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Toxoplasma Infections ■ ■DEFINITION Toxoplasmosis is caused by infection with the obligate intracellular parasite Toxoplasma gondii. Acute infection acquired after birth is typi cally asymptomatic, but some immunocompetent individuals can pres ent with systemic or ocular disease. Acute infection is thought to result in the lifelong chronic persistence of cysts in the host's tissues. The classic presentation of toxoplasmosis is encephalitis in immunocom promised individuals (especially HIV-positive individuals or transplant recipients) in whom latent infection has reactivated. Among the clini cal manifestations of the disease are lymphadenopathy, encephalitis, myocarditis, pneumonitis, and retinitis. Congenital toxoplasmosis is an infection of newborns that results from the transplacental passage of parasites from an infected mother to the fetus. These infants may be asymptomatic at birth, but many children later manifest signs and symptoms, including chorioretinitis, strabismus, epilepsy, and psycho motor retardation. Toxoplasmosis can also present as acute disease (typically chorioretinitis) associated with food- or waterborne sources. ■ ■ETIOLOGY T. gondii is an intracellular coccidian that infects both birds and mam mals. Up to a third of the world's population is thought to be infected latently with this organism. There are two distinct stages in the life cycle that are transmissible to humans (Fig. 235-1). Tissue cysts that contain bradyzoites are transmitted in undercooked meat. After an intermediate host (e.g., a human, mouse, sheep, pig) ingests the cyst, it is rapidly digested by the acidic-pH gastric secretions. Sporulated oocysts that contain sporozoites are products of the sexual cycle in feline intestines and acquired by ingestion of food or water contami nated with infected cat feces. Bradyzoites or sporozoites are released, enter the intestinal epithelium, and transform into rapidly dividing Intermediate host: birds, mammals, humans Bradyzoites encyst within the CNS and muscle of the infected host. Oocysts are excreted in cat feces. Contaminated soil is ingested by birds, mammals, and humans. Definitive host FIGURE 235-1 Life cycle of Toxoplasma gondii. The cat is the definitive host in which the sexual phase of the cycle is completed. Oocysts shed in cat feces can infect a wide range of animals, including birds, rodents, grazing domestic animals, and humans. The bradyzoites found in the muscle of food animals may infect humans who eat insufficiently cooked meat products, particularly lamb and pork. Although human disease can take many forms, congenital infection and encephalitis from reactivation of latent infection in the brains of immunosuppressed persons are the most important manifestations. CNS, central nervous system. (Courtesy of Dominique Buzoni-Gatel, Institut Pasteur, Paris.)

tachyzoites. The tachyzoites can infect and replicate in all mammalian cells except red blood cells. The parasite actively penetrates the cell and forms a parasitophorous vacuole. Parasite replication continues within the vacuole. After the parasites reach a critical mass, intracellular sig naling within the host and the parasite results in parasite egress from the vacuole. The host cell is destroyed, and the released tachyzoites infect adjoining cells. Parasites can disseminate throughout the body as free tachyzoites or within phagocytic cells in the bloodstream or via lymphatics. Tachyzoites actively invade host cells and can cross epithelial and endothelial barriers.

The tachyzoite replication cycle within an infected organ causes cytopathology and clinical symptoms. Most tachyzoites are eliminated by the host's humoral and cell-mediated immune responses. Tissue cysts containing bradyzoites develop 7–10 days after systemic tachyzo ite infection. These tissue cysts occur in various host organs but persist principally within the central nervous system (CNS) and muscle. The development of this chronic stage completes the asexual portion of the life cycle. Active infection in the immunocompromised host is usu ally due to the spontaneous release of encysted parasites that undergo rapid transformation into tachyzoites within the CNS that cannot be contained by the immune system. The sexual stage in the life cycle takes place in the cat (the defini tive host) and is defined by the formation of oocysts within the feline host intestine. This enteroepithelial cycle begins with the ingestion of the bradyzoite tissue cysts and, after several intermediate stages, culminates in the production of gametes. Gamete fusion produces a zygote, which envelops itself in a rigid wall and is secreted in the feces as an unsporulated oocyst. After 2–3 days of exposure to air at ambient temperature, the noninfectious oocyst sporulates to produce eight sporozoite progeny. The sporulated oocyst can be ingested by an intermediate host. It is in the intermediate host that T. gondii completes its life cycle. CHAPTER 235 Sporulated oocysts are environmentally hardy and very infectious; they are thought to be sources of waterborne outbreaks such as those reported in Victoria (British Columbia, Canada) and in South Amer ica. In the Northern Hemisphere, T. gondii strains are predominantly of three genotypes. Strains found in South and Central America are more Toxoplasma Infections virulent than those from the Northern

Hemisphere, are frequently of the type I virulent genotype or atypical geno types, and are more likely to be associ ated with symptomatic disease, usually ocular posterior uveitis. Ocular toxo plasmosis should be considered in a person from Central or South America

with ocular symptoms and retinal abnormalities. Severe disease, includ ing sepsis, fever of unknown origin, and pneumonia, has been reported and should be considered in a patient with travel history to South or Central America. There have been reports of outbreaks in North America among individuals who have ingested under cooked game, especially venison, and these strains appear more virulent as the attack rate is often high. Prevalence of T. gondii in Africa suggests T. gondii infection is common and that some strains may also be quite virulent. Tachyzoites infect all nucleated cells in the host, replicate, and cause tissue damage. Toxoplasmic encephalitis ■ ■EPIDEMIOLOGY T. gondii infects a wide range of mam mals and birds. Its seroprevalence depends on the locale and the age of the population. Generally, hot arid climatic conditions are associated with a low prevalence of infection. In the United States and most European

countries, the seroprevalence increases with age and exposure. In the United States, seroprevalence has steadily decreased, with 11% of individuals >6 years old having serologic

evidence of Toxoplasma exposure in a 2011–2014 survey, with foreign-born Americans having a higher rate of seroprevalence. In most other regions of the world, the seroprevalence is higher, with a seroprevalence as high as 78% reported in Brazil. Because of increased awareness of foodborne infections, the prevalence of seropositivity has decreased worldwide over the past two decades, although it remains very high in Central and South America.

■ ■TRANSMISSION Oral Transmission Most cases of human Toxoplasma infection are thought to be acquired by the oral route. Transmission can be attribut able to ingestion of sporulated oocysts from contaminated soil, food, or water. During acute feline infection, a cat may excrete as many as 100 million oocysts per day. These sporozoite-containing oocysts are highly infectious and may remain viable for many years in soil or water. Humans infected during an oocyst-transmitted infection develop stage-specific antibodies to the oocyst/sporozoite. Children and adults also acquire infection from tissue cysts contain ing bradyzoites. Undercooking or insufficient freezing of meat is an important source of infection in the developed world. Toxoplasmosis has been associated with eating raw or undercooked food including ground beef, lamb, or venison or drinking unpasteurized goat milk. More recent epidemiologic studies have associated acute infections with ingestion of untreated water or shellfish (oysters, mussels, and clams). Transmission via Blood or Organs In addition to being trans mitted orally, T. gondii can be transmitted directly from a seropositive donor to a seronegative recipient in a transplanted heart, heart–lung, kidney, liver, or pancreas. Viable parasites can be cultured from refrig erated anticoagulated blood, which may be a source of infection in individuals receiving blood transfusions. T. gondii reactivation has been reported in bone marrow, hematopoietic stem cell, and liver transplant recipients as well as in individuals with AIDS. Finally, laboratory personnel can be infected after contact with contaminated needles or glassware or with infected tissue. PART 5 Infectious Diseases Transplacental Transmission On average, about one-third of all women who acquire infection with T. gondii during pregnancy transmit the parasite to the fetus; the remainder give birth to normal, uninfected babies. Of the various factors that influence fetal outcome, gestational age at the time of infection is the most critical (see below). Recrudescent maternal infection is rarely the source of congenital disease, although rare cases of transmission by immunocompromised women (e.g., those infected with HIV or those receiving high-dose glu cocorticoids) have been reported. Thus, women who are seropositive before pregnancy usually are protected against acute infection and do not give birth to congenitally infected neonates. There is essentially no risk for congenital infection if the mother becomes infected ≥6 months before conception. If infection is acquired <6 months before conception, the likelihood of transplacental infection increases as the interval between infection and conception decreases. Women with documented acute toxoplasmosis should be counseled to use appropriate measures to prevent pregnancy for 6 months after infection. In pregnancy, if the mother becomes infected during the first trimester, the incidence of transplacental infection is lowest (~15%), but the disease in the neonate is most severe. If maternal infection occurs during the third trimester, the incidence of transplacental infec tion is greatest (65%), but the infant is usually asymptomatic at birth. Infected infants who are normal at birth may have a higher incidence of learning disabilities and chronic neurologic sequelae than uninfected children. Only a small proportion (20%) of women infected with

T. gondii develop clinical signs of infection. Often the diagnosis is first appreciated when routine postconception serologic tests show evidence of specific antibody. Chronic toxoplasmosis has not been thought to affect pregnancy, but there have been recent studies suggesting a greater

incidence of adverse pregnancy outcomes without evidence of

reactivated toxoplasmosis. The lingering effects of chronic infection are controversial (see below) and an area of ongoing investigation. ■ ■PATHOGENESIS Upon the host's ingestion of either tissue cysts containing bradyzoites or oocysts containing sporozoites, the parasites are released from the cysts by the digestive process. Bradyzoites are resistant to the effect of pepsin and invade the host's gastrointestinal tract. Within enterocytes (or other gut-associated cells), the parasites undergo morphologic transformation, giving rise to invasive tachyzoites. From the gastroin testinal tract, parasites disseminate to a variety of organs, particularly lymphatic tissue, skeletal muscle, myocardium, retina, placenta, and the CNS. At these sites, the parasite infects host cells, replicates, and invades the adjoining cells. In this fashion, the hallmarks of the infec tion develop: cell death and focal necrosis surrounded by an acute inflammatory response. In the immunocompetent host, both the humoral and the cellular immune responses control infection; parasite virulence and tissue tropism may be strain specific. Tachyzoites are sequestered by a variety of immune mechanisms, including induction of parasiticidal antibody, activation of macrophages with radical intermediates, production of interferon γ (IFN-γ), and stimulation of CD8+ cytotoxic T lym phocytes. These antigen-specific lymphocytes are capable of killing both extracellular parasites and target cells infected with parasites. As tachyzoites are cleared from the acutely infected host, tissue cysts con taining bradyzoites begin to appear, usually within the CNS, skeletal muscle, and the retina. Toxoplasma secretes signaling molecules into infected host cells, and these molecules modulate host gene expression, host metabolism, and host immune response. It was initially thought that cysts with bradyzoites are not eliminated by the immune system, but more recent studies in the murine model indicate that both CD8+ T cells and alternatively activated macrophages are able to kill cysts in vivo. The ability to eliminate cysts may depend on the genetic back ground of the infected host as well as the parasite genotype that initially infected the host. Immunocompromised or fetal hosts lack the immune factors neces sary to control the spread of tachyzoite infection. This altered immune state allows the persistence of tachyzoites and gives rise to progressive focal destruction in affected organs (i.e., necrotizing encephalitis, pneumonia, and myocarditis). It is thought that all infected individuals have persistent infection with cysts containing bradyzoites with lifelong infection remaining sub clinical. Although bradyzoites are in a slow metabolic phase, bradyzoites can replicate, and cysts do rupture within the CNS. These subclinical cycles of cyst ruptures followed by development of new bradyzoitecontaining cysts are the probable source of recrudescent infection in immunocompromised individuals and the most likely stimulus for the persistence of antibody titers in the immunocompetent host. The persistence of toxoplasmosis has been hypothesized to be a contributing factor to a variety of neuropsychiatric conditions, includ ing schizophrenia and bipolar disease, but the contribution of chronic toxoplasmosis to human disease remains controversial. In rodents, chronic T. gondii infection has significant effects on behavior, increas ing predation. Epidemiologic studies such as the National Health and Nutrition Examination Survey (NHANES) study show a correlation between T. gondii seropositivity and a number of chronic diseases, including diabetes and cognitive dysfunction. ■ ■PATHOLOGY Cell death and focal necrosis due to replicating tachyzoites induce an intense mononuclear inflammatory response in any tissue or cell type infected. Tachyzoites rarely can be visualized by routine histo pathologic staining of these inflammatory lesions. However, immu nofluorescent staining with parasitic antigen–specific antibodies can reveal the organism. In contrast to the inflammatory process caused by tachyzoites, bradyzoite-containing cysts cause inflammation only at the early stages of development. Once the

cysts reach maturity, the inflam matory process is blunted, and the cysts remain relatively immunologi cally quiescent within the brain matrix until they rupture.

Lymph Nodes During acute infection, lymph node biopsy dem onstrates characteristic findings, including follicular hyperplasia and irregular clusters of tissue macrophages with eosinophilic cytoplasm. Granulomas rarely are evident in these specimens. Although tachyzo ites are not usually visible, parasites can be demonstrated by subinocu lation of infected tissue into mice, with resultant disease, or by PCR. PCR amplification of DNA fragments of Toxoplasma genes is effective and sensitive in establishing lymph node infection by tachyzoites. Eyes In the eye, infiltrates of monocytes, lymphocytes, and plasma cells may produce uni- or multifocal lesions. Granulomatous lesions and retinochoroiditis can be observed in the posterior chamber after acute necrotizing retinitis. Other ocular complications include irido cyclitis, cataracts, and glaucoma. T. gondii is the most common cause of posterior uveitis in immunocompetent individuals and ocular toxo plasmosis is a common clinical presentation in outbreaks. Central Nervous System During CNS involvement, both focal and diffuse meningoencephalitis can be documented, with evidence of necrosis and microglial nodules. Necrotizing encephalitis in patients without AIDS is characterized by small diffuse lesions with perivas cular cuffing in contiguous areas. In the AIDS population, polymor phonuclear leukocytes may be present in addition to monocytes, lymphocytes, and plasma cells. Cysts containing bradyzoites frequently are found contiguous with the necrotic tissue border. As a conse quence of antiretroviral therapy (ART) for AIDS, the incidence of toxoplasmosis has decreased in the developed world. The incidence of toxoplasmosis in underresourced settings is not known due to lack of diagnostic infrastructure but is likely to be higher than in the United States, particularly in regions of the world with populations with large numbers of untreated patients living with HIV. Lungs and Heart Among patients with AIDS who die of toxoplas mosis, 40–70% have involvement of the lungs and heart. Interstitial pneumonitis can develop in neonates and immunocompromised patients and rarely in immunocompetent individuals. Thickened and edematous alveolar septa infiltrated with mononuclear and plasma cells are apparent. This inflammation may extend to the endothelial walls. Tachyzoites and bradyzoite-containing cysts have been observed within the alveolar membrane. Superimposed bronchopneumonia can be caused by other microbial agents. Cysts and aggregates of parasites in cardiac muscle tissue are evident in patients with AIDS who die of toxoplasmosis. Focal necrosis surrounded by inflammatory cells is associated with hyaline necrosis and disrupted myocardial cells. Pericardi tis is associated with toxoplasmosis in some patients. Gastrointestinal Tract Rare cases of human gastrointestinal tract infection with T. gondii have presented as ulcerations in the mucosa. Acute infection in certain strains of inbred mice (C57BL/6) results in lethal ileitis within 7–9 days. This inflammatory bowel disease has been recognized in several other mammalian species, including pigs and nonhuman primates. Other Sites Pathologic changes during disseminated infection are similar to those described for the lymph nodes, eyes, and CNS. In patients with AIDS, the skeletal muscle, pancreas, stomach, and kidneys can be involved, with necrosis, invasion by inflammatory cells, and (rarely) tachyzoites detectable by routine staining. Large necrotic lesions may cause direct tissue destruction. In addition, secondary effects from acute infection of these various organs, including pancreatitis, myositis, and glomerulonephritis, have been reported. ■ ■HOST IMMUNE RESPONSE Acute Toxoplasma infection evokes a cascade of protective immune responses in the immunocompetent host. Toxoplasma enters the host at the gut mucosal level and evokes a mucosal immune response that includes the production of antigen-specific secretory IgA. Titers of serum IgA antibody directed at the tachyzoite surface antigen p30/ SAG1 are a useful marker for

congenital and acute toxoplasmosis. Within the host, T. gondii rapidly induces detectable levels of both IgM and IgG serum antibodies. Monoclonal gammopathy of the IgG

class can occur in congenitally infected infants. IgM levels may be increased in newborns with congenital infection. The polyclonal IgG antibodies evoked by infection are parasiticidal in vitro in the pres ence of serum complement and are the basis for the Sabin-Feldman dye test. However, cell-mediated immunity is the major protective response evoked by the parasite during host infection. Macrophages are activated after phagocytosis of antibody-opsonized parasites. If the parasite is not phagocytosed and enters the macrophage, monocytes, or dendritic cells by active penetration, these “Trojan horses” repre sent a mechanism for transport and dissemination to distant organs. Toxoplasma stimulates a robust interleukin (IL) 12 response by human dendritic cells.

The CD4+ and CD8+ T-cell responses are antigen-specific and fur ther stimulate the production of a variety of important lymphokines that expand the T-cell and natural killer cell repertoire. T. gondii is a potent inducer of a TH1 phenotype, with IL-12 and IFN-γ playing an essential role in the control of the parasites’ growth in the host. Regula tion of the inflammatory response is at least partially under the control of a TH2 response that includes the production of IL-4 and IL-10 in seropositive individuals. Human T-cell clones of both the CD4+ and the CD8+ phenotypes are cytolytic against parasite-infected macro phages. These T-cell clones produce cytokines that are “microbistatic.” IL-18, IL-7, and IL-15 upregulate the production of IFN-γ and may be important during acute and chronic infection. The effect of IFN-γ may be paradoxical, with stimulation of a host downregulatory response as well. Although T. gondii infection is believed to be recrudescent in patients with AIDS or other immunocompromised states, antibody titers are not useful in establishing reactivation or in following the activity of infection. An absence of positive serologies suggests an alter native diagnosis, although AIDS patients may have borderline positive or low serologies and transplant patients treated with immunosuppres sive agents including those specific for B cells may become seronega tive. T cells from AIDS patients with reactivation of toxoplasmosis fail to secrete both IFN-γ and IL-2. This alteration in the production of these critical immune cytokines contributes to the persistence of infection. Toxoplasma infection develops late in the course of AIDS (CD4+ count <100/μL), when the loss of T cell–dependent protective mechanisms, particularly CD8+ T cells, becomes most pronounced. CHAPTER 235 Toxoplasma Infections ■ ■CLINICAL MANIFESTATIONS In persons whose immune systems are intact, acute toxoplasmosis is usually asymptomatic and self-limited. This condition can go unrec ognized in 80–90% of adults and children with acquired infection. The asymptomatic nature of this infection makes diagnosis difficult in mothers infected during pregnancy. In contrast, the wide range of clinical manifestations in congenitally infected children includes severe neurologic complications such as hydrocephalus, microcephaly, intellectual disability, and chorioretinitis. If prenatal infection is severe, multiorgan failure and subsequent intrauterine fetal death can occur. In children and adults, chronic infection can persist throughout life, with little consequence to the immunocompetent host. Toxoplasmosis in Immunocompetent Patients The most common manifestation of acute toxoplasmosis is cervical lymphade nopathy. The nodes may be single or multiple, are usually nontender, are discrete, and vary in firmness. Lymphadenopathy also may be found in suboccipital, supraclavicular, inguinal, and mediastinal areas. Generalized lymphadenopathy occurs in 20–30% of symptomatic patients. Between 20 and 40% of patients with lymphadenopathy also have headache, malaise, fatigue, and fever (usually with a temperature of <40°C [<104°F]). A smaller proportion of symptomatic

individu als have myalgia, sore throat, abdominal pain, maculopapular rash, meningoencephalitis, and confusion. Rare complications associated with infection in the normal immune host include pneumonia, myocarditis, encephalopathy, pericarditis, and polymyositis. These manifestations are often associated with more virulent parasitic genotypes/strains. Signs and symptoms associated with acute infection usually resolve within several weeks, although

the lymphadenopathy may persist for some months. In one epidemic, toxoplasmosis was diagnosed correctly in only 3 of the 25 patients who consulted physicians. If toxoplasmosis is considered in the differential diagnosis, routine laboratory and serologic screening should precede node biopsy.

In North America and Europe, there are three predominant geno types, but strains are more genetically diverse in Central and South America. Genotypes of T. gondii prevalent in South America are more virulent than those typically seen in North America or Europe. These genotypes may be associated with acute or recurrent ocular disease in immunocompetent individuals and have also been associated with pneumonitis and a fulminant sepsis picture in immunologically nor mal individuals. Thus, a detailed history, particularly regarding travel and countries of residence, is critical for establishing a diagnosis. Indi viduals from South or Central America may have frequent recurrences of ocular toxoplasmosis that may require treatment and suppressive therapy. The results of routine laboratory studies are usually unremarkable except for minimal lymphocytosis, an elevated erythrocyte sedimenta tion rate, and a nominal increase in serum aminotransferase levels. Evaluation of cerebrospinal fluid (CSF) in cases with evidence of encephalopathy or meningoencephalitis shows an elevation of intra cranial pressure, mononuclear pleocytosis (10–50 cells/mL), a slight increase in protein concentration, and (occasionally) an increase in the gamma globulin level. PCR amplification of the Toxoplasma DNA target sequence in CSF is specific for active toxoplasmosis, but not sensitive. PCR of ocular fluid or bronchoalveolar lavage may also be positive in those with ocular or pulmonary toxoplasmosis, respectively. The CSF of chronically infected individuals is normal. PART 5 Infectious Diseases Infection of Immunocompromised Patients Patients with AIDS, transplant patients, and those receiving immunosuppressive therapy for lymphoproliferative disorders are at greatest risk for devel oping acute toxoplasmosis. Toxoplasmosis has also been reported after treatment with antibodies to tumor necrosis factor. The infection may be due either to reactivation of latent infection or to acquisition of parasites from exogenous sources such as blood or transplanted organs. In individuals with AIDS, >95% of cases of Toxoplasma encephalitis (TE) are believed to be due to recrudescent infection. In most of these cases, encephalitis develops when the CD4+ T-cell count falls below 100/μL. In immunocompromised hosts, the disease may be rapidly fatal if untreated. Thus, accurate diagnosis and initiation of appropriate therapy are necessary to prevent fulminant infection. Toxoplasmosis is a principal opportunistic infection of the CNS in persons with AIDS. Individuals with AIDS who are seropositive for T. gondii are at high risk for encephalitis. Before the advent of highly effective ART, about one-third of the 15–40% of adult AIDS patients in the United States who were latently infected with T. gondii devel oped TE. TE may still be a presenting infection in individuals who are unaware of their positive HIV status. Individuals may be at relatively high risk for reactivation after allo geneic hematopoietic stem cell transplantation (HSCT), particularly if complicated by graft-versus-host reaction. Weekly PCR screening of blood from patients seroposi tive prior to HSCT is recommended, although not all centers routinely monitor HSCT patients for toxoplasmosis. Screening Toxoplasma serolo gies (donor and recipient) before transplantation identifies patients

potentially at risk for reactivated toxoplasmosis. Serologies should be performed prior to initiation of immunosuppressive agents. The signs and symptoms of acute toxoplas mosis in immunocompromised patients princi pally involve the CNS (Fig. 235-2). More than 50% of patients with clinical manifestations have intracerebral involvement. Clinical findings at presentation range from nonfocal to focal dys function. CNS findings include encephalopathy, meningoencephalitis, and mass lesions. Patients FIGURE 235-2 Toxoplasmic encephalitis in a 36-year-old patient with AIDS. The multiple lesions are demonstrated by magnetic resonance imaging scanning (T1-weighted with gadolinium enhancement). (Courtesy of Clifford Eskey, Dartmouth Hitchcock Medical Center, Hanover, NH; with permission.)

may present with altered mental status (75%), fever (10–72%), seizures (33%), headaches (56%), and focal neurologic findings (60%), includ ing motor deficits, cranial nerve palsies, movement disorders, dysmet ria, visual-field loss, and aphasia. Patients who present with evidence of diffuse cortical dysfunction develop evidence of focal neurologic disease as infection progresses. This altered condition is due not only to the necrotizing encephalitis caused by direct invasion by the parasite but also to secondary effects, including vasculitis, edema, and hemor rhage. The onset of infection can range from an insidious process over several weeks to an acute presentation with fulminant focal deficits, including hemiparesis, hemiplegia, visual-field defects, localized head ache, and focal seizures. Although lesions can occur anywhere in the CNS, the areas most often involved appear to be the brainstem, basal ganglia, pituitary gland, and corticomedullary junction. Brainstem involvement gives rise to a variety of neurologic dysfunctions, including cranial nerve palsy, dysmetria, and ataxia. With basal ganglion infection, patients may develop hydrocephalus, choreiform movements, and choreo athetosis. Toxoplasma usually causes encephalitis, and meningeal involvement is uncommon. CSF findings may be unremarkable or may include a modest increase in cell count and in protein—but not glucose—concentration. Cerebral toxoplasmosis must be differentiated from other oppor tunistic infections or tumors in the CNS of AIDS patients. The dif ferential diagnosis includes herpes simplex encephalitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Involvement of the pituitary gland can give rise to panhypopituitarism and hyponatremia from inappropriate secretion of vasopressin (antidiuretic hormone). HIV-associated neurocognitive disorder (HAND) may present as cognitive impairment, attention loss, and altered memory. Brain biopsy in patients who have been treated for TE but who continue to exhibit neurologic dysfunction often fails to identify organisms. Autopsies of Toxoplasma-infected patients have demonstrated the involvement of multiple organs, including the lungs, gastrointestinal tract, pancreas, skin, eyes, heart, and liver. Toxoplasma pneumonia can be confused with Pneumocystis pneumonia. Respiratory involvement usually presents as dyspnea, fever, and a nonproductive cough and may rapidly progress to acute respiratory failure with hemoptysis, metabolic acidosis, hypotension, and (occasionally) disseminated intravascular coagulation. Histopathologic studies demonstrate necrosis and a mixed cellular infiltrate. The presence of organisms is a helpful diagnostic indicator, but organisms can also be found in healthy tissue. Infection of the heart is usually asymptomatic but can be associated with cardiac tamponade or biventricular failure. Infections of the gastrointestinal tract and the liver have been documented. Congenital Toxoplasmosis Between 400 and 4000 infants born each year in the United States are affected by congenital toxoplasmo sis. Acute infection in mothers acquiring T. gondii during pregnancy is usually asymptomatic; most women are diagnosed via prenatal serologic screening. Infection of the placenta leads to hematogenous

infection of the fetus. As gestation proceeds, the proportion of fetuses that become infected increases, but the clinical severity of the infection declines. Although infected children may initially be asymptomatic, the persistence of T. gondii can result in reactivation and clinical disease—most frequently chorioretinitis—decades later. Factors asso ciated with relatively severe disabilities include delays in diagnosis and in initiation of therapy, neonatal hypoxia and hypoglycemia, profound visual impairment (see “Ocular Infection,” below), uncorrected hydro cephalus, and increased intracranial pressure. If treated appropriately, upward of 70% of children have normal developmental, neurologic, and ophthalmologic findings at follow-up evaluations. Treatment for 1 year with pyrimethamine, a sulfonamide, and folinic acid is tolerated with minimal toxicity (see “Treatment,” below). Ocular Infection Infection with T. gondii is estimated to cause 35% of all cases of chorioretinitis in the United States and Europe. It was formerly thought that the majority of cases of ocular disease were due to congenital infection. Ocular toxoplasmosis in immunocompetent individuals occurs more commonly than was previously appreciated and has been associated with outbreaks traced to oocyst contamination of soil or water in Victoria (British Columbia) and in South America. Outbreaks have also been reported in North America after ingestion of undercooked venison. A variety of ocular manifestations are documented, including blurred vision, scotoma, photophobia, and eye pain. Macular involve ment occurs, with loss of central vision, and nystagmus is secondary to poor fixation. Involvement of the extraocular muscles may lead to dis orders of convergence and to strabismus. Ophthalmologic examination should be undertaken in newborns with suspected congenital infec tion. As the inflammation resolves, vision improves, but episodic flareups of chorioretinitis, which progressively destroy retinal tissue and lead to glaucoma, are common. The ophthalmologic examination reveals yellow-white, cotton-like patches with indistinct margins of hyperemia. As the lesions age, white plaques with distinct borders and black spots within the retinal pigment become more apparent. Lesions usually are located near the posterior pole of the retina; they may be single but are more commonly multiple. Congenital lesions may be unilateral or bilateral and show evidence of massive chorioretinal degeneration with extensive fibrosis. Surrounding these areas of involvement are a normal retina and vasculature. In patients with AIDS, retinal lesions are often large, with diffuse retinal necrosis, and include both free tachyzoites and cysts containing bradyzoites. Toxoplasmic chorioretinitis may be a prodrome to the development of encephalitis. ■ ■DIAGNOSIS Tissue and Body Fluids The differential diagnosis of acute toxo plasmosis can be made by appropriate culture, serologic testing, and PCR (Table 235-1). PCR is the mainstay for detection of organisms in tissue or biological fluids, but a negative PCR does not rule out toxoplasmosis. Isolation or PCR of T. gondii from the patient’s body fluids (blood, CSF, or bronchoalveolar lavage) reflects acute infection, whereas isolation from biopsied tissue is an indication only of the presence of tissue cysts and should not be misinterpreted as evidence of acute toxoplasmosis. Persistent parasitemia in patients with latent, asymptomatic infection is rare. Histologic examination of lymph nodes may suggest the characteristic changes described above. Demonstra tion of tachyzoites in lymph nodes establishes the diagnosis of acute toxoplasmosis. Histologic demonstration of cysts containing brady zoites confirms prior infection with T. gondii but may represent latent rather than acute infection. Serology Serologic testing has become the routine method of diag nosis. Diagnosis of acute infection with T. gondii can be established by detection of the simultaneous presence of IgG and IgM antibodies to Toxoplasma in serum. The presence of circulating IgA favors the diagnosis of an acute infection. The Sabin-Feldman dye test, the indi rect fluorescent antibody test, and the enzyme-linked immunosorbent assay (ELISA) all measure circulating IgG antibody to Toxoplasma. Positive IgG titers (>1:10) can be detected as early as 2–3 weeks after

TABLE 235-1 Differential Laboratory Diagnosis of Toxoplasmosis DISTINGUISHING CHARACTERISTICS CLINICAL SETTING ALTERNATIVE DIAGNOSIS Mononucleosis syndrome Epstein-Barr virus infection Serology/PCR Cytomegalovirus infection PCR/viral load/serology HIV infection Serology/antigen/viral load Bartonella infection (catscratch disease) Biopsy (PCR or culture)/ serology Lymphoma Biopsy Congenital infection Cytomegalovirus infection PCR Herpes simplex virus infection PCR Rubella virus infection Serology Syphilis Serology Listeriosis Bacterial culture Chorioretinitis in immunocompetent individual Tuberculosis Bacterial culture/PCR Syphilis Serology Histoplasmosis Serology/culture/antigen Chorioretinitis in AIDS patient Cytomegalovirus infection Characteristic exam Syphilis Serology Herpes simplex virus infection PCR CHAPTER 235 Varicella-zoster virus infection PCR Fungal infection PCR/culture CNS lesions in AIDS patient Lymphoma or metastatic tumor Tissue biopsy Brain abscess Culture/biopsy Toxoplasma Infections Progressive multifocal leukoencephalopathy PCR for JC virus Fungal infection Antigen/PCR/biopsy/ culture Mycobacterial infection PCR/biopsy/culture Abbreviations: CNS, central nervous system; PCR, polymerase chain reaction. Source: Reproduced with permission from JD Schwartzman: Toxoplasmosis, in Principles and Practice of Clinical Parasitology. Hoboken, Wiley; 2001. infection. These titers usually peak at 6–8 weeks and decline slowly to a new baseline level that persists for life. Antibody avidity increases with time and can be useful in difficult cases during pregnancy for establishing when infection may have occurred. The serum IgM titer should be measured in concert with the IgG titer to better establish the time of infection; either the double-sandwich IgM-ELISA or the IgM-immunosorbent assay (IgM-ISAGA) should be used. Both assays are specific and sensitive, with fewer false-positive results than other commercial tests. The double-sandwich IgA-ELISA is more sensitive than the IgM-ELISA for detecting congenital infection in the fetus and newborn. Although a negative IgM result with a positive IgG titer indicates distant infection, IgM can persist for >1 year and should not necessarily be considered a reflection of acute disease. If acute toxo plasmosis is suspected, a more extensive panel of serologic tests can be performed. In the United States, testing is available at the Remington Laboratory for Specialty Diagnostics (https://www.sutterhealth.org/ services/lab-pathology/toxoplasma-serology-laboratory). Molecular Diagnostics Molecular approaches can directly detect T. gondii in biologic samples independent of the serologic response. Results obtained with PCR have high specificity and clini cal utility in the diagnosis of toxoplasmosis but may only be available in specialty laboratories. While very specific, depending on the body fluid type tested, the sensitivity of PCR of body fluids may be low, so diagnostic algorithms typically incorporate serologic testing of blood

or body fluids. Real-time PCR, if available, can provide quantitative results. Molecular epidemiologic studies with polymorphic mark ers have been useful in correlating clinical signs and symptoms of disease with different T. gondii genotypes that may vary in virulence. Next-generation sequencing approaches (metagenomics) of blood or body fluids are often useful, particularly in immunocompromised individuals.

The Immunocompetent Adult or Child For the patient who presents with lymphadenopathy only, a positive IgM titer is an indi cation of acute infection—and an indication for therapy, if clinically warranted (see “Treatment,” below). The serum IgM titer should be determined again in 3 weeks. An elevation in the IgG titer without an increase in the IgM titer suggests that infection is present but is not acute. If there is a borderline increase in either IgG or IgM, the titers should be reassessed in 3–4 weeks. The Immunocompromised Host A presumptive clinical diag nosis of TE in patients with AIDS is based on clinical presentation, history of exposure (as evidenced by positive

serology), and radiologic evaluation. To detect latent infection with T. gondii, HIV-infected persons should be tested for IgG antibody to Toxoplasma soon after HIV infection is diagnosed. When these criteria are used, the predic tive value is as high as 80%. More than 97% of patients with AIDS and toxoplasmosis have IgG antibody to T. gondii in serum. IgM serum antibody usually is not detectable. Although IgG titers do not correlate with active infection, serologic evidence of infection almost always precedes the development of TE. It is therefore important to determine the Toxoplasma antibody status of all patients infected with HIV. Anti body titers may range from negative to 1:1024 in patients with AIDS and TE. Fewer than 3% of patients have no demonstrable antibody to Toxoplasma at diagnosis of TE. PART 5 Infectious Diseases Patients with TE have focal or multifocal abnormalities demon strable by computed tomography (CT) or magnetic resonance imag ing (MRI). Neuroradiologic evaluation should include double-dose contrast CT of the head. By this test, single and frequently multiple contrast-enhancing lesions (<2 cm) may be identified. MRI usually demonstrates multiple lesions located in both hemispheres, with the basal ganglia and corticomedullary junction most commonly involved; MRI provides a more sensitive evaluation of the efficacy of therapy than does CT (Fig. 235-2). These findings are not pathog nomonic of Toxoplasma infection, because 40% of CNS lymphomas are multifocal and 50% are ring-enhancing. For both MRI and CT scans, the rate of false-negative results is ~10%. The finding of a single lesion on an MRI scan increases the likelihood of primary CNS lymphoma (in which solitary lesions are four times more likely than in TE) and strengthens the argument for the performance of a brain biopsy. A therapeutic trial of anti-Toxoplasma medications is frequently used to assess the diagnosis. Treatment of presumptive TE with pyrimethamine plus sulfadiazine or clindamycin results in quantifiable clinical improvement in >50% of patients by day 3. Leucovorin is administered to prevent bone marrow toxicity. By day 7, >90% of treated patients show evidence of improvement. In contrast, if patients fail to respond or have lymphoma, clinical signs and symptoms worsen by day 7. Patients in this category require brain biopsy with or without a change in therapy. This procedure can now be performed by a stereotactic CT-guided method that reduces the potential for complications. Brain biopsy for T. gondii identifies organisms in 50–75% of cases. PCR amplification of CSF may also confirm toxoplasmosis or suggest alternative diagnoses (Table 235-1), such as progressive multifocal leukoencephalopathy (JC virus posi tive) or primary CNS lymphoma (Epstein-Barr virus positive). CT and MRI with contrast are currently the standard diagnostic imaging tests for TE. As in other conditions, the radiologic response may lag behind the clinical response. Resolution of lesions may take from 3 weeks to 6 months. Some patients show clinical improvement despite worsening radiographic findings. Congenital Infection The issue of concern when a pregnant woman has evidence of recent T. gondii infection is whether the fetus

is infected. PCR analysis of the amniotic fluid has replaced fetal blood sampling. Serologic diagnosis is based on the persistence of IgG anti body or a positive IgM titer after the first week of life (a time frame that excludes placental leak). The IgG determination should be repeated every 2 months. An increase in IgM beyond the first week of life is indicative of acute infection. Up to 25% of infected newborns may be seronegative and have normal routine physical examinations. Thus, assessment of the eye and the brain, with ophthalmologic testing, CSF evaluation, and radiologic studies, is important in establishing the diagnosis. Ocular Toxoplasmosis The serum antibody titer may not cor relate with the presence of active lesions in the fundus, particularly in cases of congenital toxoplasmosis. In general, a positive IgG titer (measured in undiluted serum if necessary) in conjunction with typical lesions establishes the diagnosis. If lesions are atypical and the serum antibody titer is in the low-positive range, the diagnosis is presump tive. The parasitic

antigen–specific polyclonal IgG assay as well as parasite–specific PCR may facilitate the diagnosis. PCR of ocular samples has better yield than PCR of blood, but negative PCR does not rule out the diagnosis. Diagnosis may also be established by ocular fluid Western blot or comparison of ocular fluid antibody with blood antibody (Goldmann-Witmer coefficient). The clinical diagnosis of ocular toxoplasmosis can be supported in 60–90% of cases by labora tory tests, depending on the time of anterior chamber puncture and the panel of antibody analyses used. TREATMENT Toxoplasmosis CONGENITAL INFECTION Congenitally infected neonates are treated with daily oral pyri methamine (1 mg/kg) and sulfadiazine (100 mg/kg) with folinic acid for 1 year. Depending on the signs and symptoms, prednisone (1 mg/kg per day) may be used for congenital infection. Some U.S. states and some countries routinely screen pregnant women (France, Austria) and/or newborns (Denmark, Massachusetts). Management and treatment regimens vary with the country and the treatment center. Most experts use spiramycin to treat preg nant women who have acute toxoplasmosis early in pregnancy and use pyrimethamine/sulfadiazine/folinic acid to treat women who seroconvert after 18 weeks of pregnancy or in cases of documented fetal infection. Studies suggest that treatment during pregnancy decreases the severity of infection. Many women who are infected in the first trimester elect termination of pregnancy. Those who do not terminate pregnancy are offered prenatal anti biotic therapy to reduce the frequency and severity of Toxoplasma infection in the infant. The optimal duration of treatment for a child with asymptomatic congenital toxoplasmosis is not clear, although most clinicians in the United States would treat the child for 1 year in light of cohort investigations conducted by the National Collaborative Chicago-Based, Congenital Toxoplasmosis Study. INFECTION IN IMMUNOCOMPETENT PATIENTS Immunologically competent adults and older children who have only lymphadenopathy do not require specific therapy unless they have persistent, severe symptoms. Patients with ocular toxoplas mosis are usually treated for 6 weeks with pyrimethamine plus either sulfadiazine or clindamycin and sometimes with prednisone. Trimethoprim-sulfamethoxazole (TMP-SMX) can also be given if pyrimethamine cannot be obtained (5 mg/kg bid based on TMP). Treatment should be supervised by an ophthalmologist familiar with Toxoplasma disease. Ocular disease can be self-limited without treatment, but therapy is typically considered for lesions that are severe or close to the fovea or optic disc. Prolonged treatment with TMP-SMX prevents recurrences of ocular toxoplasmosis while on treatment and is often considered in individuals with frequent flares

in a 1- to 2-year period. Flares are more common in individuals who have acquired infection in South America. Whether treatment improves long-term visual outcomes is unclear. Other clinical pre sentations of toxoplasmosis in immunocompetent individuals are treated 2–4 weeks with duration and decision to treat based upon response and severity of clinical symptoms. INFECTION IN IMMUNOCOMPROMISED PATIENTS Clinical Treatment Immunocompromised patients, such as patients with AIDS and/or transplant recipients, should be treated for acute toxoplasmosis as toxoplasmosis is rapidly fatal if untreated. The recommended treatment is pyrimethamine (200 mg load, 50 mg/d if <60 kg, 75 mg/d if >60 kg) plus sulfadiazine (1000 mg qid for <60 kg; 1500 mg qid >60 kg) plus leucovorin (10–25 mg/d) to reduce hematologic toxicity for a minimum of 6 weeks. In cases of sulfa intolerance, clindamycin (600 mg qid) can be substituted. TMP-SMX (5 mg/kg of TMP, 25 mg/kg SMX bid) appears to be an effective alternative for treatment of TE in resource-poor settings where the preferred combination of pyrimethamine plus sulfadia zine is not available. Pyrimethamine is very expensive in the United States, so many clinicians prescribe TMP-SMX if pyrimethamine cannot be obtained. Most experts continue to prefer pyrimethamine plus sulfadiazine because of better synergy between the drugs and fewer clinical failures relative to

TMP-SMX. Primary Prophylaxis in AIDS The incidence of TE has declined as the survival of patients with HIV infection has increased through the use of ART. The incidence of TE in underresourced settings is unknown because serologic testing and imaging are not available. AIDS patients who are seropositive for T. gondii and who have a CD4+ T lymphocyte count of <100/μL should receive prophylaxis against TE. The daily dose of TMP-SMX (one double-strength tablet qd) recommended for prophylaxis of Pneumocystis jirovecii pneumonia (PJP; formerly Pneumocystis carinii or PCP) is effective against TE. If patients cannot tolerate TMP-SMX, the recommended alterna tive is dapsone-pyrimethamine, which likewise is effective against PJP. Atovaquone with or without pyrimethamine also can be con sidered. Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, clarithromycin, or aerosolized pentamidine is prob ably insufficient. Discontinuing Primary Prophylaxis Prophylaxis against TE can be discontinued in HIV-positive patients who have responded to ART and whose CD4+ T lymphocyte count has been >200/μL for 3 months. Although patients with CD4+ T lymphocyte counts of <100/μL are at greatest risk for developing TE, the risk that this condition will develop when the count has increased to 100–200/μL has not been established. Thus, prophylaxis should be discontinued when the count has increased to >200/μL. Prophylaxis should be recommenced if the CD4+ T lymphocyte count again decreases to <100–200/μL. Individuals who have completed initial therapy for TE should receive treatment indefinitely until immune reconstitution, with a CD4+ T-cell count of >200/μL, is achieved with ART. Combination therapy with pyrimethamine plus sulfadiazine plus leucovorin is effective. An alternative to sulfadiazine in this regimen is clindamy cin or TMP-SMX. Discontinuing Secondary Prophylaxis (Long-Term Maintenance Therapy) Patients receiving secondary prophylaxis for TE are at low risk for recurrence when they have completed initial therapy for TE, remain asymptomatic, and have evidence of restored immune function. Individuals with HIV infection should have a CD4+

T lymphocyte count of >200/μL for at least 6 months after combined ART (cART). A repeat MRI brain scan is recommended. Secondary

prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <200/μL.

Prophylaxis in Allogeneic HSCT or Solid Organ Transplant The incidence of toxoplasmosis is lower in seropositive allogeneic HSCT given TMP-SMX prophylaxis, so prophylaxis should be given after engraftment for at least 6 months with weekly PCR monitoring performed after transplant. TMP-SMX regimens will prevent both toxoplasmosis and P. jirovecii. ■ ■PREVENTION Seronegative immunocompromised or pregnant persons should be counseled regarding sources of Toxoplasma infection. The chances of primary infection with Toxoplasma can be reduced by not eating undercooked meat and by avoiding oocyst-contaminated material (i.e., a cat’s litter box). Specifically, lamb, beef, pork, and venison should be cooked to an internal temperature of 63°C (145°F) measured in the thickest portion of the cut and rested for 3 min. Ground meat should be cooked to 71°C (145°F), whereas poultry should be cooked to 74°C (165°F). Hands should be washed thoroughly after work in the garden, and all fruits and vegetables should be washed. Freezing meat to –20°C (–4°F) also kills cysts. Ingestion of raw shellfish is a risk factor for toxoplasmosis, given that the filter-feeding mechanism of clams and mussels concentrates oocysts. If the patient owns a cat, the litter box should be cleaned or changed daily, preferably by an HIV-negative, nonpregnant person; alterna tively, patients should wash their hands thoroughly after changing the litter box. Litter boxes should be changed daily if possible, as freshly excreted oocysts will not have sporulated and will not be infectious. Patients should be encouraged to keep their cats inside and not to adopt or handle stray cats. Cats should be fed only canned or dried

commercial food or well-cooked table food, not raw or undercooked meats. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis. Ideally, blood intended for transfu sion into Toxoplasma-seronegative immunocompromised individuals should be screened for antibody to T. gondii. Although such serologic screening is not routinely performed, seronegative women should be screened for evidence of infection several times during pregnancy if they are exposed to environmental conditions that put them at risk for infection with T. gondii. HIV-positive individuals should adhere closely to these preventive measures. CHAPTER 235 Toxoplasma Infections Acknowledgment The author would like to acknowledge Dr. Lloyd Kasper for his numerous contributions to our understanding of the pathogenesis of toxoplasmosis and his essential role in preparation of this chapter for prior editions. ■ ■FURTHER READING Aerts R et al: Guidelines for the management of Toxoplasma gondii infection and disease in patients with haematological malignancies and after haematopoietic stem-cell transplantation: Guidelines from the 9th European Conference on Infections in Leukaemia, 2022. Lancet Infect Dis 24:e291, 2024. Cifuentes-Gonzalez C et al: Risk factors for recurrences and visual impairment in patients with ocular toxoplasmosis: A systematic review and meta-analysis. PLoS One A18:e0283845, 2023. Jones JL et al: Toxoplasma gondii infection in the United States, 2011–2014. Am J Trop Med Hyg 98:551 2018. Schumacher AC et al: Toxoplasmosis outbreak associated with Toxo plasma gondii-contaminated venison−high attack rate, unusual clini cal presentation, and atypical genotype. Clin Infect Dis 72:1557, 2021. Song G et al: Toxoplasma gondii seropositivity and cognitive function ing in older adults: An analysis of cross-sectional data of the National Health and Nutrition Examination Survey 2011–2014. BMJ Open 14:e071513, 2024.

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