should be performed prior to further treatment. Infected secretions are inoculated into tubes

of candida culture media [Sabouraud's dextrose slants or Nickerson's medium have the highest sensitivity (90%) and specificity (70%) for *Candida* strains] (12) and incubated at 25°C to 37°C (3). *Candida* grows quickly, often within 24 hours. Isolates from sterile sources should be subcultured and identified to the species level, but vaginal specimens need only categorization to either albicans or non-albicans. Species differentiation is based on subculture characteristics. *C. albicans* exhibits both germ tube and chlamydospore growth (3). *C. parapsilosis, tropicalis*, and *glabrata* produce neither.

Culture of yeast from blood or tissue specimens is more challenging. Automated systems such as the Bactec radiometric system (Johnston Laboratories, Towson, MD) can detect *Candida* in 2 to 4 days. Use of biphasic media further improves sensitivity, but requires 5 to 9 days for adequate growth (3). Tissue biopsy may inadvertently reveal candidal infection (when performed for other indications, not recommended if candida suspected) with partial or total destruction of the surface epithelium and filaments of fungus extending into the underlying tissues, covered by a thick film composed of inflammatory cells, necrotic debris, yeast cells, and pseudohyphae (13).

Clinical Presentations of Candidal Infections

Vulvovaginal itching and burning are the most common symptoms of *Candida* vulvovaginitis (reported by 60% of women with positive yeast cultures) (11) along with external dysuria and a white, curdled vaginal discharge. One-third of females with positive vaginal *Candida* cultures are asymptomatic, while one-fourth of women with negative cultures have symptoms (11). The symptom spectrum of vulvovaginal candidiasis goes from acute/exudative (sudden onset, heavy discharge loaded with yeast) to progressive/inflammatory (minimal discharge, few organisms, severe itching). The pruritus may be a hypersensitivity reaction and may worsen with occlusive clothing and in the premenstrual phase of the cycle (14).

Classic physical findings for *Candida* vulvovaginitis are bright erythema and skin erosions with satellite pustules. The pustules are non-follicular and are scattered around the eroded areas. The erosions are superficial with a narrow white border of scale. In advanced cases, the entire perineum may appear scalded and oozing, with excoriations and fissures. Edema may be a finding in both early and advanced disease. Inguinal lymphadenopathy may accompany perineal involvement. Speculum examination reveals inflamed, erythematous, edematous mucosa with white thrush patches and pooling of the thick, white, curd-like discharge in the posterior fornix. The cervix may become red, inflamed, and quite friable.

Males with *Candida* balanitis (inflammation of the glans penis) have swelling, itching, and burning of the glans and shaft of the penis. Symptoms are more common in uncircumcised males (75%); circumcised men with positive yeast cultures are usually asymptomatic (90%) (2). Physical findings in the male with *Candida* balanitis include edema, erythema, and peeling of the glans penis and scrotum. Transient nonprogressive penile inflammation following intercourse may be due to a hypersensitivity reaction to *Candida* in the female partner's genital tract (2).

Therapy of Vulvovaginal Candidiasis

Current recommended therapy for vulvovaginal candidiasis is use of a topical imidazole. Imidazoles inhibit fungal cell wall synthesis and are absorbed in small amounts through mucous membranes (15). There are five topical azoles for the treatment of vulvovaginal candidiasis currently available in the United Sates (butoconazole, clotrimazole, miconazole, terconazole, and tioconazole) (16) many of which have multiple dosing forms as well as multiple brand names associated. Dosing information for current intravaginal azole treatments are listed in Table 1. There are no significant differences in efficacy or safety between the currently available topically applied azole products, with the caveat that longer duration of therapy typically results in slightly higher cure rates, so choice of product can be based on cost and convenience of dosing regimen.

Oral treatment of vulvovaginal candidiasis has become quite common with the approval of single dose, oral fluconazole 150 mg (Diflucan®). Fluconazole has been shown to be as effective as intravaginal clotrimazole (200 mg/day for 3 days) (17), intravaginal miconazole (1200 mg single dose) (18), and oral ketoconazole (400 mg/day for 5 days) (19). Short-term response rates of 94% (symptomatic) and 85% (mycologic) have been reported (20). The older oral medication used for

Table 1 Topical Azoles for Treatment of *Candida* Vulvovaginitis

Generic name	Formulation	Daily dose	Duration of dosing
Butoconazole	2% cream	5 g	3 days
Butoconazole[a]	2% cream	5 g	1 day
Clotrimazole	1% cream	5 g	7–14 days
Clotrimazole	2% cream	5 g	3 days
Miconazole	2% cream	5 g	7 days
Miconazole	4% cream	5 g	3 days
Miconazole	Suppository	100 mg	7 days
Miconazole	Suppository	200 mg	3 days
Miconazole	Suppository	1200 mg	1 day
Terconazole[a]	0.4% cream	5 g	7 days
Terconazole[a]	0.8% cream	5 g	3 days
Terconazole[a]	Suppository	80 mg	3 days
Tioconazole	6.5% ointment	5 g	1 day

[a]Available only by prescription in the United States.

vulvovaginal candidiasis, ketoconazole (Nizoral®), may still be considered for use in recurrent or resistant cases, but its use is limited by gastrointestinal side effects and ability to cause idiosyncratic hepatitis. When taken daily (400 mg for 14 days, then 100 mg for 6 months), ketoconazole has been shown to reduce recurrence rates in complex cases (21).

Currently recommended alternative treatments for use in resistant cases or women with azole allergies include nystatin, boric acid, and gentian violet. Nystatin (Mycostatin®) is a polyene antifungal, which binds to sterols in the fungal membrane, causing membrane incompetence and allowing intracellular components to leak out (15). Polyenes are not well absorbed orally or via mucous membranes. Boric acid powder is placed in capsules, with a 30-day cure rate of 72% when given as 600 mg daily for 14 days (22). Boric acid therapy can provide a very low-cost alternative for therapy of yeast vaginitis for resource-limited settings. Gentian violet (1% solution painted onto the affected areas two or three times a week) can provide rapid symptomatic relief, but is quite inconvenient due to permanent staining of skin and clothing. Gentian violet is fungicidal via interference with fungal enzymes (15).

Vulvovaginal Candidiasis in Pregnancy

Vaginal colonization with yeast occurs in 30% to 40% of all pregnancies (23). The attack rate is higher in the third trimester and symptomatic recurrence is more common than that in nonpregnant patients. The cause of increased prevalence in pregnancy is not known, but theories include fungal growth promotion via estrogen receptors on the vaginal mucosa and within the yeast cells, as well as improved fuel for growth due to higher mucosal glycogen content (23). Intra-amniotic infection with yeast is exceedingly rare with intact membranes, but can be seen in the presence of a foreign body, such as a cerclage or an intrauterine device, and may cause preterm labor or spontaneous abortion by invading the umbilical cord and major fetal organs (15). Up to 80% of infants that pass through an infected birth canal at delivery are colonized with yeast typically resulting in oral colonization (thrush) or diaper dermatitis, both easily treated with local therapy (24). Congenital cutaneous candidiasis is a disseminated papulovesicular to pustular dermatitis involving mainly the head, neck, palms, and soles, which resolves rapidly with topical antifungal therapy and carries little risk of progression to systemic infection in normal neonates (24).

Treatment of *Candida* vulvovaginitis in pregnancy is typically limited to topical azoles and nystatin (16,25). For many years, nystatin was the primary drug used for *Candida* vulvovaginitis in pregnancy because its extremely poor absorption was felt to improve its safety (pregnancy category B) (25). As studies have proven, the increased efficacy of the azole antifungal agents, miconazole, clotrimazole, butoconazole, and terconazole, has become the mainstays of therapy in pregnancy. They have been used extensively in human pregnancy with no adverse effects or increase in congenital malformations noted, but most remain pregnancy category C due to the absence of adequate controlled human studies. There is no clear leader from this group in terms of efficacy and patient satisfaction, so selection may be based on availability and cost. Seven-day treatment is usually needed in pregnancy due to the higher rates of treatment failure and recurrence. Cure rates are typically 5% to 10% lower than those in nonpregnant women for the same dosing regimen.

None of the alternative agents are recommended for use in pregnancy. Fluconazole is associated with fetal loss in animal studies with several small human studies that have shown no safety concerns, but are not adequate to recommend use in pregnancy (pregnancy category C) (25). Ketoconazole given orally has been shown to increase abortion and fetal loss in mice and rats, with no adequate human studies to document its effect on human pregnancy; therefore, its use for vaginitis in pregnancy is not recommended (pregnancy category C) (25). Boric acid is not recommended in pregnancy due to limited absorption of borate through the mucous membranes (less than 1 mg/mL serum levels). Gentian violet is not recommended for use in pregnancy because no adequate studies have been performed to judge its safety (pregnancy category C).

Recurrent Vulvovaginal Candidiasis

Almost one-half of women with an initial infection will have additional episodes. The subsequent attacks may be newly acquired cases or persistent infection due to incomplete eradication. Studies of culture-proven vaginal candidiasis with appropriate antifungal therapy show persistence of the same *Candida* strain in 20% to 25% of patients at 4- to 6-week follow-up (1). Recurrent candidal vaginitis may be due to chronic recolonization of the vagina from the intestine. Studies have shown a high strain correlation between the vagina and the intestine in those with intestinal colonization (1), but several studies of intestinal treatment with nystatin and ketoconazole have shown reduction or complete eradication of intestinal yeast with no impact on vaginal recurrence rates (21,26).

The role of male-partner penile colonization in promoting recurrent vaginitis is unresolved. Evidence in favor of a role for this includes a fourfold higher rate of asymptomatic penile colonization and the presence of *Candida* in the ejaculate of partners of women with recurrent vaginitis (1). Evidence against this includes the lack of documentation of sexual transmission previously outlined and the lack of improved recurrence rates following treatment of the male partner. Attention to hygiene should be recommended in all cases of *Candida* vaginitis. A trial of therapy in the male partner may be attempted if other therapy is unsuccessful in resolving recurrent infections.

All patients with recurrent episodes of vulvovaginal candidiasis without an obvious precipitating factor should be evaluated for underlying systemic disease (diabetes, HIV, or other debilitating disease) and use of over-the-counter or "home" remedies for the perineal and vaginal areas. Patients with continued pruritus without evidence of organisms may be experiencing an allergic reaction, not only to the *Candida*, but also to the antifungal medications in which case the inflammation should improve following cessation of therapy. Refractory vaginitis is a multifocal problem with no single solution. Inadequate therapy, resistant organisms, intestinal colonization, male-partner colonization, vaginal flora abnormalities, immunodeficiency, hypersensitivity reaction, and hampered barrier function may all be involved to a differing extent in individual patients with recurrent candidal

infections. Adequate evaluation, with therapy aimed at individual components, is the best approach.

Systemic Candidiasis

Systemic candidiasis typically occurs in debilitated patients with diabetes, acquired immunodeficiency syndrome, intravenous drug use, malignancies, chemotherapy, prolonged antibiotic or steroid therapy, and intravenous hyperalimentation (27). Systemic infection can be subdivided into disseminated infection, fungemia, and single-organ infection (meningitis, endocarditis, pneumonia, arthritis, peritonitis, laryngitis, endophthalmitis, and urinary tract infections). Systemic candidal infection is usually associated with an indwelling foreign body (intravenous catheter, Foley catheter, endotracheal tube, etc.). Symptoms are variable; however, persistent fever, in spite of broad-spectrum antibiotic coverage, is the most frequent clue, but may be masked in patients on high-dose steroids. Hypotension and mental status changes (confusion to obtundation) are also common signs. The diagnosis of disseminated candidiasis may be difficult. Blood cultures may be negative in 40% to 60% of cases proven by autopsy. Tissue biopsy, culture of fluids from sterile spaces, and urine cultures may be used to enhance detection in those at risk.

Treatment of systemic candidiasis has been changed significantly with the recent approval of new medications including additional second-generation triazoles (voriconazole and posaconazole) and a novel class of antifungals, the echinocandins (caspofungin, micafungin, and anidulafungin) (28,29). These new products have replaced amphotericin B and 5-fluocytosine for the treatment of candidemia with the echinocandins currently recommended as the drugs of choice due to higher efficacy and voriconazole/posaconazole as second-line treatment due to similar efficacy to amphotericin with a much improved side effect profile (28). Choice of echinocandins is usually based on local availability and cost. Unfortunately, survival rates for systemic candidiasis remain quite low despite improved therapy due to delays in diagnosis (resulting in delayed treatment) and the severity of underlying disease, particularly immunocompromise and diminished renal function (27). Since the new triazoles and echinocandins are quite expensive, amphotericin B and 5-fluocytosine continue to be commonly used in low-resource settings.

Systemic Candidiasis in Pregnancy

Systemic candidiasis in women of childbearing age is quite rare, but occasionally seen in cases with significant underlying disease (25). There are no adequate controlled studies during pregnancy for any of the medications used for systemic candidiasis; however, the life-threatening nature of this infection clearly outweighs any concerns over impact of the medications on pregnancy. Animal data available for both caspofungin and micafungin showed fetal loss and other issues (impairment of ossification for caspofungin and visceral abnormalities for micafungin) in both rats and rabbits with inadequate human data, resulting in both being labeled as pregnancy category C (25). The most experience exists for amphotericin B (pregnancy category B) (25), but the increased efficacy of the echinocandins should still be considered in the selection of treatment. Consultation with infectious disease specialists and hospital infection control officers is recommended for these unusual life-threatening infections in pregnancy.

HELMINTHIC INFECTION IN PREGNANCY

Introduction

Helminths are parasitic worms that spend at least a portion of their life cycle in an animal or human host. Helminths include cestodes (tapeworms), trematodes (flukes), and nematodes (roundworms). Helminthic infection has a worldwide distribution, but is more prevalent in underdeveloped countries. Although the prevalence rates have fallen in the developed world, helminthic infection has by no means disappeared. Life-threatening parasitic infection in pregnancy is uncommon in industrial nations of the world, but may be seen in individuals who have recently immigrated from less developed areas.

The effects of helminthic infection on pregnancy, although generally benign, should be recognized and treated. Anemia is a common feature of intestinal parasitic infection (owing to intestinal blood loss) and may compound anemia of pregnancy. Malnutrition may occur as a result of competition for nutrients. Chronic helminthic infection may lead to a debilitated state, with the possibility of superimposed bacterial infection. Since most helminthic infections in pregnancy are only mildly symptomatic, previously most were treated symptomatically until the postpartum period when definitive treatment was given. More recently, there have been increasing recommendations not to delay treatment, particularly in cases impacted by anemia. Each organism, however, has to be considered individually for therapeutic recommendations.

The diagnosis of helminthic infection must be individualized, but may be suspected on the basis of gastrointestinal symptoms (nausea, vomiting, and diarrhea) and a history compatible with exposure. With notable exceptions, helminthic infection is diagnosed by demonstration of eggs or larvae in feces. In heavy infection, eggs and larvae may be seen directly in saline wet mounts. To evaluate lighter infections, concentration must be performed via zinc sulfate flotation or formalin–ether sedimentation prior to saline wet-mount examination. Traditionally, examination of stool specimens from 3 consecutive days has been recommended to increase sensitivity in detection of ova and parasites in lightly infected cases. In moderately to heavily infected cases, a single-specimen evaluation should be as effective as multiple testing (30).

A description of the classification system for helminths is followed by review of the more commonly identified helminths. The chapter is completed by a description of the commonly used anthelmintic agents and their status for use in pregnancy and lactation. Treatment recommendations for all of the helminths detailed in this chapter are based on (i) the current treatment guidelines in the CDC parasites A to Z Web site (www.cdc.gov/parasites/az/index.html) section for each organism (obtained by selecting the organism from the index and then selecting "Resources for Health Care Professions") or (ii) The Medical Letter article entitled "Drugs for Parasitic Infections" available at The Medical Letter Web site (www.medicalletter.org). Additional information regarding laboratory diagnosis of helminthic infections can be obtained

at the DPDx Web site (www.dpd.cdc.gov/dpdx/HTML/DiagnosticProcedures.htm), which is a service of the CDC Division of Parasitic Diseases and Malaria. Links to the applicable sections of the Medical Letter "Drugs for Parasitic Infections" may also be accessed via the treatment tab for each organism on the DPDx Web site.

Classification and Description of Common Helminthic Infections

All helminths are classified as Platyhelminthes (flatworms) or Nematoda (roundworms). Flatworms are further divided into cestodes and trematodes (Table 2). Cestodes, or tapeworms, have segmented bodies consisting of proglottids attached via the neck zone to a head or scolex. The scolex provides attachment and locomotion via grooves, suckers, and hooks extending from its surface (Fig. 1). Tapeworms are hermaphroditic, with both male and female reproductive organs contained in each segment. There is no organized digestive tract; nutrients are absorbed via the integument. Excretory and nervous systems are present, but only in primitive form (31).

Trematodes, or flukes, have a flattened, leaf-like body with one or more ventral muscular suckers to provide attachment. Flukes are monoecious (hermaphroditic), with separate male and female reproductive organs that connect at the common genital atrium. Trematodes have a more advanced alimentary canal, nervous system, and excretory system (Fig. 2). All trematodes require a period of external development in a snail host (31). Nematodes are unsegmented worms with an external cuticle, developed internal organ structures, and somatic musculature (Fig. 3). Most nematodes are dioecious (heterosexual), with male and female sexual differentiation, and mating required for reproduction. The alimentary, excretory, and nervous systems of nematodes are more differentiated than those of other helminths. Most nematodes undergo four molts, with shedding or resorption of the old external cuticle, and formation of a new cuticle (31).

Cestodes

Taenia saginata and Taenia solium

Taenia saginata and *T. solium* have a worldwide distribution and cause taeniasis or tapeworm infection. Adult taenias are 3 to 8 m in length and comprise a small scolex (1–2 mm) and multiple proglottids, each about 0.5 cm × 1–2 mm in size (32). Taenia eggs are yellow to brown and spherical, with thick shells (Fig. 4). The life cycle of the taenias involves a definitive host (humans) and an intermediate host (*T. saginata*, cattle; *T. solium*, pigs). Eggs are passed in feces and reach pastures where they are ingested by the intermediate host. The larvae hatch and migrate to the muscle tissue, where they remain until the raw beef or pork is ingested by the definitive host. The infective form (cysticerci) requires 3 to 5 months to mature to adulthood. Taenia adult worms may live in the human small intestine for 25 years. The diagnosis of taenia infection is based on identification of eggs or proglottid segments in the patient's stool specimen (32).

T. solium eggs can be directly infective if ingested by humans, causing cysticercosis. Extreme care must be taken in

Table 2 Classification of Helminths

Platyhelminthes		
Cestodes (tapeworms)	***Trematodes (flukes)***	***Nematodes (roundworms)***
Taenia saginata	Schistosoma mansoni	Enterobius vermicularis
Taenia solium	Schistosoma japonicum	Trichuris trichiura
Diphyllobothrium latum	Schistosoma haematobium	Trichinella spiralis
Hymenolepis nana	Schistosoma intercalatum	Ascaris lumbricoides
Hymenolepis diminuta	Fasciola hepatica	Capillaria hepatica
Echinococcus granulosus	Fasciola gigantica	Capillaria philippinensis
Echinococcus multilocularis	Fasciolopsis buski	Strongyloides
Multiceps multiceps	Clonorchis sinensis	Ancylostoma
Dipylidium caninum	Opisthorchis felineus	Necator
	Opisthorchis viverrini	Tricostrongylus
	Gastrodiscoides hominis	Toxocara
	Watsonius watsoni	Ternidens
	Heterophyes heterophyes	Angiostrongylus
	Metagonimus yokogawai	Metastrongylus
	Paragonimus westermani	Anisakis
		Lagochilascaris
		Gongylonema
		Thelazia
		Gnathostoma
		Wuchereria
		Brugia
		Onchocerca
		Loa loa
		Dipetalonema
		Mansonella
		Dracunculus
		Dirofilaria

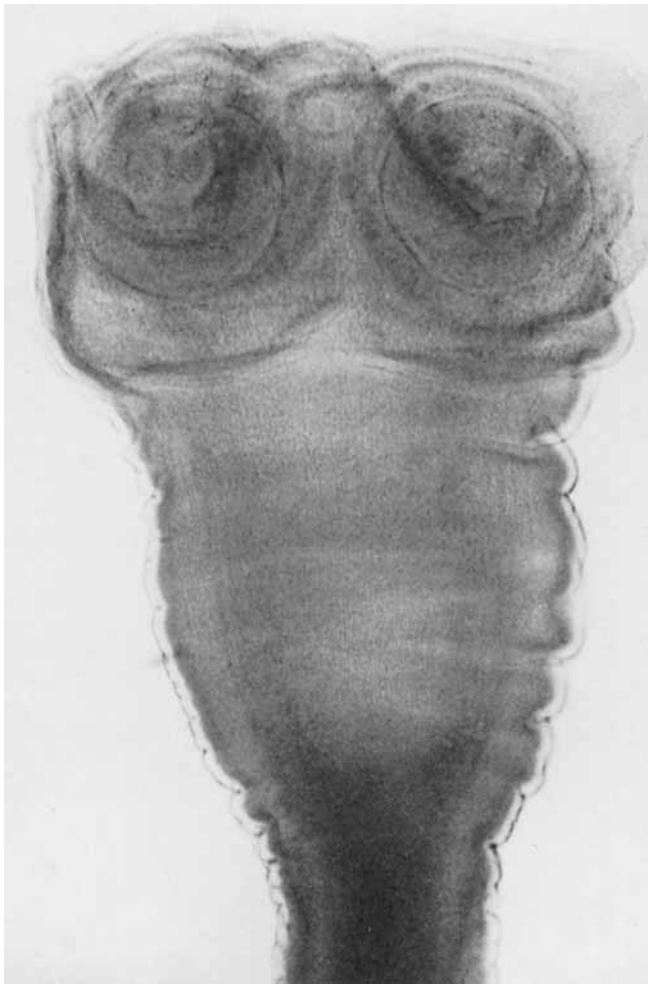

Figure 1 *Taenia saginata* adult scolex, showing suckers. *Source*: From Ref. 32.

handling all specimens with taenia eggs, as *T. solium* are not easily distinguished from *T. saginata* (32). Cysticercosis is the disease caused by larval migration throughout the body. Cysticercosis may be severe, even fatal, due to inflammation of vital organs, particularly cardiac muscle (33).

The clinical effects of taeniasis are usually minimal, but a minority of cases report abdominal discomfort, vomiting, and diarrhea (31). Rare cases of appendicitis and intestinal obstruction do occur. The treatment of choice is praziquantel (single 5–10 mg/kg oral dose), regardless of pregnancy status; niclosamide (single 2-g oral dose) is an alternative. Taenia infection generally has minimal effects on pregnancy and can typically be left untreated until the postpartum period, unless a symptomatic infection with *T. solium* is diagnosed (owing to the risk of cysticercosis).

Diphyllobothrium latum

Diphyllobothrium latum, or fish tapeworm, is found in northern Europe, North America, and Japan, specifically in temperate areas with cold, clear lakes. *D. latum* adult worms are 4 to 10 m long, with a small scolex (3 × 1 mm) and wide, short proglottids (32). The eggs are yellow to brown and ovoid, with an operculum (a lid-like structure). The life cycle begins as eggs that are passed in feces into water, where they hatch 2 weeks later, with coracidium released. The coracidium are ingested by copepods, where they develop to the procercoid

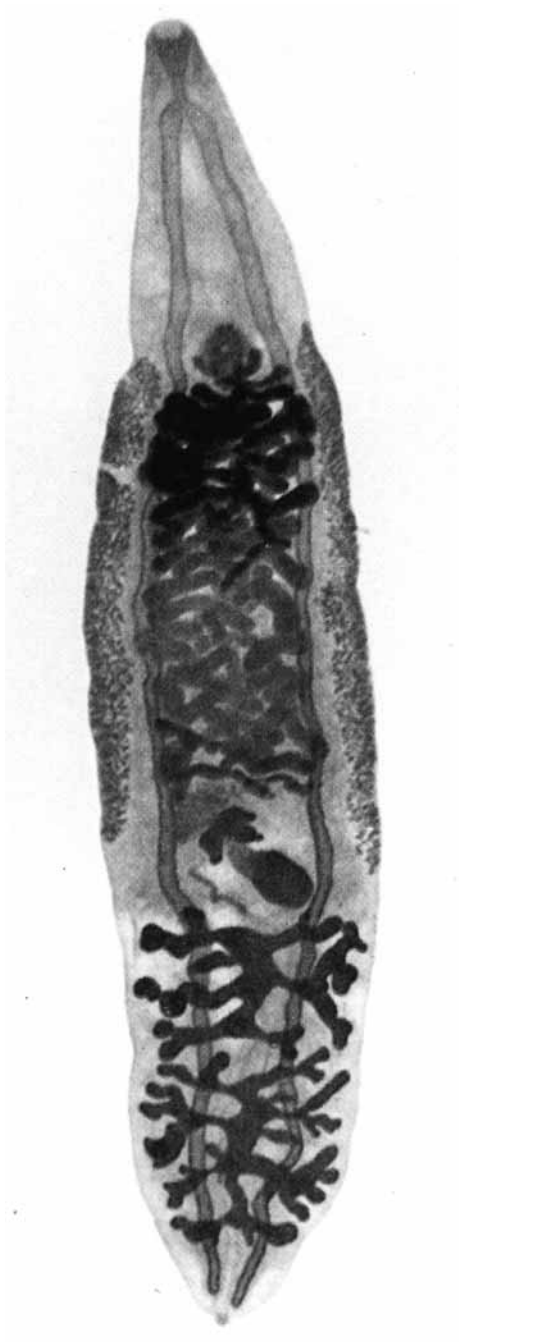

Figure 2 *Clonorchis sinensis* adult fluke (carmine stain). *Source*: From Ref. 32.

stage. Following ingestion of the copepod host by fish, the infective form (plerocercoid or sparganum) matures to await ingestion of raw fish by humans or other carnivores. *D. latum* migrates to the small intestine, where it attaches and matures to an adult. The adult worm may survive for up to 25 years, releasing its eggs in the feces (32). Diagnosis is based on finding eggs in feces (34).

Fish tapeworm infection may be asymptomatic or may have mild-to-severe gastrointestinal symptoms. Praziquantel (single 5–10 mg/kg oral dose) and niclosamide (single 2-g oral dose) are the most commonly used therapies. Unless infection is severe, anthelmintic therapy is typically delayed until the postpartum period. Diphyllobothriasis may cause vitamin B_{12} deficiency in pregnancy, owing to malabsorption; therefore, vitamin B_{12} supplementation is recommended.

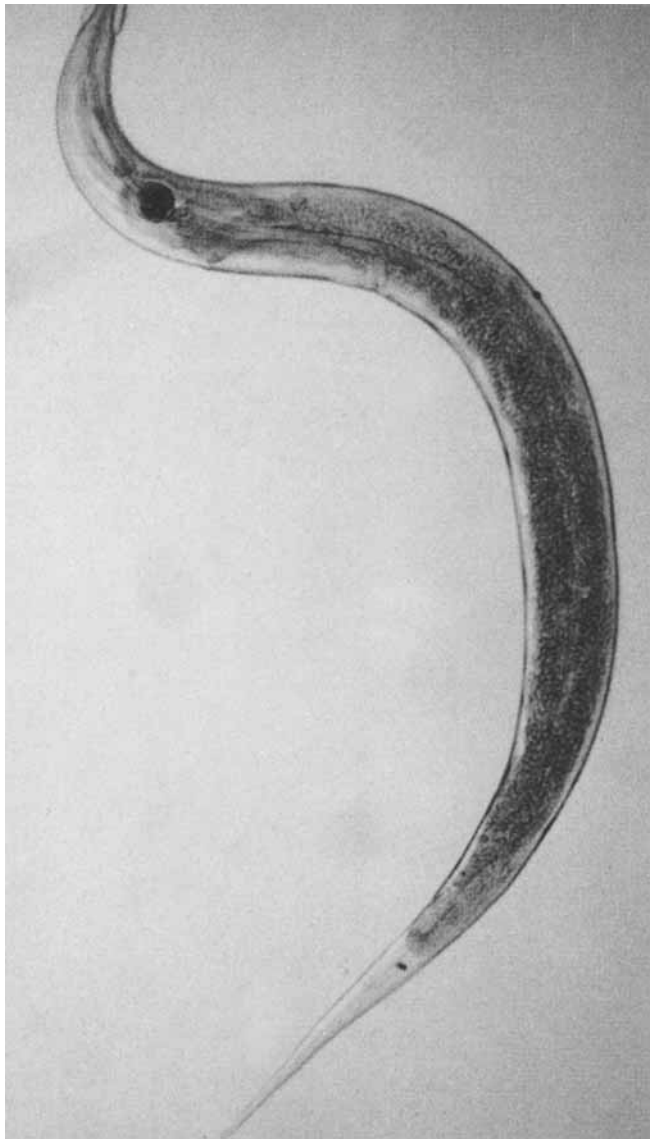

Figure 3 Enterobius vermicularis adult female. *Source*: From Ref. 32.

Hymenolepis nana

Hymenolepiasis or dwarf tapeworm infection is cosmopolitan in distribution. *Hymenolepis nana* adult worms are small tapeworms measuring 2 × 4 cm, with short wide proglottids (32). The eggs are spherical with a thin hyaline shell (Fig. 5). The definitive hosts of *H. nana* are mice and humans; beetles are intermediate hosts. The life cycle involves passage of eggs in feces with subsequent ingestion by beetles. The beetles are eaten by mice in the natural life cycle. Humans can be infected directly, by ingestion of the eggs. In humans, the eggs hatch, cysticercoids develop in the wall of the small intestine, and tapeworms emerge into the lumen of the intestine to mature to adulthood. Eggs are then passed in feces to restart the cycle. Hymenolepiasis is diagnosed by the finding of characteristic eggs in feces (32).

The clinical effect of dwarf tapeworm infection in humans is variable. There may be no symptoms or gastrointestinal complaints (diarrhea, nausea, anorexia, or vomiting) (31). The course is generally not severe. Praziquantel (single 25 mg/kg oral dose) is the drug of choice. Pregnancy is not threatened by hymenolepiasis, and treatment is typically deferred to the postpartum period.

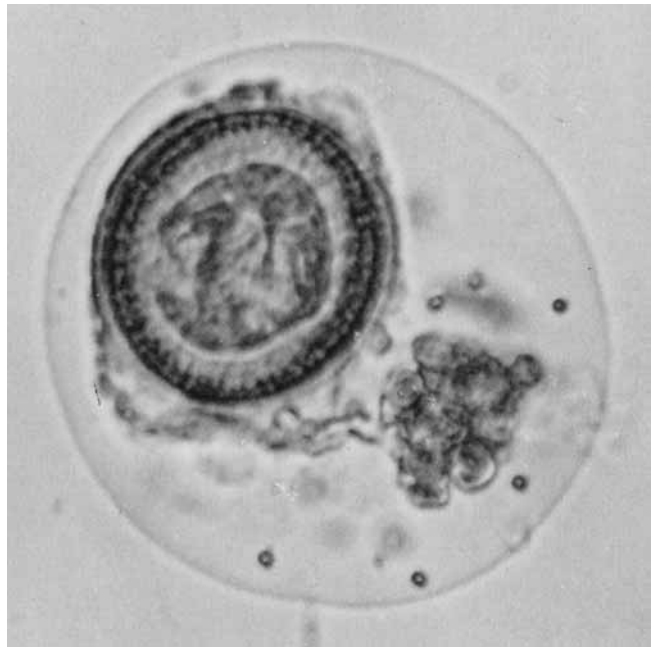

Figure 4 Taenia egg (*T. solium* and *T. saginata* eggs are indistinguishable). *Source*: From Ref. 32.

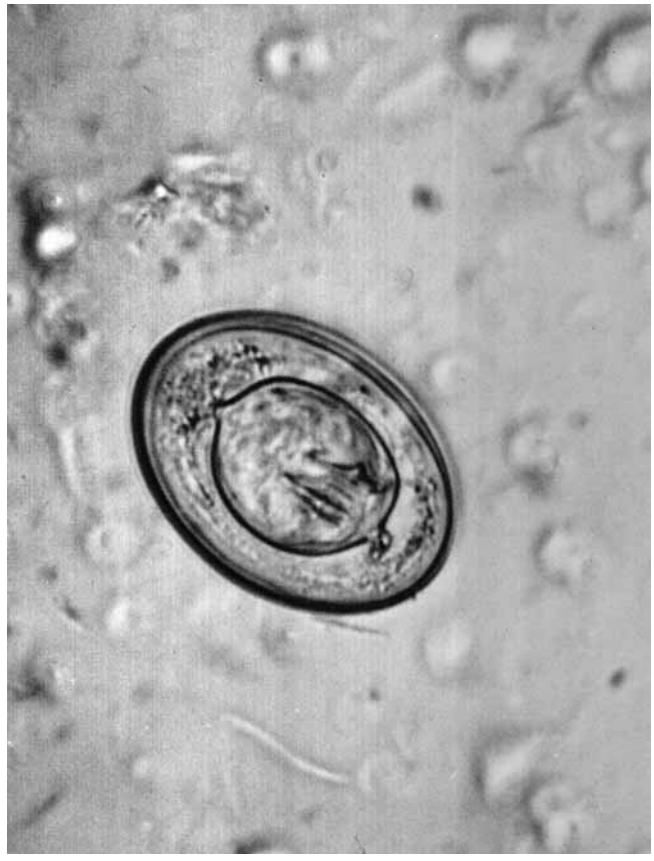

Figure 5 Hymenolepis nana egg. *Source*: From Ref. 32.

Echinococcus granulosus, Echinococcus multilocularis, and Multiceps multiceps

The definitive hosts of echinococcus and multiceps species are dogs and wild carnivores. On occasion, humans are an incidental host, infected by the ingestion of infective eggs. The embryos hatch in the intestine and migrate through the body to various organs, where cysts develop. Clinical diagnosis is

based on biopsy of the cyst/granuloma area or on immunologic testing.

Symptoms occur as the cysts enlarge and create a space-occupying lesion (31). *Multiceps multiceps* cysts are commonly located in the subarachnoid space and may cause meningitis (31). Pregnancy can be threatened if the echinococcal cysts are located in the uterine muscle. Intrauterine growth retardation and even impairment of labor may result from uterine cysts. Migration and encystment in vital organs can be life-threatening. Treatment is immediate, regardless of pregnancy status. Surgery to resect the cyst is the best therapy. Albendazole (440 mg orally BID × 1–6 months) can be used to reduce cyst size prior to surgery and may resolve smaller cysts without surgery. If surgery is not feasible and antepartum therapy is needed, praziquantel [100 mg/kg orally (divided into three doses) × 1 day, followed by 50 mg/kg/day orally (divided into three doses per day) × 28 days] is an alternative therapy that may be preferred for use in pregnancy (35), but it is not as effective in reducing cyst size.

Trematodes

Schistosoma mansoni, Schistosoma japonicum, and Schistosoma haematobium

Schistosomiasis or bilharziasis is mainly seen in the Middle East, Africa, and South America, but can be found in immigrant populations worldwide. Adult flukes are 0.5 to 2 cm in length, with females longer than males. Male flukes are wider with a posterior fold, the gynecophoric canal, in which the female rests. All schistosoma eggs are non-operculate with a transparent shell and either a lateral spine (*S. mansoni*) or terminal spine (*S. japonicum*) (32). Schistosoma adult worms live in the small blood vessels of the pelvic venous plexi. The female lies within the canal of the male for copulation and oviposition. The eggs migrate through the vessel wall and intervening tissues to reach the bladder or bowel, from which the eggs are excreted. If passed into water, the eggs hatch into a miracidial form that can penetrate and infect snails, the intermediate host. While in the snail, the miracidia mature to cercariae. The cercariae burst out of the snail host into water, where they directly infect humans through skin penetration. The schistosomule is transported via the venous system, through the heart and pulmonary vessels, to be propelled into the arterial system by the left ventricle. The schistosomules mature in the large vessels prior to migration to the terminal vascular beds, where the life cycle is completed (36). All therapies destroy only the flukes and have no effect on the migrating eggs (36). Diagnosis of schistosomal infection is based on the finding of eggs in urine, feces, or vaginal secretions, or the identification of adult worms or eggs in biopsy of the granulomas.

Initial infection (schistosome penetration) results in itching and papular rash. The migration of immature flukes causes fever, cough, allergic symptoms, and gastrointestinal complaints 2 to 4 weeks after initial exposure. Chronic schistosomiasis may cause anemia, cirrhosis, and urogenital disease. In females, this may include obstructive uropathy, abdominal pain, menorrhagia, salpingitis, oophoritis, sterility, and ectopic pregnancy (36). Praziquantel (20 mg/kg orally BID × 1 day for *S. mansoni, S. haematobium* or *S. intercalatum*, or 20 mg/kg orally TID × 1 day for *S. japonicum* or *S. mekongi*) is the treatment of choice for schistosomiasis.

Schistosome infiltration of the placenta has been reported, but is quite rare (36). Infection of a fetus with schistosomiasis was last reported in 1920 (36). Schistosomiasis has been associated with a number of adverse pregnancy outcomes including spontaneous abortion, preterm labor, low birth weight, and maternal morbidity/mortality, but additional prospective data are needed to quantify the impact (37). Heavy maternal schistosomal infection has been associated with decreased hemoglobin levels and increased prevalence of anemia in pregnant women, additive upon the typical anemia of pregnancy. Maternal anemia is strongly associated with low birth weight and maternal mortality (particularly in cases with antepartum or postpartum hemorrhage). Chronic schistosomiasis has also been associated with increased release of pro-inflammatory cytokines, which have been implicated in both the decreased appetite seen with schistosomiasis (which may contribute to low birth weight through maternal malnutrition) and with inflammation of the placenta (which may cause abortion and preterm labor) (37).

In the past, treatment of schistosomiasis in pregnant women was typically postponed until after delivery, but with more information associating maternal infection with adverse pregnancy outcomes, World Health Organization (WHO) recommended in 2002 that pregnant women with schistosomiasis be treated with praziquantel (dose same as listed above for nonpregnant adults) upon diagnosis and that pregnant women not be excluded from mass drug administration (MDA) programs aimed at the elimination of schistosomiasis (38,39). The "informal" WHO recommendation remains controversial since praziquantel is not specifically licensed for use in pregnancy, but efforts are underway to obtain the prospective human safety data needed to convince resistant in-country authorities to implement this recommendation (37).

Nematodes

Enterobius vermicularis

Enterobiasis or pinworm infection is universally distributed and is mainly seen in children. Adult male worms are small (2–3 mm) and females are larger (8–13 mm), both with long, pointed tails (40). Pinworm eggs are elongated with one flat side and have thick, colorless shells (Fig. 6). The definitive hosts for *Enterobius vermicularis* are humans. The female pinworms exit the rectum to lay eggs on the perianal skin overnight. The eggs embryonate in 4 to 6 hours to become infective. Eggs that are ingested hatch and develop in the lower intestinal tract (the cecum, appendix, and colon). Ingestion is facilitated by hand-to-mouth transmission or fomites. The adult worms may live for several months in the colon and rectum (32). Diagnosis is based on clinical suspicion and cellulose tape prep from perianal skin. Eggs are not found in feces. Cellulose tape prep is performed by taking clear cellulose tape, touching it to the perianal skin, and then adhering it to a microscope slide for examination (32). The tape prep is most accurate if done immediately upon arising, prior to bathing. The symptoms of pinworm infection are all related to the perianal egg deposition. Insomnia, restlessness, perianal itching/inflammation, and perianal bacterial infection

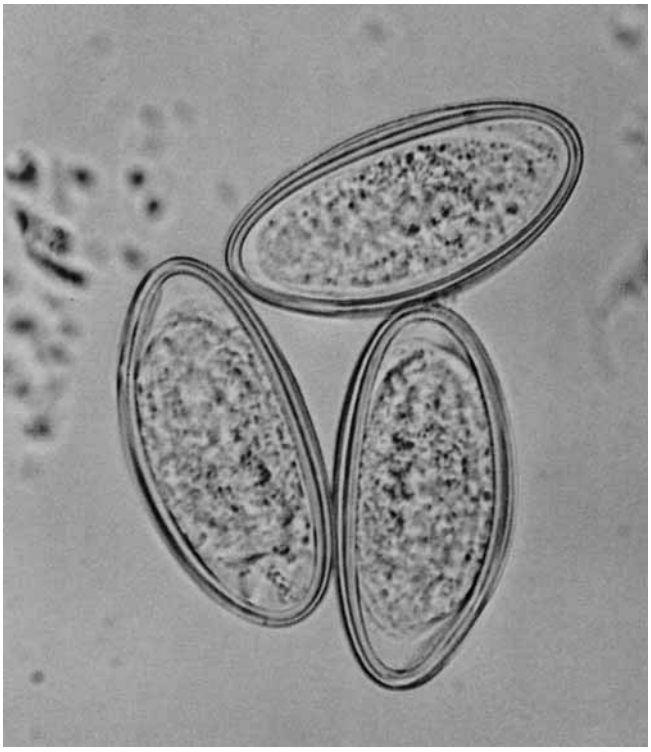

Figure 6 Enterobius vermicularis eggs. *Source*: From Ref. 32.

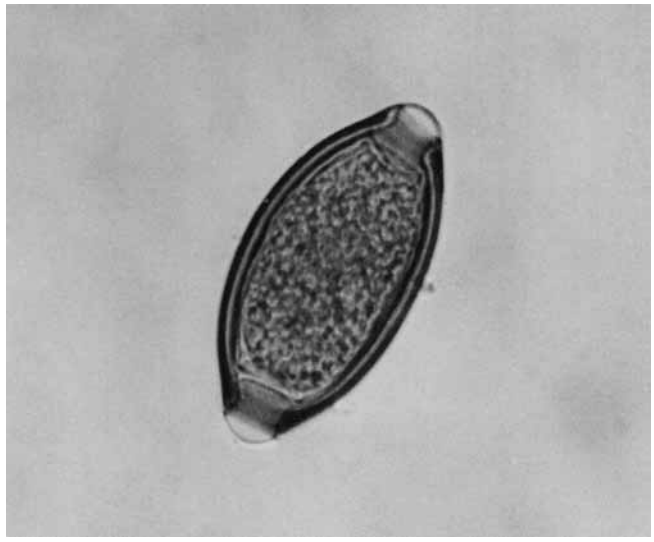

Figure 7 Trichuris trichiura egg. *Source*: From Ref. 32.

(secondary to excoriation) are the common clinical effects (31). Albendazole (single 400-mg oral dose followed by a second dose 14 days later), mebendazole (single 100-mg oral dose, followed by a second dose 14 days later), and pyrantel pamoate [single 11-mg base/kg (maximum 1-g base) oral dose, followed by a second dose 14 days later] are the drugs most commonly used for treatment. The entire family should be treated simultaneously, and clothing and bedding should be washed with hot water or chlorine bleach.

Pinworms can migrate through the vagina, uterus, and fallopian tubes, but no detrimental effect on the fetus or the pregnancy has been reported (41). Therapy is typically delayed until after delivery, unless the infection is potentially compromising the pregnancy. Pyrantel pamoate can be used after the first trimester (41).

Trichuris trichiura

Trichuriasis, or whipworm infection, is cosmopolitan in warm, moist areas. Adult whipworms are 3 to 5 mm long, with a slender, whip-like anterior end used to thread its way into the colonic mucosa (32). Whipworm eggs are barrel shaped, with a thick shell and plugs at each end (Fig. 7). Humans are the definitive host for *Trichuris trichiura*. Whipworm eggs pass in feces into the soil for further development. Infective eggs are ingested and hatched. The larvae migrate to the large intestine, where they mature to adulthood. The adult worms may remain in the colon for more than 10 years. Whipworm infection is diagnosed by finding eggs in feces (32).

Symptoms vary from none, in light infection, to colitis with bloody, mucous diarrhea in heavier infestation (31). Chronic infection can result in rectal prolapse, due to inflammation. Whipworm may be treated with albendazole (400 mg orally × 3 days), mebendazole (100 mg orally BID × 3 days), or ivermectin (200 μg/kg/day orally × 3 days). The impact of whipworm infection on pregnancy is mainly anemia due to increased gastrointestinal blood loss. Fetal infection has not been reported. Therapy for pregnant women is typically deferred until after delivery.

Trichinella spiralis

Trichinosis has a worldwide distribution, but is most prevalent in Europe and North America. The adult *Trichinella spiralis* are 1 to 4 mm in length (32). The female is viviparous, delivering larvae; thus, there is no external egg stage. All carnivorous species, including humans, are the definitive hosts. Most human infections result from ingestion of inadequately cooked meat. Bear, wild pig, boar, horse, and dog meat are the usual sources, but pork is the most common cause in the United States (42). Adult worms, living in the small intestine, release larvae into the mucosal epithelium. The larvae enter the bloodstream and migrate to muscle tissue, where they embed and mature to the infective stage. A cyst envelops the larva, and it remains infective until the cyst calcifies, killing the larva. When meat containing encysted larvae is ingested, the cysts are dissolved by gastric secretions, and the infective larvae are released. Within 36 hours, maturation occurs, and within a week larvae are produced, to become encysted in this new host. Diagnosis of trichinosis is based on the history of ingestion of undercooked meat and a compatible clinical picture (32). Definitive diagnosis requires either laboratory detection of specific antibodies or muscle biopsy finding encysted larvae (31).

The clinical effects of trichinosis in humans range from no symptoms to fatality. The initial ingestion of infected meat may cause diarrhea and gastroenteritis. The majority of symptomatology results from the larval migration and the resultant inflammatory response. Fever, edema, dyspnea, urticaria, weakness, and myositis are common manifestations (31). The ocular muscles are generally the most severely affected, but myocardial involvement is the most common cause of death (42). Therapy is a combination of anthelmintic agents, corticosteroids, anti-inflammatory agents, and supportive care (40). Mebendazole (200–400 mg orally TID × 3 days followed by 400–500 mg

orally TID × 10 days) and albendazole (400 mg orally BID × 8–14 days) are the recommended drugs. Anthelmintic destroy adult worms, not the larvae; however, once larval production ceases the disease is self-limited; symptoms resolve as soon as all larvae are encysted.

Trichinosis in pregnancy typically follows a moderate course, but may result in abortion, preterm labor, or intrauterine fetal death (42). Intrauterine infection has been reported twice, resulting in fetal/neonatal death (42). Trichinosis in pregnancy should be treated with mebendazole or albendazole as above when the maternal condition is such that the benefit to the mother outweighs the potential risk to the fetus.

Ascaris lumbricoides

Ascariasis or roundworm infection is most prevalent in warm, moist climates, but can be seen anywhere. Adult worms are quite large (15–30 cm long), with males longer and thinner than females (32). Ascaris eggs have thick, bile-stained shells (Fig. 8). Humans are the definitive host. The life cycle begins as eggs are passed in feces into soil or water. The infective eggs are then ingested, with larvae released in the small intestine. The larvae migrate through the venous system to the lungs, where they cross into alveoli and climb the bronchial tree. The larvae are then swallowed, and return to the small intestine, to mature into adults (32). The life span of adult ascaris is less than 1 year (41). Ascariasis is diagnosed by finding eggs in feces or on barium enema, when elongated filling defects occur (31).

There are two types of clinical disease related to ascariasis. Loeffler's syndrome is heralded by inflammation and pulmonary symptoms due to the migration of the larvae. Migration of the adult worms may cause obstruction of the bile duct or the appendix (41). Migration of adult females into the hepatic duct allows eggs to be released into the liver, resulting in multifocal abscess formation (31.) Most patients, however, have minimal or no symptoms. Albendazole (single 400-mg oral dose), mebendazole (100 mg orally BID × 3 days or single 500-mg oral dose), and ivermectin (single 150–200 μg/kg oral dose) are recommended for treatment.

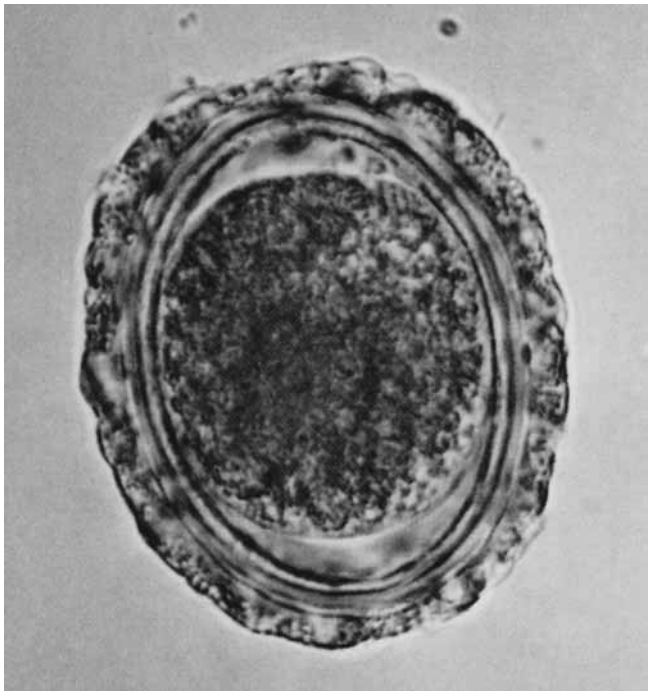

Figure 8 Ascaris lumbricoides egg. *Source*: From Ref. 32.

Ascariasis in pregnancy is generally asymptomatic. Transplacental infection has been reported, but is quite rare (41). Pregnant women should, however, be treated prior to labor or cesarean section, because of the risk of adult worm migration, stimulated by the stress of labor or general anesthetics.

Capillaria hepatica and Capillaria philippinensis

Hepatic capillariasis has a worldwide distribution, whereas intestinal capillariasis is seen mainly in the Philippines and Thailand. The adult worms are 2 to 4 mm long (32). *Capillaria hepatica* adults live in the liver parenchyma, whereas *C. philippinensis* adults remain in the small intestine. *Capillaria* eggs have striated shells and are unembryonated. Humans are incidental hosts; birds and rodents are the definitive hosts. The *C. hepatica* life cycle involves passage of eggs into feces, which then embryonate and are ingested by rodents (or humans). The larvae hatch and migrate to the liver to mature. The adult worms deposit eggs in the liver, where they remain until the rodent is consumed by a carnivore. In digestion, the eggs are released from the liver and pass in the carnivore's feces to restart the cycle (32). *C. philippinensis* eggs pass into water, where they are ingested by fish, and develop to the infective stage. Birds (or humans) are infected by eating raw fish. The adult worms live in the birds' (or human's) intestine and pass eggs in its feces (32).

Hepatic capillariasis is quite uncommon in humans and requires liver biopsy for diagnosis. Intestinal capillariasis is more common and can be diagnosed by finding eggs in feces (32). The clinical course resembles sprue, with diarrhea and severe gastrointestinal symptoms (31). Human autoinfection can occur, worsening the prognosis significantly.

Capillariasis in pregnancy may be left untreated until postpartum if symptoms are mild. Severe cases must be treated antepartum. Mebendazole (100 mg twice a day for 3 days) is the drug of choice, regardless of pregnancy status (40).

Strongyloides stercoralis

Strongyloidiasis has a worldwide distribution, but is most common in warm climates with a high water table. Adult worms are all females. They measure 2 to 3 mm in length and live in the small intestine. *Strongyloides* eggs are thin shelled (32). Female worms deposit eggs in the intestinal mucosa, where they hatch, releasing larvae. The larvae migrate into the lumen and pass in the feces into soil. Following maturation in the soil, infective larvae infect humans through direct skin penetration. The larvae then migrate, via the venous system and lungs, to the intestine, where they mature to adulthood and lay eggs. The entire life cycle may occur outside the body (in soil) or inside the body (internal autoinfection) (32). Strongyloidiasis is difficult to diagnose. Fecal concentration techniques are required to find larvae in feces, owing to the low number present.

The clinical effects of *Strongyloides stercoralis* infection include rash or pruritus (penetration phase); pneumonitis and cough (migration phase); and abdominal pain, diarrhea,

nausea, and vomiting (intestinal phase) (31). Immunosuppressed patients are at high risk from fulminant autoinfection. The drug of choice for treatment is ivermectin (200 μg/kg/day orally × 2 days) with albendazole (400 mg orally BID × 7 days) listed as an alternative. Strongyloidiasis in pregnancy may be left untreated until postpartum if symptoms are mild. Severe cases should be treated antepartum.

Necator americanus and Ancylostoma duodenale

Hookworm infection is common throughout Africa, Asia, and the South Pacific. Adult worms are small (7–11 mm in length), with females being larger than males. Hookworm eggs are thin shelled and colorless (32). Adult hookworms may live in the human intestine for 5 to 15 years, with the eggs being passed in feces. The eggs enter soil, hatch, and mature to third-stage (infective) larvae (Fig. 9). Infective larvae directly penetrate human skin and migrate, via the lungs, to the small intestine, where they mature to adulthood (41). Hookworm infection is diagnosed by finding eggs in feces (32).

Light hookworm infection is asymptomatic. Heavy infection produces hypochromic macrocytic anemia, due to intestinal blood loss (31). Treatment is albendazole (single 400-mg oral dose), mebendazole (100 mg orally BID × 3 days or single 500-mg oral dose), or pyrantel pamoate [11 mg base/kg/day (maximum 1-g base) orally × 3 days].

Prior to modern therapy, severe hookworm infection in pregnancy was associated with significant maternal (27%) and perinatal (23%) mortality (41). Maternal anemia, if untreated, may result in debilitation and heart failure (43). This maternal morbidity may cause fetal loss through abortion, preterm delivery, or stillbirth. Congenital infection has been reported (41). In 2002, WHO published a new guidance document recommending immediate treatment of hookworm infections in pregnant women beyond the first trimester, based in part on 20 years of experience using mebendazole in antenatal clinics in Sri Lanka without excess adverse events (38,39). Clinical trials of anthelmintic treatment for hookworm in pregnancy suggest that treatment is safe and may reduce maternal anemia, low birth weight, and infant mortality (44). Addition of iron therapy to anthelmintic treatment may further improve maternal anemia (44).

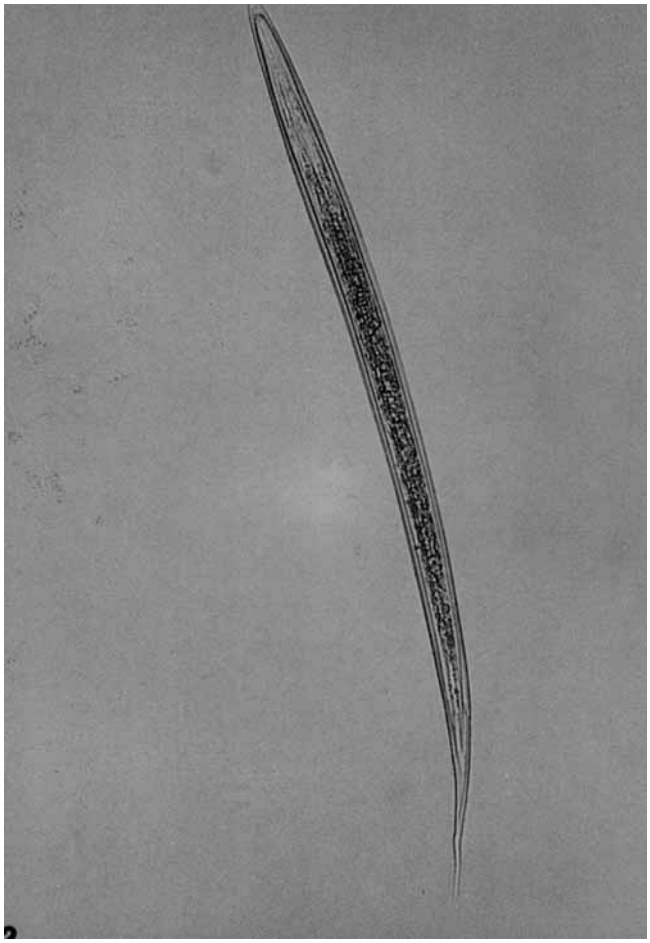

Figure 9 Necator/Ancylostoma (hookworm) infective third-stage larva. *Source*: From Ref. 32.

Toxocara canis

Toxocara canis (visceral larva migrans) is cosmopolitan, with dogs as the definitive host. The adult worms are 4 to 10 cm long and inhabit dog intestines. Toxocara eggs are thick shelled and spherical. Humans are incidental hosts (32). *Toxocara* eggs pass into soil, mature, and are ingested by rodents. Upon ingestion, the larvae are released and migrate throughout the body. Dogs ingest infected meat, with release of larvae in the stomach and maturation in the intestine. Human infection, called visceral larva migrans, occurs via ingestion of infective eggs with subsequent larval release and migration (32). Clinical diagnosis is based on history of contact with a pet and clinical examination. Laboratory diagnosis can be made by serologic testing for larval antigens, but there is some cross-reactivity with *Ascaris lumbricoides*. Clinical diagnosis is considered sufficient for treatment.

Human infection generally occurs in children who have contact with outdoor pets. The clinical syndrome varies based on the number of migrating larvae and the degree of inflammation and immune response to those larvae. It may include fever, cough, wheezing, abdominal pain, and hepatomegaly. Eosinophilia is usually present. Treatment with steroids and anti-inflammatory medications is indicated to reduce the inflammation associated with migration of the larvae. Albendazole (400 mg orally BID × 5 days) and mebendazole (100–200 mg orally BID × 5 days) are the recommended anthelmintic treatments. Infections during pregnancy may be left untreated until postpartum if symptoms are mild. Severe cases must be treated antepartum.

Anthelmintic Agents and Their Status for Use in Pregnancy

Anthelmintic agents are quite effective, with cure rates of 70% to 100% following a single course of therapy (34). Niclosamide, praziquantel, and pyrantel pamoate are the anthelmintic agents commonly used in pregnancy (Table 3). Mebendazole and albendazole are avoided, if possible, owing to the teratogenicity in rat and rabbit models but have quite a bit of reassuring human data despite the absence of large randomized trials to prove safety. Ivermectin is also avoided if possible due to teratogenicity in animals with very limited human experience thus far. Table 4 summarizes the classification of anthelmintic agents for use in pregnancy or lactation.

Pyrantel pamoate, a pyrimidine derivative, acts by paralyzing nematodes, allowing them to be expelled. Its action is similar to depolarizing neuromuscular blocking agents (41).

Table 3 Summary of anthelmintic Therapy and Recommendations for Treatment in Pregnancy

	First choice	Alternative
Cestodes		
Taenia[c]	Praziquantel	Niclosamide
Diphyllobothrium[c]	Praziquantel + vitamin B_{12}	Niclosamide+ vitamin B_{12}
Hymenolepis[c]	Praziquantel	
Echinococcus[a]	Surgery	Albendazole/praziquantel
Trematodes		
Schistosoma[b]	Praziquantel	
Nematodes		
Enterobius (pinworm)[c]	Pyrantel pamoate	Albendazole/mebendazole
Trichuris (whipworm)[c]	Mebendazole/albendazole	Ivermectin
Trichinella[b]	Steroids + mebendazole/albendazole	
Ascaris[d]	Albendazole/mebendazole	Ivermectin
Capillaria[c]	Mebendazole	
Strongyloides[c]	Ivermectin	Albendazole
Ancylostoma/necator (hookworm)[c]	Pyrantel pamoate + iron	Albendazole/mebendazole
Toxocara (visceral larva migrans)[c]	Steroids + albendazole/mebendazole	

[a]Treat immediately. [b]Treat in second or third trimester. [c]Treat postpartum unless severe. [d]Treat prior to delivery.

Table 4 Summary of Pregnancy/Lactation Recommendations

Anthelmintic agent	Pregnancy use category	Recommendations for breastfeeding women
Albendazole	C	NR (no data)
Mebendazole	C	Compatible
Ivermectin	C	NR (no data)
Pyrantel pamoate	B[a]	Compatible
Niclosamide	B	NR (no data)
Praziquantel	B	Compatible

[a]Based on available data, but never assigned by the FDA. *Abbreviation*: NR, Not recommended.

Pyrantel pamoate is very poorly absorbed, with half remaining in the intestinal tract unabsorbed. This poor absorption is the basis for its recommendation as first-line therapy in pregnancy. Blood levels of pyrantel pamoate are quite low, but it is not known whether it crosses the placenta. Animal teratology studies were negative, and no human malformations have been reported (compatible with pregnancy category B, but never labeled by the FDA). Pyrantel pamoate is considered safe for use while breastfeeding, due to its low absorption. Side effects (gastrointestinal complaints) are generally minimal and are not increased in pregnancy. Pyrantel doses can be calculated from the pamoate form or the free base (1 mg base = 2.9 mg pamoate form). Anthelmintic doses are 5 to 10 mg/kg pyrantel base or 15 to 30 mg/kg pyrantel pamoate (maximum daily dose, 1-g pyrantel base) (41).

Niclosamide, a salicylanilide, inhibits oxidative phosphorylation in the cestode mitochondria, killing the worm on contact. Niclosamide has been shown to have no teratogenic effect in rat and rabbit studies (45). No human malformations have been reported (pregnancy category B). The drug is poorly absorbed, but no information is available on niclosamide levels in breastmilk or on its ability to cross the placenta. There are inadequate data to assure the safety of uninterrupted breastfeeding following niclosamide therapy. Since single-dose therapy is used, temporary interruption (24 hours) of breastfeeding with disposal of milk can accommodate this therapy.

Praziquantel (an isoquinolone) is the drug of choice for most trematode infections in pregnancy (43). It is well tolerated with minimal side effects (36). Studies of teratogenicity have been negative in mice, rats, and rabbits (46,47). There are no reports of human malformations (pregnancy category B). Praziquantel is secreted in breastmilk at 29% of the maternal serum level (34). Praziquantel use is considered compatible with breastfeeding. In order to reduce potential infant exposure with single-dose maternal therapy, the mother can pump and discard the milk for 1 to 2 days to allow clearance of the drug.

Ivermectin is an anthelmintic macrocyclic lactone similar to macrolide antibiotics but with no antibiotic activity. Its activity against helminths comes from affecting ion channels in the cell membrane to increase permeability causing cell death. Ivermectin is a pregnancy category C drug, due to animal data suggesting teratogenicity, without controlled data in humans. There are only a few case reports of ivermectin use in pregnancy thus far, but there were no issues noted in those cases. Use of ivermectin in pregnancy is thus recommended only when the benefit to the mother outweighs any potential risk to the fetus. Ivermectin is excreted into breastmilk at low levels so its use during breastfeeding is likewise recommended only if the benefit to the mother outweighs any risk to the infant.

Albendazole and mebendazole (benzimidazole derivatives) are the drugs of choice for treatment for most nematode infections. Both are pregnancy category C based on animal data suggesting teratogenicity without controlled data in

humans. Mebendazole has been used extensively in the second and third trimesters in Sri Lanka, Nepal, and Madagascar, where it is routinely used for deworming in antenatal clinics without evidence of increased adverse outcomes (48). Both albendazole and mebendazole have been used in a number of second- and third-trimester clinical trials to study the benefit of deworming in pregnancy with more than 400 women having been exposed with no increase in adverse events reported (44). There was a case series from Sri Lanka reporting increased congenital anomalies with first-trimester mebendazole use so that is not recommended unless the maternal condition is severe enough to require immediate treatment without regard for fetal risks (49). Mebendazole has very limited excretion in breastmilk so is compatible with breastfeeding. There are inadequate data on albendazole to recommend use during breastfeeding.

PROTOZOAN INFECTIONS IN PREGNANCY

Trichomoniasis

Trichomonas vaginalis is an extracellular flagellated single-cell protozoon that colonizes the female lower urogenital tract and male urethra. Humans are the only host for *T. vaginalis* and the organisms cannot survive outside their human hosts for very long. *T. vaginalis* replicates by binary fusion of the trophozoite form. Trichomoniasis is transmitted from person to person, typically via genital contact at the time of sexual intercourse. Although transmission via fomites, such as towels or clothing, has been theorized, non-venereal transmission has not yet been documented.

Diagnosis of trichomoniasis has classically been performed by wet-mount microscopy, which is highly specific, but not very sensitive missing up to 40% of infections. There are two FDA-cleared rapid tests for detection of trichomoniasis in vaginal secretions, OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Massachusetts), and the Affirm VIP III (Becton Dickenson, San Jose, California). Both were developed as point-of-care tests with results in 10 and 45 minutes respectively. Both have improved sensitivity over wet mount (>83%), but even though the specificity is quite high (>97%), false-positive test results can be a problem in low-prevalence settings (50). Trichomonas culture is also sensitive and highly specific. Several nucleic acid detection techniques are available for diagnosis of trichomoniasis and are particularly useful for diagnosis in men due to higher sensitivity than the previously used culture techniques.

Colonization with *T. vaginalis* is asymptomatic in most males and initially in many females, but it is estimated that 50% to 90% of women with vaginal colonization will ultimately become symptomatic if left untreated (23). Symptoms in women include a profuse, malodorous, frothy, yellow-green vaginal discharge and vulval itching or burning. Males have symptoms consistent with non-gonococcal urethritis, including urethral discharge, local itching/burning, and pain with urination. Treatment of trichomoniasis is typically limited to drugs from the nitroimidazole family—metronidazole (single 2-g oral dose or 500 mg orally BID × 7 days) and tinidazole (single 2-g oral dose) (50). Simultaneous treatment of all sexual partners prior to next sexual contact is recommended to prevent immediate recolonization. There has been some controversy over the legal status of providing trichomoniasis treatment to the patient to deliver to his/her partners in the absence of direct contact between the partners and the health-care system, but many U.S. states have now enacted legal protection for partner-delivered therapy for sexually transmitted diseases. Assessment of local standard of care and legal requirements is recommended prior to initiating a practice of partner-delivered therapy.

Trichomoniasis in pregnancy has been associated with adverse pregnancy outcomes including premature rupture of membranes and preterm delivery. A large multicenter trial was conducted to see whether treatment of asymptomatic trichomoniasis at the end of the second trimester could reduce the rate of preterm birth (51). Unfortunately, this study reported a somewhat increased rate of preterm delivery in the treated women as compared with the placebo group. This increase has not been confirmed in other studies and there has been much discussion of potential limitations of this trial (including the timing and dosage of the treatment), but to date there has been no benefit identified for treatment of asymptomatic pregnant women (52). By contrast, treatment of symptomatic pregnant women with metronidazole (single 2-g oral dose) is recommended upon diagnosis (50). Metronidazole has no evidence of teratogenicity in animal studies and extensive use during human pregnancy (pregnancy category B). Some women may prefer to await completion of the first trimester prior to treatment to avoid exposure during organogenesis. Tinidazole has evidence of increased fetal mortality in animal studies with no controlled human studies (pregnancy category C). Since tinidazole has no advantage over metronidazole with potential for increased risks, tinidazole is not recommended for use during pregnancy. Metronidazole is excreted into breastmilk at levels similar to those found in maternal plasma after oral dosing, thus the American Academy of Pediatrics recommends that women pump and discard breastmilk for 12 to 24 hours following maternal single-dose oral metronidazole therapy to reduce infant exposure (50). It should be noted that the levels seen in the infant after maternal therapy during breastfeeding are lower than levels achieved in infants directly treated with metronidazole. Tinidazole is also excreted into breastmilk at levels similar to maternal plasma following oral dosing. Since tinidazole is still detectable in breastmilk up to 72 hours after the last dose, pumping and discarding milk for 3 days are recommended to reduce infant exposure.

Lice

Head Lice

Pediculosis capitis is caused by *Pediculus humanus capitis,* an ectoparasite that infests the human head. Humans are the only hosts. Adult lice require human blood to survive and die within 1 to 2 days if unable to feed. Adult lice live for about 30 days attached to the proximal hair shafts to provide close proximity to the scalp for feeding. Adult females may lay up to eight eggs (nits) per day adjacent to the scalp to allow the warmth from the head to incubate them. The nits are small (<1 mm) white-yellow oval eggs that hatch to form nymphs within a week, leaving the empty shell attached to the hair shaft. The nymphs are initially tiny, but grow rapidly to

become adults in about 7 days when the lifecycle begins again. The diagnosis is based on seeing either adult lice or nits in the hair.

Pediculosis capitis is quite common with the estimated 6- to 12-million infestations per year in the United States alone, mostly in school-aged children. Head lice are usually transmitted via head to head contact with an infected individual, but may be transmitted via fomites such as hats, towels, combs, or bed linens recently used by an infected person. The high prevalence among school children is thought to be due to frequent contact through sports or play as well as the sharing of combs and hair brushes. Infestation with head lice is not related to the level of hygiene. Clinical manifestations of infection are typically itching of the scalp due to hypersensitivity to the louse bites. Itching may not occur until 4 to 6 weeks after the first infection due to the time required to develop an allergic reaction. Although adult lice move from person to person, head lice are not known to transmit other diseases (53).

The diagnosis of pediculosis is often made by the infected person or a family member seeing the adult lice or nits in the hair or on a comb or brush. A number of further diagnostic techniques have been employed including visual inspection (with or without magnification), use of combing (either dry with a special fine-toothed comb or wet following washing and application of a conditioner), shampooing with use of a strainer to collect the rinse water, and collection of hair clipping from hairdressers (54). In comparison, self-diagnosis is almost as sensitive (80%) as wet or dry combing, with visual inspection being by far the least sensitive technique, even with magnification. Since dry combing requires less equipment (only need the fine-toothed comb; no need to wash and condition the hair as required for wet combing) and can thus be performed in any setting, it is typically the diagnostic test of choice, particularly in school-based screening.

Treatment of head lice is recommended for all infected persons. It is important to assess household members of an infected individual for active infection (as described above) in order to treat all infected household members at the same time. Prophylactic treatment of anyone who shares the same bed with an infected person has been recommended, but mass treatment of the entire household is not. Treatment of head lice is performed using a pediculicide applied to the hair and scalp then washed off. Since the medications typically kill only adult and nymph lice (not the nits), retreatment is usually required in 7 to 9 days to kill any recently hatched lice. Commonly used products available over-the-counter in the United States are pyrethrins combined with piperonyl butoxide (Pronto®, RID®) and the synthetic pyrethrin, permethrin 1% lotion (Nix®). Pyrethrins are neurologic toxins to insects by alterations of the sodium channels resulting in neurologic paralysis and death to exposed insects. Worldwide resistance to pyrethrins appears to be increasing, so repeating treatment beyond a third dose is not recommended (55). Alternative products used primarily for resistant cases that do not respond to treatment with a pyrethrin include Malathion 0.5% lotion, benzyl alcohol 5% lotion, and lindane 1% shampoo (all available only by prescription) (56). Supplemental measures, such as thorough combing to remove nits, washing of bed linens, bombs, and brushes in hot water, and sealing unwashable items in sealed plastic bags for 2 weeks, may assist in eradication of infection, but are not essential. Since the adult lice and nits die rapidly when removed from the human host, extensive household cleaning is not typically required. There is no role for household fumigation or other use of insecticides in the management of pediculosis.

Pediculosis capitis during pregnancy follows a similar course to nonpregnant adults so treatment prior to delivery is not required, but there is typically a desire to treat due to the itching and psychologic distress of carrying a parasite in a visible location. Permethrin is the drug of choice for treatment in pregnancy and breastfeeding due to the low systemic absorption (<2% of the applied dose) and rapid clearance (53). There was no teratogenicity noted in animal studies of permethrin and there are no controlled human trials so it is a pregnancy category B drug. Observational reviews of use in humans have not identified any increased risk of adverse pregnancy outcomes (53). Permethrin use is considered to be compatible with use during breastfeeding due to the very low levels found in breastmilk. Malathion is also a pregnancy category B drug, but is typically not used in pregnancy or breastfeeding. Lindane and benzyl alcohol have been associated with abnormal neurodevelopment in animal teratogenicity studies (pregnancy category C) so should not be used in pregnancy unless absolutely necessary.

Body Lice

Pediculosis humanus corporis is caused by the ectoparasite *Pediculus humanus humanus*. Similarly to head lice, humans are the only host for body lice. The life cycle is quite similar to head lice, with the entire lifecycle occurring on hair shafts in close proximity to the skin. Body lice infestations typically occur in conditions of poor hygiene and overcrowding, such as those seen among homeless individual or in refugee camps. The primary clinical manifestation is itching, with the potential for skin thickening in chronically infected areas.

A major difference between head lice and body lice is the ability of body lice to transmit other diseases. Typhus, trench fever, and endemic relapsing fever have all been transmitted by body lice (57). *Pediculus humanus humanus* has recently been shown to be capable of transmitting *Yersinia pestis* as well and may have contributed to the transmission of the Black Plague (58). Body lice are diagnosed by visualization on clothing or skin, which may require magnification. Body lice can typically be resolved by improved hygiene, including use of a clean change of clothing at least weekly with laundering of clothing and towels in hot water (59). Treatment with a pediculicide is not typically required, but if needed the same medications used for head lice are used for body lice. There are no specific issues related to pregnancy.

Pubic Lice

Pediculosis pubis is caused by the ectoparasite, *Phthirus pubis*. As was true for head and body lice, humans are the only host for pubic lice and the life cycle is quite similar. Similar to head lice, pubic lice have not been reported to transmit other diseases. A common lay term for pubic lice is "crabs" due to the more rounded crab-like appearance of pubic lice compared with the more elongated head and body lice. Pubic lice are found on the coarse body hair located in the pubic

region, but may also be seen on other coarse body hairs including beards, mustaches, eyelashes, eyebrows, and axillary hair. Transmission of pubic lice is generally via body contact during sexual intercourse, thus pubic lice are most commonly found in adults. Finding of pubic lice on the eyelashes or head of a child raises the question of potential sexual abuse; however, fomites such as towels, clothing, and bed linens may be involved in transmission so sexual contact is not always involved.

Treatment of pubic lice is usually performed with permethrin 1% lotion or pyrethrin with piperonyl butoxide applied to the affected area and washed off 10 minutes later (60). Alternative therapies include Malathion 0.5% lotion and ivermectin. Unlike head lice, a second treatment is required only after 9 to 10 days if live lice are noted at that time. A notable exception to the use of these medications is infection of eyebrows or eyelashes that are most commonly treated by physical removal of lice and nits, with application of ophthalmic-grade petrolatum ointment two to four times per day for 10 days. Supplemental measures including physical removal of nits, laundering of clothing and bed linens in hot water, and placement of unwashable items in sealed plastic bags for 2 weeks are more strongly recommended than that was the case for head lice. Also all sexual partners for the past month should be informed of their risk for infection and treated prior to resuming sexual contact. Since pubic lice is a sexually transmitted disease, it is prudent to evaluate for the presence of other sexually transmitted diseases (60). Pregnant women should be treated with the primary therapies of permethrin or pyrethrin; use of Malathion and ivermectin in pregnancy should be avoided if possible.

Scabies

Scabies is an ectoparasitic infestation caused by the human itch mite, *Sarcoptes scabiei var hominis*, for which humans are the only host in which replication can occur. Animal mites can infest human skin temporarily, but cannot replicate in humans and thus their infestation is self-limited. Adult female mites make characteristic serpentine burrows into the skin, usually between fingers and around the wrist in humans, where they lay 2 to 3 eggs per day as the burrow lengthens (61). Eggs hatch in 3 to 4 days to form larvae, which exit the serpentine burrow to dig a shallow molting pouch. Larvae develop into nymphs and then adults within 10 to 14 days inside the molting pouch. Adult male mites leave their molting pouch to burrow into the molting pouch of an adult female mite in order to fertilize the female who then continues to be fertile the remaining month of her life. Once impregnated, the adult female mite leaves the molting pouch to find a site to begin her own serpentine burrow and egg deposition, thus restarting the life cycle.

The diagnosis of scabies can be made clinically based on the presence of characteristic burrows or visible mites. Skin scraping can be performed to look for mite or eggs, but treatment should be provided for suspected cases without confirmation of the presence of mites since a typical infection may involve only 10 to 15 female mites (61). In addition to microscopic examination of skin scrapings with oil, skin scrapings can also be submitted for PCR to detect *S. scabiei* DNA. When using PCR to verify resolution of infection, it is important to wait at least 28 days after the last treatment to allow time for skin to shed with new epithelium developed, since the DNA from dead organisms will persist in the skin until it has been shed (62). Scabies is transmitted by close interpersonal contact, particularly in crowded living conditions. Outbreaks have been identified in nursing homes, hospitals, orphanages, and refugee camps (63). Transmission may occur with sharing of a bed and often occurs among adults via sexual contact. Children may be infected via sharing of beds or direct contact during play. Scabies is not considered to be an indication of potential sexual abuse due to its frequency in non-abused children. Fomites, such as clothing, towels, and sheets, may be involved with spread in some cases, but are not thought to be a major contributor.

The primary clinical manifestation of scabies is itching due to a hypersensitivity reaction to the organism, which may take several weeks to develop following first exposure, but may develop rapidly with subsequent exposures. A classic rash occurs with visible burrows on the hands, wrists, and ankles. Papules may occur in those locations as well as on the forearms, axilla, breasts, and penis. The visible burrows and papules are the sites from which mites could possibly be obtained via skin scraping. The treatment of choice for uncomplicated scabies is permethrin 5% cream (Elimite®) applied to the entire body below the neck with specific attention to folds and creases including those between the fingers and toes as well as beneath the nails, which is washed off after 8 to 14 hours (64,65). A second application a week later may be required to eliminate all mites. Note that this is a higher dose of permethrin than that used for lice and this product is not available over-the-counter in the United States. Alternative treatments include ivermectin (200 μg/kg/day in 2 doses 14 days apart), crotamiton 10% lotion or cream, and lindane 1% lotion but all have a lower efficacy than topical permethrin for uncomplicated scabies (64,65). Supplemental measures such as washing of clothes, bed linens, and towels in hot water may be helpful, but are not essential for uncomplicated scabies as there are few organisms involved.

Treatment of scabies in pregnancy is typically performed with permethrin (64) (pregnancy category B) for which there is no evidence of teratogenicity in animals and there are no controlled studies in humans. There is a retrospective study of women who received either permethrin 4% lotion ($n = 196$) or benzyl benzoate 25% lotion ($n = 444$) for treatment of scabies during pregnancy (primarily second and third trimesters, but 10% first trimester as well) (66). They found no difference in pregnancy outcomes between treated women and their matched controls. They did note a higher need for retreatment with benzyl benzoate lotion than with permethrin (16.4% vs. 9.7%), compatible with the higher efficacy for permethrin seen in nonpregnant adults.

In debilitated or immunocompromised individuals, an aggressive form of scabies called crusted or Norwegian scabies may develop. Crusted scabies is highly infectious with potentially more than a million organisms infecting a single individual. The crusting patches and gray flaky plaques may be difficult to distinguish from psoriasis or eczema and may be localized, extensively covering the hands, feet, trunk, face, and scalp. Optimal treatment for crusted scabies is not yet known, but current recommendations are combined treatment with a topical scabicide (daily dose as described above) and oral

ivermectin (200μg/kg/day) on days 1, 2, 8, 9, and 15 with additional treatments on days 22 and 29 if needed (64). Supplemental measures including washing of all bed linens, clothing towels, and other items of direct contact are essential to eliminate the infestation due to the high volume of organisms and the propensity for the flaky plaques to fall of bearing high numbers of mites. Close cropping of nails may also be of benefit. Increased rates of crusted scabies have not been described during pregnancy in the absence of underlying debilitation. Treatment of crusted scabies in pregnant women should be individualized with the use of ivermectin if clinically indicated for the health of the mother.

Malaria

Malaria is typically caused by infection with one of four protozoa, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, or *Plasmodium malariae*. Humans are infected with malaria when bitten by an *Anopheles* mosquito carrying the organism. Plasmodium sporozoites are transferred from the mosquito to the human bloodstream, where they travel to the liver and infect liver cells. Inside the liver cells, the sporozoite matures to a schizont, which then ruptures releasing merozoites that invade erythrocytes and either multiple asexually to develop a ring stage schizont (which will again rupture releasing merozoites) or develop into a gametocyte. The gametocytes can then be taken up by the *Anopheles* mosquito to begin the mosquito portion of their life cycle, which includes fertilization of the female gametocyte in the mosquito stomach, maturation in the mosquito midgut wall, and migration of the mature sporozoites to the mosquito salivary gland for injection during the next mosquito blood meal to begin the human portion of the life cycle.

Clinical symptoms of malaria are similar to those of a flu-like illness, with fever, chills, headache, myalgia, malaise, arthralgia, weakness, nausea, vomiting, and diarrhea (67). The degree of symptoms and speed of disease progression varies depending on the infecting organism (*P. falciparum* is typically most severe), the level of parasitemia, and the immune status of the individual. Symptoms can develop as quickly as 7 days or as long as 2 months following exposure. Severe infections with *P. falciparum* can progress rapidly to acute renal failure, central nervous system involvement, severe anemia, respiratory distress syndrome, and death. Malaria is estimated to cause about 1 million deaths per year, mostly due to *P. falciparum* infections in children in Africa, but there are deaths each year among developed world travelers who visit the developing world, particularly the African region. Physical finding associated with malaria include hepatomegaly, splenomegaly, fever, increased respiratory rate, weakness, and mild jaundice.

In the developed world, suspicion of malaria based on identification of potential exposure is the first key to diagnosis. Diagnosis is based on either identification of parasites in blood by microscopy or detection of malaria antigens or enzymes in blood. On microscopic examination of blood smears, the gametocyte form is typically the easiest to identify as other forms (such as ring-stage schizont) may be quite difficult to distinguish. More recently, a variety of rapid diagnostic tests (RDTs) have been developed to detect either antibodies or enzymes produced by the *Plasmodium* organisms, allowing expanded diagnosis in resource-poor settings (67). Assistance with diagnosis and treatment in the United States can be obtained from the U.S. Centers for Disease Control and Prevention (CDC, www.CDC.GOV), who maintain a malaria control hotline for emergency assistance. Outside the United States, The WHO (www.who.org) maintains guidelines for diagnosis and treatment of malaria and assists with drug procurement in the developing world.

Treatment for malaria is based on the infecting organism and the likelihood of resistance based on the location in which the infection was acquired. The WHO updated their malaria treatment guidelines (67) in 2010 to stress the need for diagnosis prior to treatment and to promote a move toward use of artemisinin-based combination therapy (ACT) as opposed to monotherapy to reduce the spread of artemisinin resistance already widely seen in Southeast Asia. In the United States, chloroquine-sensitive malaria is usually treated with chloroquine as the first-line therapy. Atovaquone–proguanil (Malarone®), artemether–lumefantrine (Coartem®), or quinine plus doxycycline or tetracycline are currently the first-line regimens for *P. falciparum* infections likely to be chloroquine resistant. Since treatment guidelines have recently been undergoing frequent modification to keep up with changing patterns of resistance, it would be advised to check the WHO or CDC Web site or other frequently updated resources for current recommendations prior to initiating treatment.

The best treatment for malaria, however, is prevention. There are a number of recommended prophylactic regimens for travel into malaria-endemic areas. Atovaquone–proguanil (Malarone) and doxycycline can be used in all areas, with chloroquine and mefloquine (Lariam®) limited to areas with no evidence of resistance and primaquine limited to areas with only *P. vivax* infections. Supplemental measures are also quite important to avoid contact with the *Anopheles* mosquito including using insecticide-treated bed nets, limiting exposed skin by wearing long pants and sleeves, using insecticide spray or lotion on exposed skin, and staying in a mosquito-resistant building in the evening when mosquitoes are most likely to bite.

Malaria in pregnancy is associated with high risk of maternal and perinatal morbidity and mortality, presumably due to impaired immune response to the infection. Increased adverse outcomes include spontaneous abortion, fetal death, preterm birth, low–birth weight infants, and maternal death (68). The increase in maternal mortality may be directly related to severe malarial infection or may be due to the impact of severe anemia-causing congestive heart failure or death due to postpartum hemorrhage. Malaria organisms can be sequestered in the placenta, where they may be resistant to treatment and may also increase fetal pathology.

Treatment of malaria in pregnancy is also impacted by type of organism and likelihood of chloroquine resistance. For chloroquine-sensitive malaria, chloroquine is the drug of choice, as it is for nonpregnant adults. For chloroquine-resistant malaria, quinine plus clindamycin is currently the first-line therapy for the first trimester due to lack of experience with either of the other first-line combinations (atovaquone–proguanil or artemether–lumefantrine, both pregnancy category C) (67,68), with the caveat that one of those regimens should be used if quinine/clindamycin is either unavailable or is not tolerated. The 2010 WHO guidelines recommend use of ACT known to be effective in the local area

after the first trimester due to the enhanced efficacy (67), whereas the CDC recommendations are to continue the use of quinine plus clindamycin throughout pregnancy unless intolerance or treatment failure is seen. Quinine is pregnancy category C and is known to cross the placenta, but extensive experience has revealed no increase in adverse pregnancy outcomes with its use. Clindamycin is pregnancy category B with no teratogenicity seen in animal studies and extensive human experience with no increase in adverse outcomes seen.

Prophylaxis for pregnant travelers is very complicated since both primaquine and doxycycline are contraindicated during pregnancy and atovaquone–proguanil is also not recommended for pregnancy use. Chloroquine is considered safe, but has little benefit in areas with extensive resistance. Mefloquine is pregnancy category C and should not be used in pregnancy unless prophylaxis for travel to an area with chloroquine resistance is absolutely needed and only after the first trimester due to animal data showing embryotoxicity (69). Supplemental measures (as discussed above) are even more important for pregnant women due to the limitations of other prevention and treatment options.

Elimination of malaria will clearly require more than treatment of symptomatic individuals and prophylaxis for travelers. Two techniques recommended by WHO are mass screening and treating of asymptomatic individuals who are infected and MDA. Mass screening and treatment requires much higher levels of resources than MDA so it is the technique most commonly employed. To date, MDA campaigns have not been able to achieve complete eradication with the exception of one closed island community with limited contact with the outside world where *P. falciparum* was eradicated rapidly (5 weeks), but it took 5 years to eradicate *P. vivax* (67). Inclusion or exclusion of pregnant women from MDA has been quite controversial due to the frequent use of drugs not commonly used in pregnancy being contrasted with the severe consequences of malarial infection during pregnancy. Reviews of data to date indicate no increase in adverse pregnancy outcome with inclusion in MDA or the more specific use of intermittent preventive therapy (IPT) targeting pregnant women [usually performed as one dose at quickening (18–20 weeks) with a second dose a month or more later (68,70)]. One key issue raised has been the importance of using highly effective drugs if MDA or IPT are to be used in pregnancy as opposed to using older, less effective, or completely ineffective drugs simply because there is more experience with them in pregnancy. Exposure to an ineffective drug in pregnancy is all risk with no benefit.

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