Protozoan Parasites

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Educational Gaps

1. Parasitic infections are traditionally considered diseases of poor countries. Although this is true for many parasitic infections, a number of infections continue to occur in developed countries and have a substantial public health impact. (1)
2. Given the global consequences and high health burden of parasitic infections, enhanced epidemiologic surveillance, better diagnostic tools, more therapeutic options, and expeditious vaccine development are still needed, despite recent advances in prevention and treatment. Further understanding of the epidemiology of these infections and their sequelae are needed to formulate public health strategies. (2)(3)

Objectives

After completing the article, the reader should be able to:

1. Appreciate the epidemiology and risk factors associated with protozoan infections.
2. Recognize clinical features of protozoan infections, identify diagnostic laboratory tests, and discuss limitations of the tests.
3. Discuss the clinical management of protozoan infections as well as preventive measures, including care of household and sexual contacts.

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INTRODUCTION

Parasitic infections continue to have a substantial socioeconomic impact and are associated with high morbidity and mortality globally, despite recent advances in prevention and treatment. The need for improved epidemiologic surveillance, more accurate diagnostic tools, newer medications to combat resistance, and faster vaccine development continues to be considerable.

In the United States, the Centers for Disease Control and Prevention (CDC) identified five "neglected parasitic infections" (NPIs) affecting a substantial number of individuals. (1) Commonalities among these infections include underrecognition due to a lack of clinical awareness and optimal diagnostic tests and limited means for therapy and prevention. This article focuses on six protozoan parasitic infections, highlighting new diagnostic tests and reviewing

epidemiology and management: cryptosporidiosis, giardiasis, amebiasis, malaria, toxoplasmosis, and trichomoniasis.

Cryptosporidiosis and giardiasis are endemic infections in the United States, predominantly seen in children in northern states during warm months in association with recreational water use. (4)(5)(6) *Cryptosporidium* sp, *Giardia lamblia,* and *Entamoeba histolytica* (amebiasis) are all intestinal parasites transmitted feco-orally via consumption of contaminated food and water and sexual activity. All three enteric parasites have a small infective dose and have been associated with outbreaks. (7) Newer tests with better sensitivity and specificity than stool microscopy are now available to aid in the diagnosis of these infections.

In the United States, immigrants and travelers from endemic areas are the most likely population to have amebiasis or malaria. (8)(9) Malaria, caused by *Plasmodium* sp, continues to claim the lives of 1300 children every day, despite a 42% decline in the global mortality rate since 2000. (10) In nonendemic areas, 15% of imported cases are seen in children, and malaria continues to pose a challenge to clinicians caring for travelers, with delays in diagnosis of up to 2 weeks. (11)

Toxoplasmosis and trichomoniasis are two of the five NPIs. (The other three parasitic infections of Chagas disease, cysticercosis, and toxocariasis are not discussed in this article.) (1) Both diseases disproportionately affect low-income populations and ethnic minorities. (2)(3) Toxoplasmosis can cause significant debilitation among affected infants and is the second most common cause of foodborne illness resulting in death. (12) Trichomoniasis is "more common than chlamydia, gonorrhea and syphilis infections combined," but control efforts have been insufficient. (3)

CRYPTOSPORIDIUM (CRYPTOSPORIDIOSIS)

Epidemiology

Cryptosporidium sp are a well-known cause of diarrhea worldwide. Two species cause most of the infections in humans: *C hominis* infects humans only, while *C parvum* also affects bovines and other mammals.

In the United States, where cryptosporidiosis is a nationally notifiable illness, 7000 to 9000 (2.5 to 2.9 per 100,000 population) cases were reported for 2009 and 2010, with most cases occurring in children 1 to 9 years of age. (4) The incidence of infection was highest in the northern states and peaked in the summer and fall, mirroring increased communal and recreational water use.

Transmission of infection is via the fecal-oral route. Numerous oocytes are shed in the stool, but as few as 10 ingested oocysts can result in infection. Furthermore, oocysts remain infectious in the environment for months. Outbreaks have been reported in recreational water facilities, child care centers, and in association with contaminated drinking water systems. (7)

Clinical Manifestations

The incubation period for cryptosporidiosis is 1 to 4 weeks, with an average of 7 days. Although asymptomatic infections occur, affected patients generally experience voluminous, nonbloody, and watery diarrhea. The clinical presentation may vary, depending on the infecting species. *C hominis* is associated with malaise, vomiting and nausea, and increased oocyst shedding and duration; *C parvum* is associated with diarrhea only. (13)

For most immunocompetent patients, cryptosporidiosis is self-limited and symptoms usually last 1 to 2 weeks. However, malnourished children or those with T-cell immunodeficiency may have a severe and protracted course that lasts for weeks to months, resulting in dehydration and death.

Atypical and extraintestinal manifestations may be seen among patients with acquired immune deficiency syndrome (AIDS). (14) Pneumatosis cystoides intestinalis, which are multiple gas-filled sacs in the intestinal wall, can lead to pneumoperitoneum. Cholecystitis, pancreatitis, and respiratory disease may also been seen.

Diagnosis

The diagnosis of cryptosporidiosis can be established by: 1) microscopic examination of stool for oocysts using modified acid-fast stain, direct immunofluorescence, or auramine phenol stain; 2) stool antigen detection via enzyme immune assay (EIA) or immunochromatography; and 3) stool molecular testing via polymerase chain reaction (PCR). Visualization is highly specific, but sensitivity is low. Antigen detection, especially with EIA, has better sensitivity and high specificity (80%–100%), is commercially available, and does not require a skilled technician, unlike oocyst visualization. PCR has both high sensitivity and specificity as well as the ability to differentiate species. However, PCR is expensive to perform.

Therapy

Therapy is usually not required among immunocompetent patients in whom the symptoms are self-limited in 1 to 2 weeks. For patients with depressed immune function, therapy may be necessary.

Nitazoxanide is the only drug for cryptosporidiosis approved by the U.S. Food and Drug Administration (FDA). It is approved for use among children at least 12

months of age; the dosing recommendations are listed in Table 1. Treatment with nitazoxanide results in decreased duration of diarrhea; most cases resolve within 3 days of therapy, and oocysts become undetectable in stools within 7 to 10 days after start of treatment. (15)

Human immunodeficiency virus (HIV)-infected patients with CD4 counts less than 200 cells/μL or immunocompromising conditions with equivalent degrees of T-cell function are at highest risk for severe and prolonged infection. Nitazoxanide may be ineffective in this population. (14) Restoration of immune status with use of antiretroviral therapy or withdrawal of immunosuppressing medications is necessary for treatment.

Prevention

Regulatory changes leading to enhanced treatment of surface water supplies and prevention of transmission through drinking water were made following the cryptosporidiosis outbreak in Wisconsin in 1993. Ground water supplies are also required to have additional treatment and filtration. (4)

Travelers to high-risk areas or those who intend to drink untreated water sources (eg, hikers, campers) are advised to boil water for at least 1 minute or use water filters certified by the National Safety Foundation (Table 2).

Cryptosporidium sp are resistant to chlorination. Avoidance of swallowing water when in swimming pools, river, or lakes is advised. Those who have been recently infected with cryptosporidiosis should not swim in recreational water for at least 2 weeks after the resolution of diarrhea.

Other preventive measures include washing of hands and raw foods, barrier protection during oral-anal sex, and avoidance of contact with human and animal feces.

GIARDIA LAMBLIA (GIARDIASIS)

Epidemiology

G lamblia, also known as *G intestinalis* or *G duodenalis,* causes giardiasis and is one of the common parasitic enteropathogens worldwide. In the United States, it is the most common intestinal parasitic infection, with 19,000 cases reported annually. The highest number of cases occurs in the northeast states among children ages 1 to 9 years during the summer. (5)

Ingestion of as few as 10 cysts can result in infection. Infected humans and animals may contaminate water and food products with fecal matter. Outbreaks have occurred in child care settings and in association with contaminated water supplies. (7)

Clinical Manifestations

Infected individuals may remain asymptomatic or may exhibit acute or chronic symptoms. The incubation period is 1 to 4 weeks. An infected individual presents with acute watery, nonbloody, foul-smelling, and greasy diarrhea; abdominal distention; and anorexia with or without fever. Symptoms usually last 1 week, but infective cysts may be shed for months. Occasionally, symptoms become chronic, resulting in bouts of diarrhea for months to years and resulting malabsorption and failure to thrive.

Extraintestinal and postinfectious complications with giardiasis have been described and include cholecystitis, ocular pathologies, allergies, reactive arthritis, myopathy, and irritable bowel syndrome. (16)

Diagnosis

Visualization of cysts or trophozoites in the stool with trichrome stain has a sensitivity of 70%. To improve sensitivity, the test may be repeated thrice on separate days

TABLE 1. **Therapy for Cryptosporidiosis and Giardiasis**

MEDICATION	CHILDREN	ADULTS	DURATION (DAYS)
Cryptosporidiosis			
Nitazoxanide	1–3 y: 100 mg every 12 h 4–11 y: 200 mg every 12 h ≥12 y: 500 mg every 12 h	500 mg every 12 h	3
Giardiasis			
Nitazoxanide	1–3 y: 100 mg every 12 h 4–11 y: 200 mg every 12 h ≥12 y: 500 mg every 12 h	500 mg every 12 h	3
Tinidazole	50 mg/kg single dose (maximum 2 g)	2 g single dose	—
Metronidazole	5 mg/kg/dose every 8 h	250 mg every 8 h	5–7

TABLE 2. **Resources**

Cryptosporidiosis	
• Specific recommendations for water filter	http://www.cdc.gov/parasites/crypto/gen_info/filters.html
Giardiasis	
• Prevention of infection	http://www.cdc.gov/parasites/giardia/prevention-control.html
Malaria	
• Malaria, by country	http://www.cdc.gov/malaria/travelers/country_table/a.html
• Drug selection, dosing, duration	http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf
• Prophylaxis	http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria
Toxoplasmosis	
• Recommended temperature for cooking meat	http://www.foodsafety.gov/keep/charts/mintemp.html

in a week. Medications (eg, antibiotics, antacids, laxatives, enema) that may alter the morphology of the parasites should be withheld for 3 days.

Stool antigen testing with either immunofluorescence assay or EIA has sensitivity and specificity of 85% to 100% and is available commercially.

When the stool test results are negative and suspicion for giardiasis remains high, string test, duodenal aspiration, or duodenal biopsy may be employed.

Therapy

Therapy is not routinely administered to asymptomatic individuals. For those who are symptomatic, metronidazole administered for 5 to 7 days or a single dose of tinidazole has a cure rate of greater than 85%. Nitazoxanide is administered for 3 days. Although metronidazole is often used, only tinidazole and nitazoxanide are approved by the FDA for this indication (Table 1).

In cases of relapse, the recommendation is to repeat administration of the same drug. Patients with frequent infections should be evaluated for repeated exposures and immunodeficiency (hypogammaglobulinemia and combined variable immunodeficiency).

Prevention

In addition to sanitation and proper hygiene, children should be excluded from child care until asymptomatic and refrain from swimming for 1 week. Boiling, filtration, or treatment of water is recommended for campers and hikers. Barrier protection during oral-anal sex is recommended. Specific recommendations for prevention of infection are available at the CDC website (Table 2).

ENTAMOEBA HISTOLYTICA (AMEBIASIS)

Epidemiology

E histolytica and *E dispar* are morphologically similar but genetically different species. *E histolytica* is considered invasive and pathogenic while *E dispar* is not. This distinction was recognized in the 1990s and has implications for diagnosis and management.

As with giardiasis and cryptosporidiosis, feco-oral transmission of *E histolytica* occurs with ingestion of contaminated food and water or via sexual activity. Ingested cysts undergo excystation to become trophozoites, which then multiply by binary fission to produce more cysts. Trophozoites may colonize the large bowel or may invade tissue and induce cell destruction. Cysts survive in the environment for weeks to months and are responsible for transmission. As few as 10 cysts (or less) can cause infection.

Amebiasis accounts for an estimated 100,000 annual deaths worldwide. It is considered endemic in Central and South America, Africa, and Asia. In the United States, immigrants and travelers from endemic areas, institutionalized persons with poor sanitary conditions, and men who have sex with men are considered at high risk for amebiasis. (8)

Clinical Manifestations

Most infected people remain asymptomatic; only 10% manifest symptoms within 2 to 4 weeks, although some may take years to become ill after ingestion of cysts. Asymptomatic infected individuals may excrete cysts intermittently for years.

Intestinal and extraintestinal diseases may be seen among symptomatic patients (Table 3). Intestinal disease can range from diarrhea to a more severe and complicated

TABLE 3. **Clinical Manifestations and Recommended Therapy for Amebiasis**

CLINICAL MANIFESTATION	THERAPY
Asymptomatic infection with *Entamoeba histolytica*	Intraluminal agent • Paromomycin (× 7 days) Children/adult: 25–35 mg/kg per day divided into 3 doses • Iodoquinol (× 20 days) Children: 30–40 mg/kg per day (maximum 2 g) divided into 3 doses Adults: 650 mg every 8 h • Diloxanide furoate (× 10 days) Children: 20 mg/kg per day divided into 3 doses Adults: 500 mg every 8 h
Intestinal disease • Dysentery • Necrotizing colitis • Toxic megacolon • Ameboma	• Metronidazole (×7–10 days) Children: 35–50 mg/kg per day divided into 3 doses Adults: 500–750 mg every 8 h • Tinidazole (× 3–5 days) Children: 50 mg/kg every 24 h (maximum 2 g) Adults: 2 g every 24 h *followed by* Intraluminal agent (same dose as above)
Extraintestinal diseases • Liver abscess • Pericardial, pleural, or peritoneal involvement • Brain abscess • Cutaneous amebiasis	Metronidazole or tinidazole (same dose as above) *followed by* Intraluminal agent (same dose as above)

presentation, including amebomas. An ameboma, also called an amebic granuloma, is a mass that develops from inflammation of the colon and can be mistaken for a tumor. Patients with amebic colitis usually present with gradual progression over several weeks of diarrhea (bloody in 70% of patients) and abdominal pain; only 10% may develop fever. (8)

The most common extraintestinal manifestation is hepatic abscess, 90% of which are located in the right lobe. Affected patients present with fever (>85%), abdominal pain (>84%), and hepatomegaly (>30%). (8) Hepatic abscesses may rupture in about 20% of cases, leading to pleural, peritoneal, or pericardial involvement with associated high mortality. Patients with amebic colitis and neurologic symptoms may have brain abscess from hematogenous spread. Cutaneous amebiasis may result from prolonged exposure to the tissue-invasive trophozoites excreted in the feces, extension of a ruptured appendiceal or liver abscess, or through direct infection of the skin.

Diagnosis

Traditionally, stool examination for cysts and trophozoites has been used for diagnosis. However, stool examination is unable to differentiate nonpathogenic *Entamoeba* sp (*E dispar* and possibly *E moshkovskii*) from *E histolytica*. In addition, its sensitivity is poor, missing almost two-thirds of cases. The current recommendation is to use the commercially available *E histolytica*-specific antigen test on fresh stool samples to differentiate *E histolytica* from *E dispar*. Stool molecular and isoenzyme analysis have better specificity but are not readily available.

Serum antibodies to *E histolytica*, detected by EIA, are present in more than 70% of patients with colitis and extraintestinal diseases as well as 10% of patients with asymptomatic infection. The presence of antibodies, however, does not differentiate between past or acute infection. In acute cases where amebiasis is highly suspected, testing should be repeated in 1 to 2 weeks to check for seroconversion. Visualization of trophozoites on tissue biopsies is considered the gold standard for diagnosis.

Therapy

Therapy for *Entamoeba* depends on the species and degree of involvement (Table 3). Asymptomatic intestinal colonization with *E dispar* does not require treatment. In contrast,

colonization with *E histolytica* requires treatment due to the high risk for invasive illness and potential transmission (Table 3).

Invasive illnesses are treated with the nitroimidazoles metronidazole or tinidazole. Compared to metronidazole, tinidazole is better tolerated and administered for a shorter duration (Table 3). These drugs are absorbed well after oral administration and are ineffective for intraluminal clearance of infection.

As many as 60% of patients may have persistent intraluminal parasites, despite therapy with these drugs. Intraluminal agents must be used following therapy with imidazoles to avoid recurrences and decrease transmission. Intraluminal agents used for therapy include paromomycin, iodoquinol, and diloxanide furoate (Table 3). These agents are poorly absorbed from the gastrointestinal tract and attain high intraluminal concentrations. Diloxanide furoate is not readily available commercially in the United States.

Adjunctive therapy for invasive illness may include drainage of abscesses, especially if there is no clinical response after 72 hours of therapy.

Prevention

Testing of contacts or household members of patients with amebiasis is recommended, as is treatment of asymptomatic infections. Barrier protection during sexual activity is also recommended.

Travelers to endemic areas should boil drinking water for at least 1 minute. As with cryptosporidiosis, use of a water filter with an absolute pore size of 1 micron or smaller is recommended. Fruits should be peeled and vegetables washed thoroughly.

PLASMODIUM (MALARIA)

Epidemiology

Plasmodium sp long known to cause malaria in humans include *P falciparum*, *P malariae*, *P vivax,* and *P ovale*. The 2004 outbreak in Borneo and subsequent reports of human infections led to recognition of a fifth malaria-causing species: *P knowlesi*. The nocturnal-feeding *Anopheles* mosquitoes transmit these parasites.

P falciparum, predominately found in sub-Saharan Africa, is considered the most lethal of all parasites (not just protozoans). *P vivax* is found primarily in Asia and South America, while *P ovale* is most common in Africa. *P malaria* has wide distribution and can be found in Africa, South America, and Asia. *P knowlesi* is found in Southeast Asia. In contrast to the other *Plasmodium* sp, *P knowlesi* and *P falciparum* cause rapidly progressive, severe malaria.

An estimated 3.4 billion people are at risk for malaria. Malaria continues to be one of the leading causes of death in developing countries. In 2012, there were approximately 627,000 malaria deaths. (10) Ninety percent of the deaths occurred in sub-Saharan Africa and were caused by *P falciparum*.

In the United States, aggressive efforts in the 1950s led to the elimination of malaria. However, *Anopheles* sp are still prevalent in the southern states, raising the possibility of reemergence of malaria. In the United States, 1500 to 2000 cases are diagnosed annually. (9) Most are imported, with 75% occurring in United States residents who have a history of recent travel to endemic areas and 25% in residents of other countries. Fifteen percent of cases occurred in children younger than age 18 years. In addition, mosquitoes inadvertently carried by airlines may transmit *Plasmodium* sp to humans in and around international airports in nonendemic areas, resulting in a condition known as "airport" malaria. Other modes of acquisition are laboratory-acquired, transfusion-related, and congenitally transmitted.

Clinical Manifestations

After a mosquito bite, most nonimmune individuals become symptomatic within 1 to 4 weeks. Delayed diagnosis has been seen in patients who took antimalarial prophylaxis drugs and in patients infected with *P vivax* and *P ovale*. Both *P vivax* and *P ovale* have a dormant stage in the liver, with relapses occurring months to years later.

Initial symptoms of malaria are nonspecific and include flulike symptoms of fever, chills, headache, and myalgia. As the disease progresses, febrile paroxysms related to the release of the merozoites from the red blood cells may be appreciated every 48 hours for *P falciparum*, *P vivax,* and *P ovale* and every 72 hours for *P malariae*. Abdominal pain, jaundice, and hepatosplenomegaly may also be seen.

Malaria can be categorized as either uncomplicated or severe. Disease severity depends on the *Plasmodium* sp, prior exposure, and immune status of the patient. Severe illness is associated with *P falciparum*, pregnancy, young age, and hyperparasitemia (>5%). The World Health Organization (WHO) defines clinical and laboratory criteria for severe illness (Table 4). (17) Compared to adults, children with severe malaria are more likely to have shorter duration of illness (2 vs 7 days), convulsions, neurologic sequelae, and invasive bacterial infection. (17)

TABLE 4. **Clinical and Laboratory Features of Severe Malaria According to the World Health Organization (17)**

CLINICAL FEATURES	LABORATORY FEATURES
• Impaired consciousness (including unarousable coma)	• Hypoglycemia (<40 mg/dL [<2.2 mmol/L]) • Metabolic acidosis (plasma bicarbonate <15 mEq/L [15 mmol/L])
• Prostration, ie, generalized weakness so that the patient is unable to sit, stand, or walk without assistance	• Severe normocytic anemia (hemoglobin <5 g/dL [50 g/L], packed red blood cell volume <15% in children; hemoglobin <7 g/dL [70 g/L], packed red blood cell volume <20% in adults) • Hemoglobinuria • Hyperlactatemia (lactate >45.1 mg/dL [>5 mmol/L])
• Multiple convulsions: >2 episodes within 24 h	• Renal impairment (serum creatinine >3 mg/dL [>265 μmol/L]) • Pulmonary edema (radiologic)
• Deep breathing and respiratory distress (acidotic breathing)	
• Acute pulmonary edema and acute respiratory distress syndrome	
• Circulatory collapse or shock; systolic blood pressure <80 mm Hg in adults and <50 mm Hg in children	
• Acute kidney injury	
• Clinical jaundice plus evidence of other vital organ dysfunction	
• Abnormal bleeding	

Diagnosis

Microscopy with thick and thin blood smears is the mainstay for establishing the diagnosis and is a helpful indicator of severity of infection and response to treatment. Because of the greater concentration of blood, stained thick blood film has better sensitivity in detecting infection, especially in low-level parasitemia, while stained thin blood film is used for speciation. These tests should be repeated every 12 to 24 hours for three sets to increase sensitivity. The primary drawback for these tests is the need for skilled personnel.

Rapid diagnostic test (RDT), used in resource-poor countries, was approved by the FDA in 2007. This test, which detects specific malaria antigens, has the ability to detect infections due to *P falciparum* and *P vivax* rapidly, and based on limited data, *P ovale* and *P malaria* as well. RDT may not be able to detect infection when there is low-level parasitemia. Regardless of the result (positive or negative), RDTs should be confirmed by microscopy, with subsequent parasite load count if positive.

Molecular tests are especially useful in confirming the species, but these tests are not widely available. Detection of antibodies to *Plasmodium* indicates past exposure but not current infection.

Therapy

Management approach depends on disease severity, the patient's ability to tolerate medications, drug resistance, and species. Most uncomplicated cases can be treated on an outpatient basis with oral medications. Patients with severe disease should be hospitalized for immediate administration of medication and aggressive supportive care. The CDC no longer recommends exchange transfusion (ET) for patients with greater than 10% parasitemia or end-organ damage because this therapy results in no difference in outcome between those treated and those not treated.

Patients who are unable to tolerate oral antimalarial medications or those who have severe malaria are given intravenous quinine with clindamycin, doxycycline, or tetracycline. Intravenous therapy is continued until patients can tolerate oral medications. Because infusion with quinine may result in cardiac arrhythmias, hypotension, and hypoglycemia, patients are admitted to intensive

care units for frequent monitoring. In the United States, quinine is the only FDA-approved medication for treatment of severe malaria. However, artesunate, which is now the WHO-preferred medication for severe malaria, can be obtained from the CDC under an investigational new drug protocol.

Chloroquine is the drug of choice for patients able to tolerate oral medication who have uncomplicated infection acquired from chloroquine-sensitive areas. Those from areas with chloroquine resistance may be given: 1) atovaquone-proguanil; 2) artemether-lumefantrine; 3) quinine plus doxycycline, tetracycline, or clindamycin; or 4) mefloquine.

For infections caused by *P vivax* or *P ovale*, primaquine should be administered concurrently with the previously mentioned choices to eradicate dormant forms in the liver. Patients should be tested for glucose-6-phosphate dehydrogenase deficiency before administration of primaquine.

Detailed information on drug selection, dosing, and duration is available at the CDC website (Table 2).

Prevention

Travelers to endemic areas should take precautions to prevent mosquito bites through avoidance of outdoor nocturnal activities, use of physical barriers such as bed nets and long-sleeved shirts, and use of insect repellants.

Choice of chemoprophylaxis is based on predominant species, drug resistance in the area, patient age, and tolerance to medication. The CDC provides information on malaria per country and the recommended prophylaxis per country (Table 2).

TOXOPLASMA GONDII (TOXOPLASMOSIS)

Epidemiology

Toxoplasmosis is caused by the intracellular parasite *T gondii*. This parasite exists in three forms: trophozoite, bradyzoite, and sporozoite. Each form plays a role in transmission. The rapidly multiplying trophozoites invade cells during infection, the bradyzoites are present in tissue cysts and slowly multiply, and the sporozoites are present in oocysts. Cats are the definitive host, with one seroprevalence study showing 48% of cats having antibodies to *T gondii*. (18) Other animals, including birds, rats, pigs, cows, and chickens, become intermediate hosts after ingestion of the oocysts and harbor *T gondii* in tissue cysts. Free-range chickens, pigs, and wild game have a higher prevalence of *Toxoplasma* infection due to easy access to contaminated food, water, and infected wildlife. (19)

Humans acquire infection primarily by ingestion of oocysts through contaminated food or water or by consumption of raw meat containing *T gondii* in tissue cysts. Together with *Salmonella* and *Listeria*, *Toxoplasma* is one of the top three causes of foodborne illness resulting in death. (12) Other modes of acquiring infection include transplacental transmission to the fetus and receipt of transplanted organ or blood from infected donors.

Seroprevalence among countries varies, with the highest seen in South America and some parts of Asia (>60%). In the United States, the seroprevalence has been declining, with 11% of women of childbearing age infected with *Toxoplasma*. The decrease is believed to be related to multiple factors, including improved reduction in cysts in meat products, intensified education on proper cooking of meat and disposal of cat wastes, use of meat-enhancing solutions (salt solutions added to meat to improve taste and texture and to prolong half-life) that inactivate the tissue cysts, and increased use of frozen meals (deep freezing also inactivates the cysts). (20) The highest seroprevalence is seen among African-Americans, Hispanics, immigrants, and those from low-income populations. (2)(20)

Clinical Manifestations

Immunocompetent patients who become infected are generally asymptomatic. Twenty percent may have flulike illness or develop nontender, nonsuppurative cervical lymphadenopathy. Symptoms are usually self-limiting over 6 weeks.

Ocular toxoplasmosis or retinochoroiditis can lead to blindness and may occur as a result of congenital infection or postnatally acquired infection. Affected individuals may be asymptomatic, complain of eye pain, have reduced vision, develop floaters (spots in vision), or have strabismus or leukocoria. (21)

Among immunocompromised patients, such as those with HIV infection, a newly acquired or reactivated infection may result in encephalitis, myocarditis, pneumonitis, and hepatitis. Ocular toxoplasmosis in these patients is usually fulminant and has a poor prognosis despite treatment. *Toxoplasma*-seropositive HIV-infected patients with a CD4 count less than 100 cells/μL have a 30% chance of reactivation.

Women who acquire the infection during pregnancy are usually asymptomatic. Unfortunately, infection acquired during pregnancy carries an overall 30% risk of transmission to the fetus. Timing of acquisition of infection correlates with the risk of transmission to the fetus: 6% when infection is acquired at 13 weeks of gestation, increasing to 40% at 26 weeks and 72% at 36 weeks. (22) Transmission

occurring at an earlier gestational age results in a more severely affected fetus.

Clinical presentation varies widely in the affected fetus and may range from asymptomatic infection to fetal death. The triad of chorioretinitis, hydrocephalus, and intracranial calcifications is highly suggestive of congenital toxoplasmosis. Other manifestations include chorioretinitis, hypotonia, spasticity, seizures, pneumonitis, pericarditis, hepatosplenomegaly, jaundice, petechiae, and growth restriction. Long-term complications include neurodevelopmental delay, blindness, and deafness. Congenitally infected patients may have chorioretinitis many years later as a result of reactivation.

Association of *Toxoplasma* infection with neuropsychiatric conditions such as schizophrenia and depression has been suggested, but a clear relationship has yet to be established. (23)

Diagnosis

Toxoplasmosis is diagnosed by serology, PCR, parasite isolation, or histology.

Although helpful in establishing acute or past infection, serology has limitations. Serum immunoglobulin (Ig)M is positive during primary infection, but it can remain positive up to 2 years, making precise determination of timing of infection acquisition difficult. In addition, rates of false-positive results can be as high as 60% in tests performed by nonreference laboratories. A positive IgM test result should be confirmed through a reference laboratory. Serum IgA and IgE antibodies may also be positive during acute infection and can last for weeks to months.

Serum IgG antibodies appear about 1 to 2 weeks after infection and persist for the person's lifetime. Seropositivity indicates risk for reactivation. To further approximate the time of infection acquisition, *Toxoplasma* IgG avidity may be conducted. The strength of attachment of IgG to the antigen develops over time following infection. Thus, the presence of high-avidity IgG indicates that primary infection occurred more than 5 months before.

Determining the timing of infection is particularly important because women who acquire primary infection during pregnancy are at higher risk of perinatal transmission and may benefit from prenatal treatment. In contrast, those who acquired the infection before conception are less likely to transmit it and do not require therapy.

Parasites may also be detected via PCR in tissues, amniotic fluid, or fetal blood. Isolation of the parasite via inoculation of mice or tissue culture indicates acute infection.

Ocular toxoplasmosis is suspected based on the presence of necrotizing retinitis next to a pigmented retinochoroidal scar. (21)

Therapy

Immunocompetent patients with asymptomatic infection or mild symptoms such as lymphadenopathy or flulike illness are usually not treated unless the symptoms are severe or persistent.

Therapy for chorioretinitis is based on severity of inflammation and distance between the lesions and the optic disk or fovea. Among immunocompetent patients, spontaneous resolution occurs within 1 to 2 months. (21)

Immunocompromised patients with toxoplasmosis are usually treated with pyrimethamine, sulfadiazine, and leucovorin for 4 to 6 weeks after resolution of symptoms, followed by lifetime secondary prophylaxis or until immunosuppression has resolved.

Although data to support effectiveness are limited, treatment is recommended for women who have acute infection during pregnancy to prevent transmission or decrease sequelae to the fetus. (2) Choice of therapy depends on the fetal gestational age and whether transplacental transmission has already occurred. Spiramycin is usually given if gestational age is less than 18 weeks and there is no evidence of fetal infection (by amniotic fluid PCR and absence of fetal abnormalities on ultrasonography). Combination therapy with pyrimethamine, sulfadiazine, and leucovorin is administered for later gestation or if there is evidence of fetal infection. Spiramycin is considered an investigational drug in the United States and is available through the FDA investigational new drug process. Infants who are congenitally infected are given pyrimethamine, sulfadiazine, and leucovorin for 1 year to mitigate sequelae associated with congenital infection.

Treatments used for toxoplasmosis are often associated with toxicities that can render implementation of therapy much more difficult. Bone marrow suppression, rash, and nausea may occur with pyrimethamine. Leucovorin is administered to reverse pyrimethamine-associated bone marrow suppression. Hepatitis, renal dysfunction, rash, leucopenia, vomiting, and diarrhea may occur with sulfadiazine.

Prevention

Pregnant women should avoid exposure to cat feces. The cat litter box should be changed daily because oocysts require 1 to 5 days to sporulate and become infective. In other countries such as France, universal screening for toxoplasmosis among pregnant women is

undertaken to facilitate earlier treatment during pregnancy. Such screening is not standard practice in the United States.

Food safety practices should include thorough washing of fruits and vegetables and avoidance of consumption of raw or undercooked meat. Cooking meat products at specific temperatures is recommended (Table 2).

Primary prophylaxis with trimethoprim-sulfamethoxazole or dapsone-pyrimethamine and leucovorin is given to toxoplasma-seropositive HIV-infected patients with CD4 counts less than 100 cells/μL.

TRICHOMONAS VAGINALIS (TRICHOMONIASIS)

Epidemiology

Trichomoniasis, caused by the protozoan parasite *T vaginalis*, is the most common nonviral sexually transmitted infection in the world, with an estimated 248 million new cases annually. (24)

In the United States, 1.1 million new cases occur annually, affecting 2.3 million women and 1.4 million men. Although most infections are asymptomatic and not life-threatening, health-related problems with trichomoniasis are now increasingly recognized, and its true public health burden may have been long overlooked. (3)(25) Health concerns include: increased risk of acquiring HIV and other sexually transmitted infections, increased risk of perinatal HIV transmission, preterm delivery, male and female infertility, and prostate cancer. (25) The poor and minorities are disproportionately affected. (3)

Clinical Manifestations

Most women with trichomoniasis are asymptomatic. Symptomatic women may have malodorous vaginal or urethral yellow-green discharge, vaginal itching, or dysuria. On physical examination, the cervix may be inflamed and show a "strawberry" appearance.

Ten percent of infected men may have urethritis presenting with dysuria or mucopurulent discharge.

Trichomoniasis in children can occur with sexual abuse or in newborns following transmission during delivery. Female newborns of mothers with trichomoniasis may have vaginal discharge. Over time, the parasites are unable to survive in the nonacidic vaginal environment of the newborn; spontaneous resolution of discharge occurs over several weeks without complications. Respiratory disease has been reported in both male and female newborns.

Diagnosis

Wet mount examination of freshly collected vaginal discharge may show the classic jerky movement of *T vaginalis*. However, this test has a sensitivity of only 50% to 70%. Culture of vaginal discharge, urine, or semen is considered the gold standard and is highly specific. Results may not be available for up to 1 week, and the test requires special transport and culture media.

Three available tests use newer techniques for detection: immunochromatographic capillary-flow enzyme immunoassay dipstick, nucleic acid probe test, and transcription-mediated amplification. These tests have faster turnaround time (minutes to a few hours) with improved sensitivity while maintaining specificity at 95% to 100%. At this time, these tests are only FDA-approved for use in specimens from females.

The Papanicolaou test may incidentally show *Trichomonas*, but it is not recommended as a screening tool because of poor sensitivity.

Therapy

The nitroimidazoles are the only FDA-approved medication for treatment of trichomoniasis. A 2-g single oral dose of either metronidazole or tinidazole is first-line therapy. If initial therapy is unsuccessful and no reinfection has occurred, use of metronidazole 500 mg orally twice a day for 7 days is recommended. In cases of second-course treatment failure, a 5- to 7-day course of high-dose (2 g daily) tinidazole or metronidazole may be considered. (25)

Metronidazole intravaginal gel is not recommended due to poor efficacy (<50%). Desensitization therapy is recommended for patients with true hypersensitivity reaction to the nitroimidazoles. (25)

Prevention

Trichomoniasis reinfection is common. Therefore, partners should be screened and treated and patients and partners should abstain from sex until both are treated and are asymptomatic. Use of condoms also helps prevent infection.

Summary

- Stool antigen detection for *Cryptosporidium* sp, *Giardia lamblia* and *Entamoeba histolytica* are now commercially available, have better sensitivity and specificity than the traditional stool microscopy, and are less dependent on personnel skill. Tests employing newer techniques with faster turnaround time are also available for diagnosing trichomoniasis.
- Nitazoxanide, the only U.S. Food and Drug Administration-approved medication for therapy of cryptosporidiosis, is effective among immunocompetent patients. However, on the basis of strong evidence from multiple clinical trials, nitazoxanide is considered ineffective among immunocompromised patients. (14)
- Giardiasis can be asymptomatic or have a chronic course leading to malabsorption and failure to thrive. It can be treated with metronidazole, tinidazole, or nitazoxanide. On the basis of growing observational studies, postinfectious and extraintestinal manifestations of giardiasis occur, but the mechanisms are unclear. Given the high prevalence of giardiasis, public health implications need to be defined. (16)
- Eradicating *E histolytica* from the gastrointestinal tract requires only intraluminal agent therapy. Therapy for invasive illnesses requires use of imidazole followed by intraluminal agents to eliminate persistent intraluminal parasites.
- Malaria is considered the most lethal parasitic infection, with *Plasmodium falciparum* as the predominant cause of mortality. *P vivax* and *P ovale* can be dormant in the liver, and primaquine is necessary to resolve infection by *P vivax* and *P ovale*.
- Among immunocompetent patients, infection with *Toxoplasma gondii* may be asymptomatic, involve localized lymphadenopathy, or cause ocular infection. In immunocompromised patients, reactivation or severe infection is not uncommon. On the basis of limited observational studies (there are no well-controlled randomized trials), therapy is recommended for acute infection during pregnancy to prevent transmission to the fetus/infant or decrease infectious sequelae to the fetus. (2)
- On the basis of growing research evidence as well as consensus, trichomoniasis is associated with many health-related concerns, including adverse pregnancy outcomes and increased risk of acquisition and transmission of human immunodeficiency virus. (3)(25) Similar to toxoplasmosis, many infections are asymptomatic, and the true public health impact of trichomoniasis is difficult to define. Further research is warranted. (2)(3)

CME quiz and references for this article are at http://pedsinreview.aappublications.org/content/37/2/59.

Parent Resources from the AAP at HealthyChildren.org

- Tips for Treating Viruses, Fungi, and Parasites: https://www.healthychildren.org/English/health-issues/conditions/treatments/Pages/Tips-For-Treating-Viruses-Fungi-and-Parasites.aspx
- Spanish: https://www.healthychildren.org/Spanish/health-issues/conditions/treatments/Paginas/Tips-For-Treating-Viruses-Fungi-and-Parasites.aspx

PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

1. A 9-year-old girl presents to your office with a 1-week history of intermittent watery, nonbloody diarrhea and malaise. Her mother tells you that the girl has had abdominal cramps and bloating associated with the diarrhea and the stools have been foul-smelling and greasy-appearing. She has also had nausea and a poor appetite. The family recently went hiking and camping. They report that they were filtering their drinking water during the trip. You perform stool antigen testing to confirm that the child has giardiasis. Which of the following is(are) the best drug(s) for the treatment for acute giardiasis?
    A. Praziquantel plus nitazoxanide.
    B. Metronidazole.
    C. Quinine plus doxycycline.
    D. Pyrantel pamoate.
    E. Ivermectin.
2. An otherwise healthy 7-year-old girl presents to your office with a 1-month history of vague abdominal complaints. She has a history of recent vacation travel to Central America. The parents deny that the girl has had any fever, vomiting, and diarrhea, although she has complained of some intermittent nausea. Her appetite has been normal and there has been no weight loss. The discomfort does not awaken her during sleep and she has been attending school regularly. On physical examination, she has normal vital signs for age. Her abdominal examination results are normal, without tenderness or hepatosplenomegaly. The parents insist that her stool be tested. You agree to send a stool sample for culture and antigen testing. An antigen test is positive for *Entamoeba histolytica*. Which of the following is the next best step in management?
    A. Asymptomatic intestinal colonization with *E histolytica* does not require treatment.
    B. Because antigen testing does not accurately distinguish *E histolytica* from *E dispar*, stool examination should be performed.
    C. Colonization with *E histolytica* needs to be treated due to the high risk for invasive illness and potential transmission.
    D. Microscopy with thick and thin blood smears is the mainstay for establishing the diagnosis.
    E. Treatment for *E histolytica* is only necessary when there are extraintestinal manifestations.
3. One of your medical students returns from a trip to rural Guatemala where she was learning medical Spanish. She has been home from Guatemala for 4 days and tells you that since the flight home she has had intermittent fevers and flulike symptoms. She admits to you that she forgot to take her antimalarial drugs while she was there. What is the best way to make the diagnosis of malaria in this individual?
    A. Blood culture.
    B. Detection of antibodies to *Plasmodium* in blood.
    C. Microscopy with thick and thin blood smears.
    D. Obtain a serum specimen for immunoglobulin (Ig)M and IgG testing.
    E. Polymerase chain reaction of blood.
4. You are examining a 1-day-old newborn in the neonatal intensive care unit. The baby had intrauterine growth restriction and had a brief seizure shortly after birth. Head ultrasonography revealed hydrocephalus and a follow-up computed tomography scan showed intracranial calcifications. Ophthalmologic examination showed chorioretinitis. Serologic examination suggests that the baby has been infected with *Toxoplasma*. Which of the following is the next best step in management?

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2016 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

A. Artesunate, which is now the World Health Organization-preferred medication for congenital toxoplasmosis, can be obtained from the Centers for Disease Control and Prevention for infants with congenital infection.
B. For those who have symptoms, metronidazole administered for 5 to 7 days or tinidazole given as a onetime dose works well and has a cure rate of greater than 85%.
C. Infants who are congenitally infected are given pyrimethamine, sulfadiazine, and leucovorin for 1 year to mitigate sequelae associated with congenital infection.
D. Nitazoxanide is the only drug for toxoplasmosis approved by the U.S. Food and Drug Administration for children younger than age 1 year.
E. Toxoplasmosis should not be treated with any drugs if it was acquired during pregnancy.

5. A 17-year-old sexually active female presents to your office with a 1-week history of vaginal itching and malodorous vaginal discharge that she describes as yellow-green. She has been afebrile but reports dysuria. On physical examination, the cervix appears inflamed and has a "strawberry" appearance. You suspect trichomoniasis. Of the following, which is the best method of diagnosing trichomoniasis in this patient?

A. Culture of vaginal discharge or urine.
B. Performing a Papanicolaou test on cervical secretions.
C. Stool antigen testing.
D. Urine culture.
E. Wet mount examination of freshly collected vaginal discharge.

Protozoan Parasites

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