8.8.4 Toxoplasmosis 1416

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section 8 Infectious diseases 1416 and quinine or clindamycin alone reduces parasitaemia and prevents extensive haemolysis and renal failure. Exchange transfu- sion should be used in fulminating B. divergens cases. Imidocarb dipropionate, which has been used for treatment of cattle babesiosis, has been successfully used in two patients in Ireland, although this drug is not approved for human treatment. Preventive measures consist of use of repellents containing N,N-diethyl-3-methylbenzamide for clothing or skin, removing ticks from the skin, and avoiding exposure for asplenic and im- munocompromised individuals. To date, no vaccine against human babesiosis is available. FURTHER READING Hildebrandt A, Gray JS, Hunfeld KP (2013). Human babesiosis in Europe: what clinicians need to know. Infection, 41, 1057–72. Lobo CA, et al. (2013). Babesia: an emerging infectious treat in trans- fusion medicine. Plos Pathog, 9, e1003387. Vannier E, Krause PJ, (2012). Human babesiosis. N Eng J Med, 366, 2397–407. 8.8.4 Toxoplasmosis Oliver Liesenfeld and Eskild Petersen ESSENTIALS Toxoplasma gondii is a protozoan parasite with worldwide distribu- tion that infects up to one-third of the world’s population. Human infection is acquired through ingestion in water or food of oocysts shed by cats, or by ingestion of bradyzoites released from cysts contained in uncooked or undercooked meat (e.g. sheep, swine, cattle). Following invasion in the intestine, tachyzoites rapidly dis- seminate throughout the host. Immune mechanisms mediate the formation of cysts, primarily in the brain, eye, and skeletal and heart muscles, where they persist for the life of the host. Presence of in- fection can be established by direct detection of the parasite in clinical samples (often by polymerase chain reaction) or by serological techniques. Clinical features and treatment Immunocompetent adults and children—primary infection is usually subclinical, but some patients develop cervical lymphadenopathy; specific treatment is not usually required. Ocular disease—choroidoretinitis; treatment with pyrimethamine and sulphadiazine is usually recommended if there are severe in- flammatory responses and/or proximity of retinal lesions to the fovea or optic disc. Immunocompromised patients—the central nervous system is the most commonly affected site. Reactivation of latent infection can cause life-threatening encephalitis. Empirical anti-T. gondii therapy is given to patients with single or multiple ring-enhancing brain lesions on imaging, positive serology, and advanced immunodefi- ciency, most commonly with the combination of pyrimethamine/ sulphadiazine and folinic acid. Patients with suspected cerebral T. gondii infection should be tested for HIV. (a) (b) (c) Fig. 8.8.3.1 (a) Babesia divergens infection in a 29-year-old Frenchman infected in Normandy. He had a splenectomy 4 months previously for idiopathic thrombocytopenia. Parasitaemia reached 30%. He was successfully treated with exchange transfusion, clindamycin, and quinine. (b) Babesia microti in a male patient, Missouri, United States of America (×100). (c) Babesia microti in a 72-year-old female patient, Massachusetts, United States of America (×150). (a) Copyright P. Brasseur; (b, c)

courtesy of Centers for Disease Control, Atlanta, GA.

8.8.4 Toxoplasmosis 1417 Congenital toxoplasmosis—infection acquired in early pregnancy may cause severe damage to the fetus or intrauterine death; infection in the second and third trimesters goes unnoticed in the newborn in most cases, but signs of disease (e.g. chorioretinitis), may occur later in life. Suspected or established maternal infection acquired during pregnancy must be confirmed by prenatal diagnosis of fetal infection using polymerase chain reaction on amniotic fluid: if this is positive it is highly probable that the fetus is infected and pyrimeth- amine/sulphadiazine and folinic acid should be given and continued throughout the pregnancy. Prevention Prevention of infection by avoiding ingestion is the strategy of choice in seronegative people. Trimethoprim-sulfamethoxazole can be used for primary and secondary prophylaxis of seropositive immunocompromised patients or seronegative recipients of organ transplants from seropositive donors. Spiramycin can be used for secondary prevention of transmission from the acutely infected mother to her fetus. Historical perspective The first human case ascribed to infection with Toxoplasma gondii was a child with hydrocephalus reported by Janku in 1923. Sabin reported the first case of encephalitis due to T. gondii in 1941. Lymphadenopathy was recognized as a key symptom by Siim, Gard, and Magnusson (1951). Encephalitis due to T. gondii in im- munocompromised patients was first reported from patients with Hodgkin's disease during immunosuppressive treatment in 1967. Aetiology, genetics, pathogenesis, and pathology Aetiology T. gondii is an obligate intracellular protozoan of the phylum Apicomplexa, subclass Coccidiasina. The parasite exists in three life-stages of medical importance: the oocyst (10 × 12 μm in size), which is the product of the parasite's sexual cycle in the intestine of all members of the cat family; the tachyzoite (2–4 μm wide and 4–8 μm long), which is the asexual invasive form; and the tissue cyst, which contains hundreds or thousands of bradyzoites in tissues (Fig. 8.8.4.1). Tissue cysts (the latent stage) remain viable through out the life of the host. Ingestion of T. gondii cysts or oocysts (the natural route of infec- tion) results in cyst (or oocyst) rupture and release of bradyzoites (or sporozoites) into the intestinal lumen, followed by rapid entry into intestinal cells and multiplication as tachyzoites. Tachyzoites are spread by disruption of infected cells, invasion of neighbouring cells, and via the bloodstream. In intermediate hosts and extraintestinal tissues of the cat, cysts containing bradyzoites are formed and persist for the life of the host. Immunodeficiency may result in reactivation of latent infection and severe disease, whereas reinfection does not appear to cause clinically apparent disease. A single case of symp- tomatic infection with an exotic strain despite previous infection with a type II strain has been published. T. gondii consists of three clonal lineages designated types I, II, III, and archetypes, which differ in virulence and geographical distribu- tion. Archtypes not belonging to type I, II or III, are more common in South America compared to Europe and the United States of America, and clinical toxoplasmosis is more severe in South America compared to Europe (Gilbert et al., 2008). The recent description of strain-specific peptides has allowed typing of strains using serum. The generation of specific gene-deficient strains of T. gondii and the sequencing of the Toxoplasma genome (http://toxodb.org) will pro- vide further insight into parasite virulence factors and specific host immune responses. Pathogenesis The inoculum size and virulence of the organism, and the genetic background and immunological status of the individual, appear to influence the course of the infection in humans. Following ac- tive invasion, T. gondii induces the formation of a parasitophorous (a) (b) (c) Fig. 8.8.4.1 Toxoplasma gondii: (a) rosette-forming tachyzoites inside a macrophage, (b) bradyzoites inside a tissue cyst, and (c) oocyst in cat faeces.

section 8 Infectious diseases 1418 vacuole containing secreted parasite proteins but excluding host proteins that would normally promote phagosome maturation, thereby preventing lysosome fusion. The molecular characterization and function of several proteins from organelles including rhoptries (specialized secretory organelles), micronemes (also a secretory or- ganelle), and dense granules have been reported. These molecules and the immunodominant tachyzoite surface antigen SAG1 are among the most promising vaccine candidates. Following intracel- lular replication and host cell disruption, parasites are disseminated via the blood stream and infect multiple organs including the cen- tral nervous system, eye, skeletal and heart muscle, and placenta. The developing immune response causes the formation of cysts in the central nervous system and skeletal muscle during the first week of infection. These persist lifelong. In immunocompromised hosts, cysts may disrupt and cause recrudescence of the infection, which then presents as life-threatening toxoplasmic encephalitis. Infection with T. gondii results in a strong and persistent Th1 re- sponse characterized by the production of interleukin 12 (IL-12), interferon-γ, and tumour necrosis factor α (TNFα). Strain-specific differences in the modulation of host cell transcription are mediated by protein kinases: ROP16 and ROP18 are released from rhoptries and injected into the host, resulting in the activation of signalling pathways and IL-12 production. The combined action of these cyto- kines and specific antibodies protects the host against rapid replica- tion of tachyzoites and subsequent pathological changes. Dendritic cells and their capacity to produce IL-12 were identified as the main activators of Th1 immune reactions. Granulocytes might also con- tribute to the early production of IL-12. The activated macrophage inhibits or kills intracellular T. gondii, which counteract these ac- tions by down-regulating surface molecules and interfering with apoptosis pathways in antigen-presenting cells, suggesting a role for these cells as ‘Trojan horses’ in early stages of infection. Sensitized CD4+ and CD8+ T lymphocytes are cytotoxic for T. gondii-infected cells. Both proinflammatory (e.g. interferon-γ and TNFα) and down-regulatory cytokines (e.g. IL-10 and transforming growth factor β) are involved in balancing this response. Within 2 weeks after infection, IgG, IgM, IgA, and IgE antibodies against multiple T. gondii proteins can be detected. Reinfection may occur, and rare cases of congenital infection have been reported in subjects infected with a type II strain and reinfected with a virulent atypical geno- type, demonstrating that cross-immunity between genotypes is not absolute. Pathology Histopathological changes in toxoplasma lymphadenitis in im- munocompetent people are frequently distinctive and often diag- nostic. They consist of reactive follicular hyperplasia, irregular clusters of epithelioid histiocytes encroaching on and blurring the margins of the germinal centres, and focal distension of sinuses with monocytic cells. Eye infection in immunocompetent patients pro- duces acute choroidoretinitis characterized by severe inflammation and necrosis. The pathogenesis of recurrent choroidoretinitis is con- troversial. Rupture of cysts may release viable organisms that induce necrosis and inflammation; alternatively, choroidoretinitis may re- sult from a hypersensitivity reaction of unknown cause. Damage to the central nervous system by T. gondii, toxoplasmic encephalitis, is characterized by multiple foci of enlarging necrosis and microglia nodules. In infants, periaqueductal and periventricular vasculitis and necrosis are distinctive of congenital toxoplasmosis. The nec- rotic areas can calcify and lead to radiographic findings suggestive but not pathognomonic of toxoplasmosis. Hydrocephalus can result from obstruction of the aqueduct of Sylvius or foramen of Monro. Tachyzoites and cysts are seen in and adjacent to necrotic foci. The presence of multiple brain abscesses is the most characteristic fea- ture of toxoplasmic encephalitis in severely immunodeficient pa- tients and is especially characteristic in AIDS. At autopsy in AIDS patients with toxoplasmic encephalitis, there is almost universal involvement of the cerebral hemispheres and a remarkable predi- lection for the basal ganglia. In

cases of congenital toxoplasmosis, necrosis of the brain is most intense in the cortex and basal ganglia. Epidemiology Infection with T. gondii in humans is naturally acquired through in- gestion of cysts or oocysts. Humans can be infected by ingestion of undercooked or raw meat (e.g. sheep, swine, cattle) containing tissue cysts, or of water or food contaminated by faeces containing oocysts from infected cats. The differences in seroprevalence of T. gondii depend on eating habits and customs that support the ingestion of cysts as the major source of infection. Epidemics of toxoplasmosis in humans and sheep attributed to exposure to infected cats indi- cate the importance of oocyst excretion by cats. Several outbreaks of toxoplasmosis through contamination of drinking water by oocysts have been reported. This is a major route of transmission under poor socioeconomic conditions, where untreated surface water is drunk. Transmission of T. gondii in organs transplanted from seroposi- tive donors to seronegative recipients remains an important cause of infection in immunocompromised patients. T. gondii can also be transmitted by blood or leucocytes from immunocompetent or im- munocompromised donors. In congenital transmission, the parasite gains access to the fetal circulation by infection of the placenta following maternal parasit- aemia. The reported birth prevalence of congenital toxoplasmosis ranges from 1 to 10 per 10 000 live births in Europe and North America. The frequency of congenital transmission depends on the time during gestation when the mother acquired her infection (Fig. 8.8.4.2). Maternal infection acquired weeks or a few months before gestation poses very little or no risk to the fetus. Infection acquired around the time of conception and within the first 2 weeks of gestation in most cases does not result in transmission, whereas rates of transmission are above 60% in the last trimester. There is an inverse relationship between frequency of transmission and severity of disease. Infection in the first and second trimester, al- though less frequent than infection in the third trimester, results in severe congenital toxoplasmosis more often (Fig. 8.8.4.3). In con- trast, maternal infection during the third trimester, although more frequent than infection in the first or second trimester, usually re- sults in subclinical infection of the newborn. It is important to be aware that the overall frequency of subclinical infection in new- borns with congenital toxoplasmosis is as high as 85%. The vast ma- jority of these neonatal infections are initially unnoticed, of which a fraction later develop choroidoretinitis. Treatment of the mother during pregnancy aims to reduce the frequency and severity of fetal infection. However, the efficacy of such treatment is debatable (see next). Treatment aimed at preventing mother-to-child transmission

 should be given within 3 weeks of infection. In practice, this is very difficult because most infections are asymptomatic. Seroprevalence increases with age. It does not vary signifi- cantly between sexes and tends to be less in cold, hot, and arid areas, and at high altitudes. Incidence of infection varies with the population group and geographical location. In El Salvador and France, seropositivity is as high as 40–50% by the fourth decade of life, compared with an overall seroprevalence of 15% in the United States of America. In various countries, seroprevalence of T. gondii has decreased by approximately one-third over the past decades. Prevention Since the infection is naturally acquired through ingestion of under- cooked cyst-containing meat or food contaminated with oocysts, infection is preventable in almost all cases. Primary prophylaxis (prevention of infection) by avoiding ingestion is the strategy of choice in seronegative people, whereas in seropositive immunocom- promised patients (e.g. people with AIDS) or seronegative recipients of organ transplants (e.g. heart, bone marrow) from seropositive donors, primary prophylaxis using trimethoprim/sulfamethoxazole has proved effective. Secondary prevention is employed to prevent transmission from the acutely infected mother to her fetus using

spiramycin, in immunocompromised patients following treatment of reactivated toxoplasmosis (maintenance therapy) using pyri- methamine/sulphadiazine. Systematic serological screening of all pregnant women is performed only in some countries. Uncertainty about the incidence of congenital infection, problems with the sensitivity and specificity of serological tests especially in the first trimester, and doubts of the benefit of treating newborns with asymptomatic congenital toxoplasmosis has hampered attempts to implement screening programmes in several countries. Neonatal screening programmes have allowed the identification of as many as 80% of infected newborns. Clinical features Infection with T. gondii may be subclinical or it may cause clin- ical signs and symptoms that vary according to the immune status of the patient and their clinical situation ('toxoplasmosis'). Four clinical situations can be distinguished: the immunocompetent patient, patients with ocular disease, the immunocompromised patient, and the patient with congenital toxoplasmosis. Immunocompetent adults and children Primary T. gondii infection in children and adults is generally asymptomatic. In approximately 10% of the patients, it causes a self-limited and nonspecific illness that very seldom requires treat- ment. The most frequently observed clinical manifestation is iso- lated cervical or occipital lymphadenopathy. Lymph nodes are not tender, do not suppurate, are usually discrete, and stay enlarged for less than 4 to 6 weeks. Very infrequently, chronic lymphadenitis, myocarditis, polymyositis, pneumonitis, hepatitis, or encephal- itis can occur in otherwise healthy individuals. Acute toxoplasma infection during pregnancy is asymptomatic in the vast majority of women. Ocular toxoplasmosis Toxoplasma choroidoretinitis can be observed in congenital or postnatally acquired disease where it results from acute infection or reactivation. Choroidoretinitis can present in infancy or early childhood or might reactivate later. It is uncommon after the age of 40. Bilateral disease, old retinal scars, and involvement of the macula are hallmarks of retinal disease in these cases. In contrast, in patients who present with toxoplasma choroidoretinitis in acute Probability of congenital infection 0 5 10 15 20 Gestational age at seroconversion (weeks) 25 30 35 40 0.5 0.4 0.3 0.2 0.1 0 0.6 0.7 0.8 0.9 1.0 Fig. 8.8.4.2 Risk of mother-to-child transmission of T. gondii by gestational age at maternal seroconversion. Reprinted from The Lancet, Vol. 369, Thiebaut R et al. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data, pages 115–22, copyright © 2007, with permission from Elsevier.

section 8 Infectious diseases 1420 toxoplasmosis typically only one eye is involved, the macula is spared, and there is no old scarring. AIDS and non-AIDS immunocompromised patients In contrast to the relatively favourable course of toxoplasmosis in most immunocompetent people, it is life-threatening in the im- munosuppressed. Toxoplasmosis almost always occurs as a result of reactivation of chronic infection. It can occur when a heart, kidney, or liver from a seropositive donor is transplanted into a seronega- tive recipient; patients with HIV/AIDS and patients receiving sec- ondary immunosuppression, including biologic therapies, are also at risk. The central nervous system is the most commonly af- fected site. Toxoplasmic encephalitis may present subacutely, grad- ually evolving over weeks, or as an acute confusional state with or without focal neurological deficits, evolving over days. Clinical features include changes in level of consciousness, seizures, focal motor deficits, cranial nerve disturbances, sensory abnormalities, cerebellar signs, movement disorders, and neuropsychiatric dis- turbances. The differential diagnosis of toxoplasmic encephalitis lesions includes central nervous system lymphoma, progressive multifocal leukoencephalopathy, infection with cytomegalovirus, cryptococcosis aspergillosis, bacterial abscess, and tuberculosis. In 0.5 Probability of intracranial lesions 0.4 0.3 0.2 0.1 0 0 5 10 15 20 Gestational age at seroconversion (weeks) (b) Risk of eye lesions (n-526) (a) Risk of intracranial

lesions (n-473) 25 30 35 40 0.6 0.7 0.8 0.9 1.0 0.5 Probability of eye lesions 0.4 0.3 0.2 0.1 0 0 5 10 15 20 Gestational age at seroconversion (weeks) 25 30 35 40 0.6 0.7 0.8 0.9 1.0 Fig. 8.8.4.3 Risk of intracranial and eye lesions in children infected with T. gondii by gestational age at maternal seroconversion. Reprinted from The Lancet, Vol. 369, Thiebaut R et al. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data, pages 115–22, copyright © 2007, with permission from Elsevier.

8.8.4 Toxoplasmosis 1421 immunocompromised patients, toxoplasmosis can also present as choroidoretinitis, pneumonitis, or multiorgan disease, presenting with acute respiratory failure and haemodynamic abnormalities re- sembling septic shock. Congenital toxoplasmosis Prenatal ultrasound examination often fails to detect a fetus with congenital toxoplasmosis. Abnormalities include intracra- nial calcification, ventricular dilatation, hepatic enlargement, ascites, and increased placental thickness. Approximately 85% of newborns with congenital infection appear normal at birth. However, if untreated, congenital toxoplasmosis may result later in loss of vision, and children born with symptoms of congenital infection can later develop psychomotor retardation, intellectual disability, and hearing loss. Fetal and neonatal disease is more se- vere the earlier in gestation the acute infection was acquired. The classic triad of chorioretinitis, hydrocephalus, and cerebral calci- fication is rather rare. None of the signs described in newborns with congenital disease are pathognomonic for toxoplasmosis and may be mimicked by other congenital infection such as cyto- megalovirus, herpes simplex virus, rubella, and syphilis. Early maternal infection can result in death of the fetus in utero and spontaneous abortion. Clinical investigation and criteria for diagnosis Infection in the immunocompetent host Immunocompetent adults and children with toxoplasma lymph- adenitis are usually not treated unless symptoms are severe or per- sistent. Characteristic histological criteria and a panel of serological tests (IgG, IgM, IgG avidity index) consistent with recently acquired infection establish the diagnosis of toxoplasma lymphadenitis in older children and adults. If required, treatment is usually admin- istered for 2 to 4 weeks, followed by reassessment of the patient's condition. The combination of pyrimethamine, sulphadiazine, and folinic acid for 4 to 6 weeks is the most common drug combination used (Table 8.8.4.1). Table 8.8.4.1 Suggested regimens for the treatment of infection with T. gondii Therapy/drug Dosage Duration Acute acquired infection Symptomatica Acute toxoplasmosis in pregnant womenb Spiramycin 3 g once a day in three divided doses without food Until termc or until fetal infection is documented Documented fetal infection (after 18 weeks of gestation)d Pyrimethamine Loading dose: 100 mg once a day in two divided doses for 2 days, then 50 mg once a day Until term plus Sulphadiazine Loading dose 75 mg/kg once a day in two divided doses (max. 4 g once a day) for 2 days, then 100 mg/kg once a day in two divided doses (max. 4 g once a day) Until term plus Leucovorin (folinic acid) 5–20 mg once a day During and for 1 week after pyrimethamine therapy Congenital toxoplasma infection in the infante Pyrimethamine Loading dose 2 mg/kg once a day for 2 days, then 1 mg/kg once a day for 2–6 months, then this dose every Monday, Wednesday, Friday 1 year plus Sulphadiazine 100 mg/kg once a day in two divided doses 1 year plus Leucovorin 10 mg three times weekly During and for 1 week after pyrimethamine therapy Corticosteroids (prednisone)f 1 mg/kg once a day in two divided doses Until resolution of signs and symptoms Choroidoretinitis in adults Pyrimethamine Loading dose 200 mg once a day, then 50–75 mg once a day Usually 1–2 weeks after resolution of symptoms plus Sulphadizine Oral, 1–1.5 g once a day Usually 1–2 weeks after resolution of symptoms plus Leucovorin 5–20 mg three times weekly During and for 1 week after pyrimethamine therapy Corticosteroidsf 1 mg/kg once a day in two divided doses Until resolution of signs and symptoms Acute/primary therapy of

toxoplasmic encephalitis in AIDS patients Standard regimens: Pyrimethamine Oral, 200 mg loading dose, then 50–75 mg once a day At least 4–6 weeks after resolution of signs and symptoms (continued)

section 8 Infectious diseases 1422 Management of maternal and fetal infection The IgG and IgM antibody status of a pregnant woman should be obtained before or early in pregnancy. The absence of IgG antibodies before or early in pregnancy allows identification of those women at risk of acquiring the infection. The presence of IgG and IgM anti- bodies indicates recent infection in approximately 40% of patients. The presence of high-avidity IgG antibodies essentially rules out an infection acquired in the previous 3 or 4 months, whereas low avidity antibodies can persist for more than 3 months after infection, especially in pregnant women. Detection of IgG and IgM antibodies establishes that the patient has been infected, whereas seronegative women should be provided with necessary information to prevent primary infection (see earlier). Absence of IgM antibodies during the first two trimesters virtually rules out recently acquired infec- tion unless the sera were obtained too early for the IgM antibody response to be detectable or too late after IgM antibodies had be- come nondetectable. The definitive diagnosis of acute toxoplasma infection or toxoplasmosis requires demonstration of a rise in titres in serial specimens (either conversion from a negative to a positive titre or a significant rise from a low to a higher titre). Treatment of women with acute acquired infection using spiramycin was thought to reduce the incidence and severity of fetal infection by approxi- mately 60%, but a recent meta-analysis of data from children diag- nosed by prenatal screening showed an effect only on intracranial lesions and not on choroidoretinitis at birth. Therapy should be started as soon as possible after diagnosis of recently acquired ma- ternal infection (Table 8.8.4.1). Since maternal infection does not necessarily result in fetal infection, suspected or established ma- ternal infection acquired during pregnancy (based on ultrasonog- raphy or serology) must be confirmed by prenatal diagnosis of fetal infection using polymerase chain reaction (PCR) on amniotic fluid. PCR has an overall reported sensitivity of between 64 and 98.8%. When the PCR is positive or it is highly probable that the fetus is infected, pyrimethamine/sulphadiazine is given in combination with folinic acid after gestational week 20 and continued throughout the pregnancy. Spiramycin is used before gestational week 18. If the initial ultrasound reveals no abnormalities, it should be repeated at least monthly until term. Hydrocephalus is an indication for thera- peutic abortion. Since fetal infection is undetected in 85% of new- borns, serology is commonly performed for neonatal diagnosis. The presence of IgG antibodies in the neonate’s serum may reflect maternal and/or its own antibodies. Testing for IgM and IgA anti- bodies will identify up to 75% of infected newborns. Maternally transferred IgG antibodies usually decline and disappear within 6 to 12 months. Immunoblots can, in most but not all cases, distin- guish maternal and fetal T. gondii specific IgG and IgM antibodies. Treatment of the fetus is followed by treatment of the symptomatic newborn throughout the first year of life, but the benefit of treating Therapy/drug Dosage Duration Leucovorin Oral, IV, or IM, 10–20 mg once a day (up to 50 mg once a day) During and for 1 week after pyrimethamine therapy plus Sulphadiazine Oral, 1–1.5 g four timses daily g or Clindamycin Oral or IV, 600 mg four times daily (up to IV 1200 mg four times daily) g Possible alternative regimens: (1) Co-trimoxazole Oral or IV, 10 mg (trimethoprim component)/kg four times daily g (2) Pyrimethamine plus leucovorin As in standard regimens g plus one of the following: Atovaquone Oral, 750 mg four times daily g Clarithromycin Oral, 1 g two times daily g Azithromycin Oral, 1200–1500 mg once a day g Dapsone Oral, 100 mg once a day g IM, intramuscular; IV, intravenous; q6 h, every 6 h; q12 h, every 12 h. a Acute acquired infection in immunocompetent patients does not require specific treatment unless

there are severe or persistent symptoms or evidence of damage to vital organs.
If such signs or symptoms occur, treatment with pyrimethamine/sulphadiazine, and leucovorin should be initiated (for dosages, see ‘Toxoplasmic choroidoretinitis in adults’). b Practices vary widely between centres. c German and Austrian guidelines recommend using spiramycin prophylaxis until 17 weeks of pregnancy followed by a 4-week course of pyrimethamine plus sulphadiazine plus leucovorin). d Practices vary widely between centres (pyrimethamine plus sulphadoxine is used in some centres, monthly alternating cycles of pyrimethamine plus sulphadiazine and spiramycin). e Practices vary widely between centres (monthly alternating cycles of pyrimethamine plus sulphadiazine and spiramycin). f When cerebrospinal protein is more than 1 g/dl and when active choroidoretinitis threatens vision. g Duration of treatment as for pyrimethamine in patient with toxoplasmic encephalitis. Table 8.8.4.1 Continued

8.8.4 Toxoplasmosis 1423 asymptomatic newborns with congenital toxoplasmosis after birth is debatable (Table 8.8.4.1). Retinochoroiditis The decision to treat active toxoplasma choroidoretinitis should be based on examination by an experienced ophthalmologist. Low titres of IgG antibody are usual in patients with active choroidoretinitis due to reactivation of congenital T. gondii infection. IgM antibodies are usually not detected. Patients with retinochoroiditis due to postnatally acquired disease usually have serological tests results consistent with an infection acquired in the recent past. PCR per- formed on aqueous humour has shown sensitivities of up to 55% that increased to 85% when used in combination with serological tests. Most ophthalmologists recommend treatment if there are se- vere inflammatory responses and/or proximity of retinal lesions to the fovea or optic disc (Table 8.8.4.1). The combination of pyri- methamine and sulphadiazine is the most commonly used regimen. Prednisolone is added if the lesion threatens the macula. The inci- dence of recurrent toxoplasma retinochoroiditis has been signifi- cantly reduced by using long-term intermittent co-trimoxazole (trimethoprim/sulfamethoxazole). Infection in the immunocompromised host In immunocompromised patients with suspected reactivation, PCR rather than serological methods are strongly recommended. Pre-emptive antiparasitic therapy should be considered in all symptomatic seropositive immunosuppressed patients suspected to have toxoplasmosis. If the clinical features suggest central ner- vous system and/or spinal cord involvement, CT or MRI is man- datory. In most studies PCR performed on cerebrospinal fluid showed sensitivities between 60% and 75% while PCR on blood samples did not achieve sensitivities greater than 30% in most studies. Empirical anti-T. gondii therapy is accepted practice for patients with multiple ring-enhancing brain lesions (usually es- tablished by MRI), positive IgG antibody titres against T. gondii, and advanced immunodeficiency. Clinical and radiological re- sponse to specific anti-T. gondii therapy supports the diagnosis of central nervous system toxoplasmosis. The most commonly used and successful regimen continues to be the combination of pyri- methamine and sulphadiazine with folinic acid (Table 8.8.4.1). Clindamycin can be used instead of sulphadiazine in patients in- tolerant of sulphonamides. Duration of treatment is recommended for 4 to 6 weeks after resolution of all signs and symptoms (often for several months or longer). After treatment of the acute phase (primary or induction treatment) in immunosuppressed patients, maintenance treatment (secondary prophylaxis) should be insti- tuted using the same regimen as for the acute phase but at half the dose. In patients with AIDS, secondary prophylaxis is usually discontinued when the patient’s CD4 count has returned to above 200 cells/μl and HIV viral load has been controlled by antiretro- virals for at least 6 months. Areas of uncertainty and future developments • Epidemiology: ■ Sources of infection, relative importance (e.g. water, meat, cats) • Pathogenesis/pathology: ■ Susceptibility of the host to infection (e.g. human leukocyte antigen types) ■ Strain differences and clinical presentation ■

Virulence factors • Diagnosis: ■ Improved avidity testing using recombinant antigens ■ Increased sensitivity of PCR on amniotic fluid • Treatment/prophylaxis: ■ Clinical treatment trials in different clinical situations, for ex- ample, eye disease and congenital toxoplasmosis using new drugs (e.g. atovaquone) • Prevention strategies/screening: ■ Co-trimoxazole for prevention of multiple episodes of recur- rent episodes of chorioretinitis ■ Atovaquone for prophylaxis of toxoplasmic encephalitis ■ Prophylaxis and treatment in bone marrow transplant recipients ■ Effectiveness of prevention strategies in pregnancy ■ Cost-effectiveness of routine screening programmes ■ Vaccination: proteins, DNA, adjuvants, and mucosal strategies FURTHER READING Cook AJ, et al. (2000). Sources of toxoplasma infection in preg- nant women: European multicentre case–control study. European Research Network on Congenital Toxoplasmosis. BMJ, 321, 142–47. Elbez-Rubinstein A, et al. (2009). Congenital toxoplasmosis and reinfection during pregnancy: case report, strain characteriza- tion, experimental model of reinfection, and review. J Infect Dis, 199, 280–5. Gilbert RE, et al. (2008). The European Multicentre Study on Congenital Toxoplasmosis (EMSCOT). Ocular sequelae of con- genital toxoplasmosis in brazil compared with Europe. PLoS Negl Trop Di, 2, e277. Gras L, et al. (2005). Association between prenatal treatment and clin- ical manifestations of congenital toxoplasmosis in infancy: a cohort study in 13 European centres. Acta Paediatr, 94, 1721–31. Hernadez AV, et al. (2017). A systematic review and meta-analysis of the relative efficacy and safety of treatment regimens for HIV-associated cerebral toxoplasmosis: is trimethoprim-sulfamethoxazole a real option? HIV Med 18, 115–124. Holland GN (2003). Ocular toxoplasmosis: a global reassessment. Part I: epidemiology and course of disease. Am J Ophthalmol, 136, 973–88. Holland GN (2004). Ocular toxoplasmosis: a global reassessment. Part II: disease manifestations and management. Am J Ophthalmol, 137, 1–17. Luft BJ, et al. (1984). Toxoplasmic encephalitis in patients with ac- quired immune deficiency syndrome. JAMA, 252, 913–17. McLeod R, et al. (2006). Outcome of treatment for congenital toxo- plasmosis, 1981–2004: the National Collaborative Chicago-Based, Congenital Toxoplasmosis Study. Clin Infect Dis, 42, 1383–94. Montoya JG, Liesenfeld O (2004). Toxoplasmosis. Lancet, 363, 1965–76. Pomares C, Montoya JG (2016). Laboratory diagnosis of congenital toxoplasmosis. Clin Microbiol, 54, 2448–54.

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