Toxoplasmosis

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Panel's Recommendations

Preventing Exposure

- Children with HIV should avoid ingesting undercooked meals that could contain tissue cysts and contact with cat feces that could contain sporulated oocysts (AIII).

Primary Prophylaxis

- Prophylaxis against *Toxoplasma* encephalitis (TE) should be administered to children with HIV who are *Toxoplasma*-seropositive and aged <1 year with CD4 T lymphocyte (CD4) cell percentage ≤26% (CD4 count ≤750 cells/mm^3), aged 1–5 years with CD4 percentage ≤22% (CD4 count ≤500 cells/mm^3), or ≥6 years with CD4 count ≤100 cells/mm^3 (AIII).
- The preferred agent for TE prophylaxis is trimethoprim-sulfamethoxazole (TMP-SMX) which is administered by weight-equivalent dosing for children (AII*). One double-strength tablet of TMP-SMX, three times weekly (or 3 consecutive days a week), is an alternative (AII*). Alternative therapies, such as dapsone/pyrimethamine plus leucovorin (BI*) or atovaquone with or without pyrimethamine (CIII), exist for those who do not tolerate TMP-SMX.
- Preventive therapy can be discontinued once a child responds to antiretroviral therapy (ART) with a sustained rise (>3 months) in children aged 1–5 years with CD4 percentage >22% (CD4 count >500 cells/mm^3) or children aged ≥6 years with CD4 count >200 cells/mm^3 (see Introduction, Table 2) (AIII). Prophylaxis should not be discontinued in patients less than 1 year of age. Primary prophylaxis should be reintroduced if these parameters are not met (BIII).

Treatment

- Most experts recommend treatment with acute toxoplasmosis during pregnancy in an attempt to prevent fetal infection. For more extensive information on diagnosis, prevention, and treatment during pregnancy with toxoplasmosis, please see the Toxoplasmosis section of the Adult and Adolescent Opportunistic Infection Guidelines.
- Empiric therapy should be strongly considered for newborns of mothers with HIV who had symptomatic or asymptomatic primary *Toxoplasma* infection during pregnancy, regardless of whether treatment was administered during pregnancy (BIII).
- The preferred treatment for congenital toxoplasmosis is pyrimethamine plus sulfadiazine, with supplementary leucovorin (folinic acid) (AII).
- The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin (AI*).
- The recommended treatment duration for congenital toxoplasmosis in infants with HIV is 12 months (AIII).
- Therapy for acquired toxoplasmosis in children with HIV is pyrimethamine plus sulfadiazine and leucovorin (AII). Older children with HIV and acquired central nervous system, ocular, or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin plus sulfadiazine (AI*).
- Acute therapy should be continued for 6 weeks, assuming clinical and radiologic improvement (BII*). Longer courses of treatment may be required for extensive disease or poor response after 6 weeks.
- Anticonvulsants should be given to children with TE who have a history of seizures but should not be administered prophylactically to children without a history of seizures (AIII).
- Corticosteroids are recommended for children with HIV and central nervous system toxoplasmosis when cerebrospinal fluid protein is highly elevated (i.e., >1,000 mg/dL) or when focal lesions with substantial mass effect are present (BIII).

Panel's Recommendations
Secondary Prophylaxis • Children who have completed initial therapy for TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) unless ART results in immune reconstitution (AI*). The preferred suppressive therapy for TE is sulfadiazine plus pyrimethamine and leucovorin (AI*). • Secondary prophylaxis can be discontinued in children on ART aged >1 year who are asymptomatic after completing TE therapy, with a concomitant and sustained rise (>3 months) to CD4 percentage >22% (CD4 count >500 cells/mm^3) in children aged 1–5 years or CD4 >200 cells/mm^3 in children ≥6 years of age (AIII). Secondary prophylaxis should be reinstituted if these parameters are not met (BIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional *Rating of Evidence: I = One or more randomized trials* ***in children***† *with clinical outcomes and/or validated endpoints; I* = One or more randomized trials* ***in adults*** *with clinical outcomes and/or validated laboratory endpoints with accompanying data* ***in children***† *from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies* ***in children***† *with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies* ***in adults*** *with long-term clinical outcomes with accompanying data* ***in children***† *from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* †Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents

Epidemiology

The major mode of transmission of *Toxoplasma gondii* infection to infants and young children is congenital, occurring almost exclusively in neonates born to mothers who sustain primary *Toxoplasma* infection during pregnancy. While *Toxoplasma* infection is typically asymptomatic in immunocompetent hosts, severe disease can occur in immunocompromised hosts or congenital infection. Comprehensive guidelines for the diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States were published in 2017.[1] The estimated incidence of congenital toxoplasmosis in the United States is 1 case per 1,000 to 12,000 live-born infants.[2-4] In people born in the United States who are aged 12–49 years, the age-adjusted *T. gondii* seroprevalence decreased from 14.1% (95% confidence limit [CL] 12.7% to 15.5%) in NHANES III (1988–1994) to 9.0% (95% CL 7.6%, 10.5%) in NHANES 1999–2004 to 6.7% (95% CL 5.3%, 8.2%) in NHANES 2009–2010 ($P < 0.001$ linear trend).[5] Older children, adolescents, and adults typically acquire *Toxoplasma* infection by eating undercooked meat that contains parasitic cysts or by unintentionally ingesting sporulated oocysts from cat feces in soil or contaminated food or water.[6] In the United States, eating raw shellfish including oysters, clams, and mussels was identified as a novel risk factor for acute infection.[7] Cats are the only definitive host for *T. gondii*. However, cats excrete oocysts in their feces only transiently after initial infection, and most studies have failed to show a correlation between cat ownership and *Toxoplasma* infection in humans.[8] Indeed, *Toxoplasma* infection in humans in the United States has declined despite increased cat ownership.[6] While the risk of toxoplasmosis transmission from indoor cats to humans is generally lower compared to outdoor cats who are exposed to mice and other rodents, it is still important for cat owners to take precautions to minimize the risk of exposure. Such precautions include keeping cats indoors, feeding cats commercial cat food rather than raw meat, providing a clean litter box, and promptly removing feces.[9,10]

The overall risk of perinatal transmission in women without HIV who acquire primary *Toxoplasma* infection during pregnancy is 29% (95% confidence interval, 25% to 33%), with variation depending

upon the trimester during which primary maternal infection occurs.[11] The risk of congenital infection is low among infants born to women who become infected during the first trimester (2% to 6%) but increases sharply thereafter, with a risk as high as 81% in women who become infected during the last few weeks of pregnancy.[11,12] Infection of the fetus in early gestation usually results in more severe disease than does infection late in gestation.[13]

The prevalence of latent *Toxoplasma* infection among women with and without HIV in the United States was assessed in a cross-sectional study of 2,525 nonpregnant women enrolled in the Women's Interagency Health Study.[14] The overall prevalence of *Toxoplasma* seropositivity was 15% and did not differ by HIV status, but a prevalence of 41% was seen among women born outside of the United States. Similarly in another study, age-adjusted seroprevalence among women of childbearing age (15–44 years) has declined over time (15%, 11%, 9%, and 7.5% in 1988–1994, 1999–2000, 2009–2010, 2011–2014, respectively) suggesting that 92.5% of women of childbearing age are susceptible to infection.[1] However, the number of toxoplasmosis deaths in people with HIV declined from 2000 to 2010.[1,15] The overall rate of perinatal transmission of *Toxoplasma* in pregnant women with HIV is unknown; however, a few cases of perinatal transmission of *Toxoplasma* in women with HIV have been reported.[16-20] People with HIV may be at increased risk of perinatal *T. gondii* transmission, and serologic testing for *Toxoplasma* should be performed in the setting of pregnancy with HIV. Perinatal transmission of *T. gondii* is rare from women without HIV who acquired *Toxoplasma* infection before pregnancy.[21] However, in people with HIV coinfection, perinatal transmission has been observed with chronic *Toxoplasma* infection (transmission rate: <4%), presumably due to reactivation of *Toxoplasma* organism replication in those who are severely immunosuppressed.[16-19] There is a higher rate of congenital toxoplasmosis when the mother has active clinical toxoplasmosis during gestation.[22] Central nervous system (CNS) infection with *T. gondii* was reported as an AIDS-indicating condition in fewer than 1% of pediatric AIDS cases before the advent of antiretroviral therapy (ART).[23] Since the advent of ART, this condition is rarely encountered in children with HIV in the United States. CNS toxoplasmosis occurred in 5 of 2,767 (0.2%) children with HIV who were enrolled in the long-term follow-up study Pediatric AIDS Clinical Trials Group 219c in the ART era.[24] *Toxoplasma* infection is considered to have occurred *in utero* in most cases of *Toxoplasma* encephalitis (TE) observed in children with HIV. More rarely, TE has been reported in older children with HIV, who presumably had primary acquired toxoplasmosis.[25,26] As in adults, the greatest risk is among severely immunosuppressed children (i.e., CD4 T lymphocyte [CD4] cell count <50 cells/mm^3).

Clinical Manifestations

In studies of non-immunocompromised infants with congenital toxoplasmosis, most infants (70% to 90%) are asymptomatic at birth.[27] However, most asymptomatic children (50% to 75%) will go on to develop late sequelae such as retinitis, visual impairment, and intellectual or neurologic impairment, with onset of symptoms occurring several months to years after birth. Symptoms in newborns may present as either generalized disease or predominantly neurologic disease, including symptoms such as maculopapular rash, generalized lymphadenopathy, hepatosplenomegaly, jaundice, hematologic abnormalities (e.g., anemia, thrombocytopenia, neutropenia), and substantial CNS disease, including hydrocephalus, diffuse intracerebral calcification, microcephaly, chorioretinitis, and seizures. Cerebrospinal fluid (CSF) protein may be mild to moderately elevated and may have mononuclear CSF pleocytosis, and these nonspecific findings should raise suspicion for CNS toxoplasmosis[28]

Toxoplasmosis acquired after birth in immunocompetent patients is most often initially asymptomatic. When symptoms occur, they are frequently nonspecific and can include malaise, fever, sore throat, myalgia, lymphadenopathy (cervical), and a mononucleosis-like syndrome featuring a maculopapular rash and hepatosplenomegaly.[29]

TE should be considered in all children with HIV with new neurologic findings, but especially among those with severe immunosuppression.[27] Although focal findings are typical, the initial presentation can vary and reflect diffuse CNS disease. Generalized symptoms include fever, reduced alertness, and seizures.

Isolated ocular toxoplasmosis is rare in immunocompromised children and usually occurs in association with CNS infection. As a result, a neurologic examination with clinical exam and neuroimaging and lumbar puncture is indicated for children with in whom toxoplasma chorioretinitis is diagnosed. Lumbar puncture is not recommended for adolescents with toxoplasma chorioretinitis who are not immunosuppressed. Ocular toxoplasmosis appears as white retinal lesions with little associated hemorrhage; visual loss can occur initially.[30]

Less frequent presentations in children with HIV with reactivated chronic toxoplasmosis include systemic toxoplasmosis, pneumonitis, hepatitis, and cardiomyopathy/myocarditis.[19,31]

Diagnosis

All infants born to mothers who have HIV and are seropositive for *Toxoplasma* are at risk for congenital toxoplasmosis.[32] Infants born to mothers from an area where *Toxoplasma* is endemic may be at a higher risk of congenital toxoplasmosis. Congenital toxoplasmosis can be diagnosed by enzyme-linked immunoassay or an immunosorbent assay to detect *Toxoplasma*-specific immunoglobulin M (IgM), immunoglobulin A (IgA), or immunoglobulin E (IgE) in neonatal serum within the first 6 months of life, or persistence of specific immunoglobulin G (IgG) antibody beyond age 12 months.[33-37] IgA may be more sensitive for detecting congenital infection than IgM or IgE.[34] However, approximately 20% to 30% of infants with congenital toxoplasmosis will not be identified during the neonatal period with IgA or IgM assays.[35]

Serologic testing is the major method of diagnosis, but interpretation of assays often is confusing and difficult. When considering a diagnosis of congenital toxoplasmosis, specialized reference laboratories can perform serology, isolation of organisms and polymerase chain reaction (PCR) and can offer assistance in interpreting results.[34]

Additional diagnostic methods for *Toxoplasma* infection in newborns include isolating the *Toxoplasma* parasite by mouse inoculation or inoculation in tissue cultures of CSF, urine, placental tissue, amniotic fluid, or infant blood. *T. gondii* DNA can be detected by PCR performed on clinical specimens (e.g., white blood cells, CSF, amniotic fluid, tissue, urine, vitreous fluid, bronchoalveolar lavage fluid, cord blood) in a reference laboratory.[34,35] *Toxoplasma* PCR assay sensitivity varies widely (15% to 85% for blood) and specificity appears to be high (>95%). Overall sensitivity is approximately 90% in amniocentesis performed in pregnant women >18 weeks of gestation and at least 4 weeks after maternal infection. In the CSF, PCR sensitivity also varied widely in studies. In, immunocompromised patients, PCR sensitivity had a sensitivity of 87% when done in the first 7 days of treatment; Studies in immunocompetent patient have shown between 69% to 100% sensitivity in patients tested early as well.[38-41] The following evaluation should be undertaken for all newborns in

whom a diagnosis of toxoplasmosis is suspected: ophthalmologic, auditory, and neurologic examinations; lumbar puncture; and imaging of the head (either computer tomography [CT] or magnetic resonance imaging [MRI] scans) to determine whether hydrocephalus or calcifications are present.

CNS toxoplasmosis is presumptively diagnosed on the basis of clinical symptoms, serologic evidence of infection, and presence of a space-occupying lesion on imaging studies of the brain.[42] TE has been rarely reported in individuals without *Toxoplasma*-specific IgG antibodies; therefore, negative serology does not definitively exclude that diagnosis, particularly in individuals with profound immunosuppression. Brain CT that demonstrates multiple, bilateral, ring-enhancing lesions, especially in the basal ganglia and cerebral corticomedullary junction, would be typical of TE. Calcifications are more typical in congenital toxoplasmosis than in TE seen later in life. MRI is more sensitive and will confirm basal ganglia lesions in most people.[43] F-fluoro-2-deoxyglucose–positive emission tomography reportedly is helpful in adults in distinguishing *Toxoplasma* abscesses from primary CNS lymphoma, but the accuracy is not high, and brain tissue is often required for diagnosis. Definitive TE diagnosis requires histologic or cytologic confirmation by brain biopsy, which may demonstrate leptomeningeal inflammation, microglial nodules, gliosis, and *Toxoplasma* cysts. Brain biopsy is reserved by some experts for individuals who do not respond to specific therapy.

Prevention Recommendations

Preventing Exposure

All children and adolescents with HIV and their caregivers should be counseled about sources of *T. gondii* infection such as raw or undercooked meat, including lamb, beef, pork, or venison. A recent case-control study also showed risk associated with eating raw oysters, clams, or mussels.[7]

According to U.S. Department of Agriculture guidelines, all whole-cut meat excluding poultry (e.g., lamb, beef, and pork) should be cooked to an internal temperature of 145°F (63°C) with a food thermometer placed in the thickest part of the meat, then the meat should be allowed to rest for 3 minutes during which time it will maintain the attained temperature. Ground meat, excluding poultry, should be cooked to at least 160°F (71°C) but do not require a rest time. All poultry should be cooked to at least 165°F (74°C). Because one study has found that *T. gondii* can survive at 147.2°F (64°C) for 3 minutes, higher temperatures should be considered for those who are immunosuppressed.[44]

Handwashing should occur after contact with raw meat and after gardening or other contact with soil; in addition, fruits and vegetables should be washed well before being eaten raw. Untreated drinking water should not be consumed. Stray cats should not be handled or adopted; a cat already in the household should be kept inside and the litter box should be changed daily, preferably by an individual without HIV who is not pregnant. Cats should only be fed canned or dried commercial food, or well-cooked table food; raw or undercooked meats should be avoided. Children and adolescents with HIV do not need to part with their cats or to have their cats tested for toxoplasmosis but should avoid contact with contaminated cat feces or soil containing contaminated cat feces. Outdoor sandboxes should be covered to avoid accidental contamination and contact with cat feces. Ingestion of undercooked meats that could contain tissue cysts and contact with cat feces that could contain sporulated oocysts should be avoided **(AIII).**

Preventing Disease

In the United States, routine *Toxoplasma* serologic screening is not recommended for children with HIV whose mother does not have toxoplasmosis because of its low incidence. Adolescents with HIV who have no history of previous *Toxoplasma* infection should undergo serologic testing. However, in regions with high incidence of *Toxoplasma* infection (≥1% per year), or for children immigrating from such regions, serologic testing can be selectively considered for children with HIV aged >12 months. In addition, serologic testing for *Toxoplasma* should be done during pregnancy with HIV.

There is a lack of good quality data in randomized placebo-controlled trials in adults and children to show a benefit from toxoplasmosis prophylaxis, although these trials may have been underpowered to detect differences.[45,46] Given that many of these trials were done prior to the advent of combination ART, the benefit of prophylaxis is likely less while on ART. Data from an observational retrospective study are used to support the recommendation that *Toxoplasma*-seropositive adolescents and adults who have CD4 counts <100 cells/mm^3 should be given prophylaxis against TE.[47] Specific levels of immunosuppression that increase the risk of TE in children are less well defined. However, adult data suggest that increased risk for developing TE in children may be extrapolated to age-appropriate CD4 parameters corresponding to advanced immunosuppression.[45,48,49]

In children with HIV, such parameters are based on age-specific CD4 count or CD4 percentage of total lymphocytes (see Introduction, Table 2). *Toxoplasma*-seropositive children with HIV aged <1 year with CD4 percentage ≤26% (CD4 count ≤750 cells/mm^3), aged 1 to 5 years with CD4 percentage ≤22% (CD4 count ≤500 cells/mm^3), or aged ≥6 years with CD4 count ≤100 cells/mm^3 should be administered prophylaxis against TE **(AIII).**

Toxoplasma-seronegative adults and adolescents with HIV who are not taking *Pneumocystis* pneumonia (PCP) prophylaxis known to be active against TE should be retested for IgG antibody to *Toxoplasma* if their CD4 counts decline to ≤100 cells/mm^3 to determine whether they have seroconverted to *Toxoplasma.* In adolescents and adults with HIV, the preferred regimen for PCP prophylaxis is one double-strength trimethoprim-sulfamethoxazole (TMP-SMX) tablet daily because of its high efficacy, relative safety, low cost, broad antimicrobial spectrum, and concurrent efficacy as TE prophylaxis.[47] Data from trials in adults support once-daily TMP-SMX as the preferred regimen in children using weight-equivalent dosing (See Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis) **(AII*).** One double-strength tablet of TMP-SMX, three times weekly (or 3 consecutive days a week), is an alternative **(AII*).**[50] Other alternative dosing schedules include TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth every day or TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth three times weekly on alternate days. Based on data from systematic reviews and adult randomized controlled trials, dapsone-pyrimethamine plus leucovorin—which is also effective against PCP—is the recommended alternative for people who cannot tolerate TMP-SMX **(BI*).**[51-54] Screening for glucose-6-phosphate dehydrogenase deficiency should be done before initiating dapsone.

Atovaquone with or without pyrimethamine also can be considered for those who cannot tolerate TMP-SMX **(CIII).** Single-drug prophylaxis with dapsone, pyrimethamine, azithromycin, or clarithromycin is not recommended. Aerosolized pentamidine does not protect against TE and also is not recommended.[47,55] Severely immunosuppressed children who are seropositive for *Toxoplasma* and

who are not receiving TMP-SMX or atovaquone should be given prophylaxis for both PCP and toxoplasmosis (i.e., dapsone plus pyrimethamine).

Discontinuing Primary Prophylaxis

Primary prophylaxis can be discontinued once a child responds to ART with a sustained rise (>3 months) in CD4 percentage >22% (CD4 count >500 cells/mm^3) in children aged 1 to 5 years, or CD4 count >200 cells/mm^3 for children aged ≥6 years **(AIII).**

Multiple observational studies[49,56,57] and two randomized trials[58,59] have reported that primary prophylaxis can be discontinued with minimal risk of TE in people who have responded to ART with an increase in CD4 count to ≥200 cells/mm^3 for ≥3 months. Although people with CD4 counts of <100 cells/mm^3 are at greatest risk of TE, the risk of TE when CD4 counts increase to between 100 to 200 cells/mm^3 has not been studied as rigorously as an increase to >200 cells/mm^3. Thus, the recommendation for adults and adolescents specifies discontinuing prophylaxis after an increase to >200 cells/mm^3. Discontinuing primary TE prophylaxis when CD4 counts have increased to >200 cells/mm^3 is recommended because prophylaxis adds limited disease prevention for toxoplasmosis and because discontinuing drugs reduces pill burden, the potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. Data do not exist on the safety of discontinuing primary TE prophylaxis for children with HIV whose immunologic status improves on ART. Therefore, based on adult data, discontinuation of TMP-SMX may be safe once a child responds to ART with a sustained rise in CD4 percentage >22% (CD4 count >500 cells/mm^3) in children aged 1 to 5 years, and CD4 count >200 cells/mm^3 in children aged at least 6 years **(AIII).** Prophylaxis should not be stopped in children aged less than 1 year. A sustained response in children has been defined as a CD4 count or percentage above the threshold level for >3 consecutive months. It should be noted that older literature may not align with new cut-off points for immunosuppression in the revised surveillance case definition for HIV.

Prophylaxis should be reintroduced children ≥6 years old with HIV **(BIII)** if the CD4 count decreases to ≤200 cells/mm^3. For children with HIV aged <6 years prophylaxis should be reintroduced, if the CD4 percentage falls below 22% (CD4 count ≤500 cells/mm^3) in children aged 1 to 5 years, and if the CD4 percentage falls below 26% (CD4 count ≤750 cells/mm^3) in children aged less than 1 year (**BIII).**

Treatment Recommendations

Treating Disease

Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital toxoplasmosis should be managed in consultation with an infectious disease specialist with expertise in managing toxoplasmosis. Although controversy exists about the efficacy of treating pregnant women who have acute toxoplasmosis in an attempt to prevent perinatal transmission,[60] most experts would recommend such therapy.[32]

For more extensive information on the diagnosis, prevention, and treatment during pregnancy with toxoplasmosis, please see the Toxoplasmosis section of the Adult and Adolescent Opportunistic Infection Guidelines.

Given that a delay in initiation of therapy was associated with poor neurologic outcomes, empiric therapy should be strongly considered for newborns of mothers with HIV who had symptomatic or

asymptomatic primary *Toxoplasma* infection during pregnancy, regardless of whether treatment was administered during pregnancy **(BIII).**[28]

These treatment recommendations for children with HIV are based on studies of children with congenital toxoplasmosis without HIV. A systematic review of cohort studies based on universal screening for congenital toxoplasmosis did not show a reduced risk of congenital manifestations with treatment during pregnancy.[60]

The preferred treatment for congenital toxoplasmosis and acquired toxoplasmosis in children with HIV is similar. For these scenarios, the preferred treatment is pyrimethamine combined with sulfadiazine, with supplementary leucovorin (folinic acid) to minimize pyrimethamine-associated hematologic toxicity **(AII).**[28,30,61-63] Although the optimal duration of therapy is undefined, the recommended duration of treatment for congenital toxoplasmosis in infants without HIV is 12 months **(AIII).**[30] Older children with HIV and acquired CNS, ocular, or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin plus sulfadiazine **(AI*).** Acute therapy should be continued for at least 6 weeks, assuming clinical and radiologic improvement **(BII*).**[64]

Longer courses of treatment may be required for extensive disease or poor response after 6 weeks. The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin **(AI*).** As an alternative to clindamycin, azithromycin has also been used with pyrimethamine and leucovorin in sulfa-allergic adults, but this regimen has not been studied in children.[65] Extrapolation of azithromycin doses used in adults corresponds to a dose of 20 mg/kg given every 24 hours (maximum 1,000 mg), but this dose has not been evaluated in children.

Another alternative in adults is atovaquone plus pyrimethamine and leucovorin, or atovaquone with sulfadiazine alone, or atovaquone as a single agent in patients intolerant to both pyrimethamine and sulfadiazine; however, these regimens have not been studied in children. In adults, atovaquone is dosed at twice the total daily dose used for PCP prophylaxis and is divided into four doses per day, but such dosing for treatment of acquired toxoplasmosis in children has not been evaluated. In a small randomized trial in 77 adults, TMP-SMX was reported to be effective and better tolerated than pyrimethamine-sulfadiazine.[66] Others have reported similar efficacy in open-label observational studies.[67,68] However, this has not yet been studied in children.

For isolated ocular toxoplasmosis in immunocompetent hosts, TMP-SMX alone is as effective as pyrimethamine-sulfadiazine.[69] However, these data have not been duplicated in people with HIV; therefore, this regimen cannot be recommended for this group of patients.

Based upon treatment of congenital toxoplasmosis in children without HIV, corticosteroids such as dexamethasone and prednisone may be beneficial in certain scenarios and are recommended for all children with HIV and CNS disease when CSF protein is highly elevated (i.e., >1,000 mg/dL) or when there is vision-threatening chorioretinitis with macular involvement or focal lesions with substantial mass effects **(BIII).** Because of the potential immunosuppressive effects of steroids, they should be discontinued as soon as possible.

Anticonvulsants should be given to children with TE who have a history of seizures but should not be administered prophylactically to children without a history of seizures **(AIII).** Anticonvulsants, if administered, should be continued at least through acute therapy for CNS toxoplasmosis.

Although the initiation of ART assists in treating many opportunistic infections and malignancies, it has not been definitively shown to improve the outcome of TE therapy. In line with adult treatment practices, many physicians would initiate ART within 2 to 3 weeks of a toxoplasmosis diagnosis, based on research demonstrating that early ART initiation significantly reduces the risk of AIDS or death in people with opportunistic infections (except tuberculosis) compared to deferred treatment.[70]

Monitoring Response to Therapy and Adverse Events, Including IRIS

Children with TE should be routinely monitored for clinical and radiologic improvement and adverse effects of treatment; changes in antibody titers are not useful for monitoring responses to therapy.

Toxoplasmosis-associated immune reconstitution inflammatory syndrome (IRIS) has been described rarely in adults with HIV and has not been described in children with HIV, although it could presumably occur.[71,72] In pregnant women with HIV, IRIS may pose additional risk to the fetus,[73] although no unique risk for pregnant women coinfected with HIV and *Toxoplasma* has been defined.

Pyrimethamine can be associated with rash (including Stevens-Johnson syndrome) and nausea. The primary toxicity of pyrimethamine is reversible bone marrow suppression (i.e., neutropenia, anemia, and thrombocytopenia). A complete blood count should be performed at least weekly in children who are on daily pyrimethamine and at least monthly in those on less-than-daily dosing. Leucovorin (folinic acid) always should be administered with pyrimethamine; increased doses of leucovorin may be required in the event of marrow suppression. Because of the long half-life of pyrimethamine, leucovorin should be continued for 1 week after pyrimethamine has been discontinued.

Adverse effects of sulfadiazine include rash, fever, leukopenia, hepatitis, gastrointestinal (GI) symptoms (e.g., nausea, vomiting, diarrhea), and crystalluria. Clindamycin can be associated with fever, rash, and GI symptoms (e.g., nausea. vomiting, diarrhea, pseudomembranous colitis) and hepatotoxicity.

TMP-SMX therapy may cause rash, pruritus, GI symptoms (nausea, vomiting, anorexia), pseudoelevations in blood urea nitrogen and serum creatinine (without changes in estimated glomerular filtration rate), photosensitivity, hyperkalemia (higher doses, chronic renal insufficiency, or with concomitant potassium sparing medications), or blood dyscrasias (e.g., anemia, neutropenia, and thrombocytopenia).[74] Atovaquone has been associated with GI symptoms (diarrhea, nausea, vomiting abdominal pain, diarrhea), rash, headache, fever, and insomnia.[75]

Drug interactions between anticonvulsants and antiretroviral drugs should be evaluated. Patients receiving corticosteroids should be closely monitored for the development of other opportunistic infections.

Managing Treatment Failure

Brain biopsy should be considered in the event of early clinical or radiologic neurologic deterioration despite adequate empiric treatment or in children who do not clinically respond to anti-*Toxoplasma* therapy after 10 to 14 days. In children who undergo brain biopsy and have confirmed histopathologic evidence of TE despite treatment, a switch to an alternative regimen may be considered.

Preventing Recurrence

People who have completed initial therapy for acquired TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) [61,62] until immune reconstitution occurs with ART. The combination of sulfadiazine plus pyrimethamine and leucovorin is strongly recommended for TE chronic maintenance therapy **(AI*).** Pyrimethamine plus clindamycin with leucovorin is recommended as an alternative to sulfadiazine plus pyrimethamine and leucovorin in people who cannot tolerate sulfa drugs **(BI*);** however, only the combination of pyrimethamine plus sulfadiazine provides protection against PCP as well. Data on adults indicate atovaquone with or without pyrimethamine can also be considered for children **(CIII).** Limited data support the use of TMP-SMX for secondary prophylaxis;[76] this regimen should be used only for people who cannot tolerate pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin **(CIII).**

Discontinuing Secondary Prophylaxis

Adults and adolescents receiving secondary prophylaxis for acquired TE are at low risk of recurrence of TE when they have successfully completed their initial therapy, continue to have no signs or symptoms of TE, and have a sustained increase in CD4 count of >200 cells/mm^3 after ART (i.e., >6 months).[49,57,59,77,78] Discontinuing chronic maintenance therapy in adolescents and adults with HIV who meet these criteria is a reasonable consideration. The highest risk of relapse appears to occur within the first 6 months after stopping secondary prophylaxis. Some specialists would obtain an MRI of the brain as part of their evaluation to determine whether discontinuing therapy is appropriate. The safety of discontinuing secondary prophylaxis after immune reconstitution with ART in children has not been studied extensively. However, given the data in adults, for children with HIV older than 1 year with history of TE, consider discontinuing secondary prophylaxis against *T. gondii* after they have completed TE therapy and are asymptomatic, and once the CD4 percentage has risen to >200 cells/mm^3 in those ≥6 years old and the CD4 percentage is >22% (CD4 count >500 cells/mm^3) in those aged 1 to 5 years for >3 consecutive months **(AIII).** Prophylaxis should be reinstituted if these parameters are not met. Children with HIV with congenital toxoplasmosis should receive 12 months of initial therapy for TE; therefore, secondary prophylaxis would not be appropriate in the first year of life.

Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	TMP-SMX 150/750 mg/m^2 body surface area once daily PO	**For Children Aged ≥1 Month:** • Dapsone 2 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO every 3 days (continued for 1 week after pyrimethamine completed due to long half-life) For Children Aged 1–3 Months and >24 Months: • Atovaquone 30 mg/kg body weight (maximum 1,500 mg) PO once daily with food For Children Aged 4–24 Months: • Atovaquone 45 mg/kg body weight (maximum 1,500 mg) PO once daily with food, *with or without* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* leucovorin 5 mg PO every 3 days Acceptable Alternative Dosage Schedules for TMP-SMX • TMP-SMX 150/750 mg/m^2 body surface area per dose PO three times weekly on 3 consecutive days per week • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily PO every day • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily PO three times weekly on alternate days	Primary Prophylaxis Indicated for: *Children With IgG Antibody to Toxoplasma and Severe Immunosuppression Who Are:* • Aged <1 year with CD4% ≤26% or CD4 ≤750 cells/mm^3, *or* • Aged 1–5 years with CD4% ≤22% or CD4 ≤500 cells/mm^3, *or* • Aged ≥6 years with CD4 count ≤100 cells/mm^3 Criteria for Discontinuing Primary Prophylaxis Note: Do not discontinue in children aged <1 year. • Aged 1–5 years with CD4 count >500 cells/mm^3 for >3 consecutive months *or* • Aged ≥6 years with CD4 count >200 cells/mm^3 for >3 consecutive months Criteria for Restarting Primary Prophylaxis: • Aged 1–5 years with CD4 count <500 cells/mm^3 *or* • Aged ≥6 years with CD4 count <200 cells/mm^3

Indication	First Choice	Alternative	Comments/Special Issues
Secondary Prophylaxis (Suppressive Therapy)	• Sulfadiazine 85–120 mg/kg body weight per day in 2–4 divided doses (maximum 2–4 g per day) PO, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO once every 3 days	• Clindamycin 7–10 mg/kg body weight per dose (max 600 mg/dose) PO three times daily, *plus* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* • Leucovorin 5 mg PO once every 3 days Children Aged 1–3 Months and >24 Months • Atovaquone 30 mg/kg body weight PO (maximum 1,500 mg) once daily with food, *plus* • TMP-SMX, 150/750 mg/m^2 body surface area PO once daily Children Aged 4–24 Months *Option 1* • Atovaquone 45 mg/kg body weight PO once daily with food, *with or without* • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) PO once daily, *plus* leucovorin (when using pyrimethamine), 5 mg PO every 3 days *Option 2* • Atovaquone 45 mg/kg body weight (maximum 1,500 mg) PO once daily with food, *plus* • TMP-SMX, 150/750 mg/m^2 body surface area PO once daily	Secondary Prophylaxis Indicated • Prior TE Note: Limited data in children is available for alternative regimens. TMP-SMX only to be used if individual is intolerant to other regimens. Criteria for Discontinuing Secondary Prophylaxis *If All of the Following Criteria are Fulfilled*: • Completed initial therapy for TE, *and* • Asymptomatic for TE, *and* • Aged ≥6 years old with CD4 >200 cells/mm^3 in those or CD4% >22% (CD4 count >500 cells/mm^3) in those aged 1–5 years for 3 consecutive months Criteria For Restarting Secondary Prophylaxis: • CD4 count ≤200 cells/mm^3 and CD4% ≤22% (CD4 count ≤500 cells/mm^3) in those aged 1–5 years Note: Sulfadiazine may be given as 2–4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight.

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	Congenital Toxoplasmosis • Pyrimethamine loading dose of 1 mg/kg body weight PO twice daily for 2 days, then 1 mg/kg body weight PO once daily for 2–6 months, then 1 mg/kg body weight PO three times weekly thereafter, *plus* • Leucovorin (folinic acid) 10 mg PO or IM three times weekly, *plus* • Sulfadiazine 50 mg/kg body weight PO twice daily *Treatment Duration* • 12 months Acquired Toxoplasmosis *Acute Induction Therapy (Followed by Chronic Suppressive Therapy)* • Pyrimethamine loading dose of 1 mg/kg body weight (maximum 50 mg) PO twice daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) PO once daily, *plus*	For Sulfonamide-Intolerant Patients: • Pyrimethamine loading dose of 1 mg/kg body weight PO twice daily for 2 days, then 1 mg/kg body weight PO once daily for 2–6 months, then 1 mg/kg body weight PO three times weekly thereafter, *plus* • Leucovorin (folinic acid) 10 PO or IM three times weekly, *plus* • Clindamycin 5–7.5 mg/kg body weight PO or IV (maximum 600 mg/dose) per dose four times daily	Congenital Toxoplasmosis • For infants born mothers with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of treatment during pregnancy. Acquired Toxoplasmosis • Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less-than-daily dosing. • The following regimens are used in adults but have not been studied in children: o TMP-SMX 5/25 mg/kg body weight per dose IV or PO given twice daily as an alternative to pyrimethamine-sulfadiazine o Atovaquone 1,500 PO twice daily administered: ▪ with pyrimethamine and leucovorin, *or* ▪ with sulfadiazine, *or* ▪ alone, for those with pyrimethamine and sulfadiazine intolerance o Azithromycin 900–1,200 mg daily (corresponding to 20 mg/kg daily, maximum 1,000 mg in children) administered with pyrimethamine-leucovorin • Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or when focal lesions with significant mass effects are present, with discontinuation as soon as clinically feasible.

Indication	First Choice	Alternative	Comments/Special Issues
	• Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) PO per dose four times daily, *plus* • Leucovorin 10–20 mg PO once daily, continued for one week after stopping pyrimethamine *Treatment Duration (Followed by Chronic Suppressive Therapy)*: • ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks)		• Anticonvulsants should be administered to people with a history of seizures and continued through the acute treatment but should not be used prophylactically. • Sulfadiazine may be given as 2 to 4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight. • Consider screening for G6PD deficiency before starting sulfadiazine or TMP-SMX in people from regions with high prevalence of severe G6PD deficiency.

Key: CBC = complete blood count; CD4 = CD4 T lymphocyte; CD4% = CD4 T lymphocyte percentage; CNS = central nervous system; CSF = cerebrospinal fluid; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; IM = intramuscular; IV = intravenous; PO = orally; TE = Toxoplasma encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole

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