Toxoplasmosis in Germany
Epidemiology, Diagnosis, Risk factors, and Treatment
Uwe Pleyer, Uwe Gross, Dirk Schlüter, Henrik Wilking, Frank Seeber

Summary

Background: With approximately 30% of the world population infected, *Toxoplasma gondii* is one of the most widespread pathogenic parasites in both humans and animals and a major problem for health economics in many countries.

Methods: This review is based on the findings of individual studies, meta-analyses, and Cochrane Reviews retrieved by a selective literature survey of the Medline and Google Scholar databases.

Results: Current data indicate a high rate of *Toxoplasma gondii* infection in Germany, ranging from 20% to 77% depending on age (95% confidence interval for 18- to 29-year-olds [17.0; 23.1]; for 70- to 79-year-olds [72.7; 80.5]). Male sex, caring for a cat, and a body mass index of 30 or more are independent risk factors for seroconversion. Postnatally acquired (food-related) infection is predominant, but maternal-to-fetal transmission still plays an important role. While most infections are asymptomatic, congenital toxoplasmosis and reactivated *Toxoplasma* encephalitis in immunosuppressed persons (transplant recipients and others) are sources of considerable morbidity. *Toxoplasma gondii* infection of the retina is the most common cause of infectious uveitis in Germany. The diagnosis and treatment of this type of parasitic infection are particular to the specific organs involved in the individual patient.

Conclusion: Desirable steps for the near future include development of an effective treatment for the cystic stage and identification of biomarkers to assess the risk of reactivation and predict the disease course.


*Toxoplasma gondii* is an extremely successful protozoan parasite that infects about one-third of the world’s population (1). The World Health Organization (WHO) estimates that, in Europe, 20% of the burden of disease transmitted through food is caused by *T. gondii* infection (2). The life cycle of this single-cell organism is complex. In humans, the main oral source of infection is believed to be eating or handling inadequately cooked or raw meat containing tissue cysts (bradyzoites), or consuming fruit, vegetables, or water contaminated with oocysts (“spores”) (3) (Figure 1). Because of the risk of mother-to-child transmission, these zoonotic routes of infection are particularly important in cases where a woman is infected for the first time during pregnancy (4). In addition to congenital toxoplasmosis, reactivated *Toxoplasma* encephalitis in immunosuppressed patients (e.g., those with AIDS or under heavy immunosuppression following stem cell or organ transplantation) and ocular toxoplasmosis are clinically significant manifestations of this disease (Figure 1). If disability-adjusted life years (DALY) per case are taken as a measure of the severity of disease, in Europe, congenital toxoplasmosis, at 2.42 DALY’s per case [95% confidence interval (CI): 1.92; 3.05], is on a level with hepatitis B (2.79 [1.46; 4.45]) and invasive pneumococcal infection (2.74 [2.71; 2.77]), and ranks ahead of tetanus infection (2.02 [1.91; 2.15]) (e1). According to the WHO, toxoplasmosis is an important public health issue (4, e2). In 2016, as part of a study of adult health in Germany (DEGS1), the Robert Koch Institute surveyed *T. gondii* seroprevalence among adults in Germany for the first time (5) and found it to be 49.1%.

The present article is based on a literature search using the search terms “diagnosis,” “encephalitis,” “Toxoplasma gondii,” and “Germany.”

Definition

*Toxoplasma gondii* is a protozoan parasite that infects about one-third of the world’s population.

Clinical significance

In addition to congenital toxoplasmosis, reactivated *Toxoplasma* encephalitis in immunosuppressed patients and ocular toxoplasmosis are clinically significant manifestations of this disease.
Learning goals
After reading this article, the reader should:
- Know the routes of infection, epidemiology, and risks of this parasitic infection
- Have a good grasp of the clinical features, organ manifestations, and sequelae of the infection
- Understand the rationale of the preventive measures and treatment options for T. gondii infection

Epidemiology
In Germany, T. gondii infections in humans are probably acquired mainly through the consumption of pork in raw sausage products (Rohwurst, Mettwurst) (5). To date there have been no reports in Germany of outbreaks caused by contaminated drinking water or surface water (e4, e5). Oocysts have also been shown to be present in air samples, so infection via the airways cannot be ruled out (e6). The influence of eating habits and food hygiene is reflected in current epidemiological data and serosurveys on infection rates. The latter are an important surrogate in the search for information about the prevalence of infection. Seroconversion rates vary greatly around Europe, ranging from 7% to 10% in Norway and the United Kingdom to 44% and 50% in France and Germany respectively (5, e7). In adults in Germany (18 to 79 years of age), the seroprevalence of IgG antibodies against T. gondii is almost 50%, rising in an almost linear fashion (1% per year) from about 20% in young adults (18 to 29 years) to 77% in the 70- to 79-year-old age group (5). Men, cat owners, and the obese (BMI ≥ 30) were more often seropositive. Vegetarian eating habits and high socioeconomic status were found to be preventive factors.

Modeling on the basis of this data suggests that every year about 6390 infections occur during pregnancy, and that an estimated 345 neonates will be clinically symptomatic (5). This is far higher than the number of children with congenital toxoplasmosis reported annually to the Robert Koch Institute (between 6 and 38); the discrepancy may be explained by considerable under-reporting and/or abortions caused by unidentified infection. At the same time, these numbers confirm the importance of this zoonosis for public health (4) (Figure 2).

Pathogenesis and pathology
The pathophysiology and clinical course of toxoplasmosis are largely determined by the complex life cycle

Infection cycle
T. gondii is transmitted in the form of oocysts (spores) excreted in the feces of infected cats (1). Thus, T. gondii can be transmitted to domestic animals and rodents as well as to humans via contaminated food.

Epidemiology
In Germany, T. gondii infections in humans are probably acquired mainly through the consumption of pork in raw sausage products. To date there have been no reports in Germany of outbreaks caused by contaminated drinking water or surface water.
MEDICINE

of T. gondii, the diversity of its strains, and the immune adaptation of the pathogen (Figure 1) (3). After ingestion of the pathogen, intestinal infection of macrophages and dendritic cells results in hematogenous spread affecting first and foremost neural (brain, eyes) and lymphatic tissue, the heart, and the lungs. In cases of acute infection with lysis of infected host cells, the presence in the blood of extracellular tachyzoites (corresponding to the development stage of a parasite in which acute, rapid replication takes place) can lead to infection of organs and of the placenta as well.

Susceptibility and the severity of clinical manifestations are both subject to the interactions of pathogen- and host-specific factors and are the focus of current research (eTable 1). In Europe and North America, about 70% to 80% of infections are caused by type II genotype, which is relatively avirulent and in ocular toxoplasmosis, for example, tends to result in a chronic recurrent course. In contrast to this, particularly in South America, the genetic diversity of T. gondii is greater and infections are also caused by type I, type III, and “atypical” (recombinant) genotypes. The

Seroprevalence
In adults in Germany (18 to 79 years of age), the seroprevalence of IgG antibodies against T. gondii is almost 50%, rising in an almost linear fashion (1% per year) from about 20% in young adults (18 to 29 years) to 77% in the 70-to 79-year-old age group.

Pathogenesis and pathology
After ingestion of the pathogen, intestinal infection of macrophages and dendritic cells results in hematogenous spread affecting especially neural (brain, eyes) and lymphatic tissue, the heart, and the lungs.
clinically more serious, often fulminant course with these types is believed to be due to greater rapidity of replication, extracellular migration of the pathogen, and reduced differentiation into bradyzoites (7, e10).

The immune system plays an important part in susceptibility and the clinical course of toxoplasmosis (eFigure). While cellular immune mechanisms control the pathogen in infected cells, *T. gondii*-specific antibodies contribute to the neutralization of extracellular tachyzoites, which in women who have been previously infected helps to protect the placenta from infection. With the aid of these immune mechanisms, the pathogen can be eliminated from practically every cell in the body.

However, under the pressure of the immune response, a few parasites in neurons and myocytes transform into bradyzoites and persist intracellularly in tissue cysts. This persistence of the pathogen requires the maintenance of a protective proinflammatory immune response and the development of immunosuppressive and regulatory T cells. This is particularly important in ocular toxoplasmosis because of the highly sensitive retina, which cannot be regenerated (7, e10). Clinical studies indicate that among other factors the balance between IL-17-producing T cells on the one hand and astrocytes and regulatory T cells on the other is important, because the retina can be damaged not just by the pathogen but also by an IL-17-mediated immune pathology (7). If immunity weakens, the infection can reactivate with renewed tachyzoite replication and tissue necrosis. This manifests clinically both in (immunocompetent) patients with re- \tachyzoite replication and tissue necrosis. This manifests clinically both in (immunocompetent) patients with reactivation and in AIDS patients with low CD4+ T cells in the brain. Despite the high prevalence of infection and pathogen persistence, clinically significant reactivated toxoplasmosis occurs only rarely in persons who are receiving strong immunosuppressants, e.g., TNF blockers in patients with ankylosing spondylitis (8, e11, e12). This may emphasize the importance of local immune mechanisms, but it may also, e.g., in AIDS patients, underline the role being played by the retrovirus itself, with impaired antiparasitic function of HIV-infected microglia.

The close relationship between the immune system and effective parasite control is also shown by studies that have identified genetic polymorphisms as risk factors in genes that are important for immune reactions (eTable 1).

**Clinical manifestations of toxoplasmosis**

In most cases toxoplasmosis is asymptomatic or accompanied by mild flu-like symptoms. Fewer than 10% of infected persons develop a mononucleosis-type pattern of symptoms including fever, headache, and aching limbs, along with lymphadenitis, especially of the cervical and occipital lymph nodes. These become hard, tender to the touch, and may remain swollen for several weeks. In a few cases, an uncharacteristic maculopapular rash, reactive arthritis, or organ findings such as hepatosplenomegaly, myocarditis, or pneumonia have been observed (1, 6).

Clinically significant manifestations include congenital and ocular toxoplasmosis and, in immunosuppressed patients, organ manifestations that can often be life-threatening (encephalitis, pneumonia) (4, 15–17).

**Congenital infection**

The WHO estimates the global annual incidence of congenital toxoplasmosis at about 190 100 cases and considers it an underestimated burden of disease with considerable sequelae (4). In Germany, between 6 and 38 cases a year are notified to the Robert Koch Institute (https://survstat.rki.de) in accordance with the Infection Protection Act (IfSG, Infektionsschutzgesetz). However, since only a minority of infected children show any clinical abnormality at birth, and only these cases are reported, the real number must be considerably higher. In fact, computer modeling suggests that more than 1200 congenitally infected children are born in Germany every year (5). Placental transmission is a risk only when the first infection occurs during a pregnancy; during a second or later infection, antibodies that persist throughout life opsonize the parasites, leading to antibody-mediated phagocytosis. Rare circumstances in which transmission can occur during pregnancy include reactivation of disease in a previously *T. gondii*-seropositive pregnant woman who is immunosuppressed, or reinfection with a different genotype of the pathogen (18).

The risk of diaplacental transmission increases with gestational age, whereas the rate of clinical manifestation goes down (e13). Infection during early pregnancy with severe damage to the fetus presumably often results in abortion. No data are available on this, as embryos aborted in Germany are seldom presented for detailed examination. Especially infection during the second trimester can result in severe damage to the child, in the form of

- Micro- or hydrocephalus
- Intracerebral calcifications
- Retinochoroiditis or microphthalmia

However, this classic triad occurs in only about 5% of the affected fetuses (19).

**Role of the immune system**

While cellular immune mechanisms control the pathogen in infected cells, *T. gondii*-specific antibodies contribute to the neutralization of extracellular tachyzoites, which in women who have been previously infected helps to protect the placenta from infection.

**Clinically significant manifestations**

Clinically significant manifestations include congenital and ocular toxoplasmosis and, in immunosuppressed patients, organ manifestations that can often be life-threatening (encephalitis, pneumonia).
Surveillance data from France indicate that after a first infection during pregnancy, about 12% of babies show clinical symptoms at birth (20). Severe CNS manifestations are identified on prenatal ultrasound (e14). Postnatally, infected infants may show poor feeding, seizures, or cerebral palsy as signs of CNS involvement. Although placental transmission in the third trimester is the most common, most fetuses infected at this time appear normal on ultrasound and are asymptomatic as neonates. In about 50% of patients, however, the latent infection leads to ocular toxoplasmosis, often bilateral, during the first 20 years of life, which cannot in all cases be distinguished from postnatally acquired infection (20). Sequelae include large scotomas, significant visual impairment, and blindness.

Ocular toxoplasmosis
Retinal infection with *T. gondii* is an important cause of irreversible visual impairment and is worldwide the most common cause of infectious posterior uveitis. In Germany, about 4% of uveitis manifestations have been traced to *T. gondii* infection (16, e15). Ocular involvement in congenital toxoplasmosis was described as early as 1923 and led to a dogmatic belief in (exclusively) mother-to-child infection. In the 1980s, as other routes of infection for postnatal toxoplasmosis were being identified, this belief was revised. Ocular toxoplasmosis (16, e16) follows a course of necrotizing posterior uveitis so characteristic that it is often regarded as “diagnosis at a glance.” As a retinochoroiditis, the infection affects the inner layers of the retina, with persistence of the pathogen in tissue cysts and a tendency to reactivations (16, e16). In Europe 5-year recurrence rates between 54% and 63% have been reported, while the reported rates in South America are even higher (up to 80%) (21, 22). Numerous risk factors have been reported, suggesting that the host–pathogen interaction is complex and, above all, immune mediated (eTable 1) (14, 21, 22).

The importance of immune status for ocular toxoplasmosis became clear at the beginning of the AIDS epidemic. At least three alleles were associated with susceptibility to ocular manifestation in AIDS patients (e17). An HLA-B35 genotype was significantly more frequently (p = 0.01; relative risk [RR] = 3.04) associated with progressive retinitis. Clinically, the presentation is often atypical and fulminant and can present a considerable diagnostic challenge requiring intracocular investigation. Repeatedly, pathogens with type I alleles have been identified (11, e18) (Figure 3).

Immunosuppression
Infection and reactivation in transplant recipients
The risks associated with transplantation are inadequately documented and probably underestimated (23–26). Toxoplasmosis can occur in recipients both of solid organs and of hematopoietic stem cell transplants and may be due to reactivation of a latent infection, to a newly acquired food-borne infection, or to tissue cysts contained in a transplant (24). Recent data show a significantly lower 6-month survival rate for *T. gondii*-seropositive recipients, especially after allogeneic stem cell transplantation (38% vs. 84%; p <0.001) and liver transplantation (50% vs. 75%; p <0.001) (23). The risk of transmission is especially high when a solid organ is transplanted from a recently infected donor into a seronegative recipient (Table). The risk is due to the tachyzoites present in blood, bone marrow, and various organs during parasitemia in the early phase of the infection. How long the risk of transmission persists after the donor has acquired the infection is not known for certain. Parasitemia has been shown as much as 5 weeks after the onset of symptoms. There is also a risk of transmission when transplants, especially of heart, liver, or kidney, from donors with tissue cysts due to chronic *T. gondii* infection are given to seronegative recipients. No exact figures are

**Table**

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**Figure 3:** Retinal image of a 27-year-old woman with recurrent ocular toxoplasmosis in the right eye. Retinal necrosis can be seen above the macula, with a fresh recurrence (central “fluffy” focus) surrounded by two older, pigmented lesions. Visual acuity is reduced to 0.63, with a deep, irreversible paracentral visual field defect (Department of Ophthalmology, Charité Campus Virchow, University Faculty of Medicine, Berlin).

**Ocular toxoplasmosis**
Retinal infection with *T. gondii* is an important cause of irreversible visual impairment and is worldwide the most common cause of infectious posterior uveitis. In Germany, about 4% of uveitis manifestations have been traced to *T. gondii* infection.

**Transplant recipients**
Toxoplasmosis can occur in recipients both of solid organs and of hematopoietic stem cell transplants and may be due to reactivation of a pre-existing latent infection, to a newly acquired food-borne infection, or to tissue cysts contained in a transplant.
available on the incidence of *T. gondii* infection when the donor is infected and the recipient seronegative, but rates of 25% to 75% in the absence of appropriate prophylaxis have been reported (e19).

Regarding solid organs, seronegative recipients of organs from seropositive donors (especially heart/lung) are at greatest risk (eTable 2). In such cases, the parasitemia results primarily in the infection of liver and lungs, with the typical signs of hepatitis and/or interstitial pneumonia (26).

The constellation with the highest risk for reactivation is transplantation of stem cells from a seronegative donor to a seropositive recipient (eTable 2). European centers report reactivation rates between 2.9% and 6% (26, 27). Mortality rates in transplant recipients who develop toxoplasmosis range from 63% to 80% (26). The German Society for Hematology and Medical Oncology (DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie) has issued specific guidelines on prevention in allogeneic hematopoietic stem cell transplantation (27). Where the recipient is seropositive, long-term medical prophylaxis with cotrimoxazole is recommended. Other preventive measures in the transplantation setting include serological screening of both donors and recipients, medicinal prophylaxis, and instruction on hygiene (26). The transplant services of various countries have published recommendations on this topic, although these vary within Europe, e.g., as to the duration of chemoprophylaxis.

### Incidence in organ donors
No exact figures are available on the incidence of *T. gondii* infection when the donor is infected and the recipient seronegative, but rates of 25% to 75% in the absence of appropriate prophylaxis have been reported.

### Mortality in transplant recipients
Mortality rates in transplant recipients who develop toxoplasmosis range from 63% to 80%.
Infection and reactivation in HIV-infected patients

The importance of cellular immunity for control of the cyst stage and the risk of reactivation is shown by the high incidence of *Toxoplasma* encephalitis in AIDS patients with fewer than 200 CD4+ T cells/μL. Before the introduction of highly active antiretroviral therapy (HAART), *Toxoplasma* encephalitis and *Toxoplasma* retinitis, present in about 30% of this risk group, were regarded as AIDS-defining opportunistic infections. Today toxoplasmosis remains the most common cause of neurological disease in HIV-positive patients, often resulting in severe pathology or even death.

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2019; 116: 434–44

Diagnosis

Because infection with *T. gondii* usually gives rise to nonspecific symptoms or none at all, it requires laboratory diagnosis (30, 31). The main investigations available are serological procedures such as ELISA and immunoblotting. The use of recombinant antigens has made an important contribution to standardization (30, e21).

If an acute infection is suspected, the patient’s serum should be tested for *T. gondii*-specific IgG and IgM antibodies (6). If organ-specific manifestations are present, local diagnostic tests are also carried out.

Prenatal diagnosis and monitoring

Especially during pregnancy, a low-positive IgM result, perhaps continuing for a long time, accompanied by the simultaneous presence of IgG antibodies—a sign of IgM persistence after a previous infection—presents a diagnostic challenge. It is assumed that the immune response with TH2 dominance, built up during pregnancy, suppresses the infection for the fetoplacental unit, plays an important role for this constellation. Absence IgM, on the other hand, is of no diagnostic significance (e22).

Abnormalities in neonates

In addition to serological studies, other diagnostic procedures used in neonates are cranial and abdominal ultrasonography (or magnetic resonance imaging) and ophthalmological examination. In neonates showing any abnormality, the cerebrospinal fluid is also investigated (serology, polymerase chain reaction [PCR], protein level). Determination of cellular immunity parameters can also supply diagnostic evidence of prenatal infection (33). Because a negative PCR result does not rule out a pregnancy-relevant infection (34, e24), and early initiation of therapy is necessary even for suspected primary infection, PCR testing of amniotic fluid is rarely carried out (35).

Diagnosis of ocular toxoplasmosis

Clinical examination often shows typical retinal findings, so that no further diagnostic investigation is needed (Figure 3). In populations with a high prevalence of infection, serological tests are often unhelpful in any case. In doubtful cases, intraocular studies to show the presence of specific intraocular antibodies or PCR to show the pathogen present in the aqueous humor or the vitreous body have proved useful (16).

Diagnosis in immunosuppressed patients

Sero logical tests are unreliable in immunosuppressed patients, especially those who are HIV-positive. In these patients, active or reactivated infection can most reliably be shown by means of PCR (36). Depending on the clinical situation, body fluids (e.g., CSF, EDTA blood, bronchoalveolar lavage fluid) or biopsy samples (e.g., brain, lung) are suitable. Since a negative PCR result does not entirely rule out active infection, histological methods may also need to be used.

Treatment

Asymptomatic infection and uncomplicated lymphadenitis do not require treatment. Patients who become infected for the first time while pregnant and those with congenital ocular toxoplasmosis need to be treated, as do immunocompromised persons (those with HIV/AIDS or neoplastic disease) and immunodeficient transplant recipients with active or reactivated infection.

Infection in HIV-infected patients

Toxoplasmosis is the most common cause of neurological disease in HIV-positive patients, often resulting in severe pathology or even death.

Abnormalities in neonates

In addition to serological studies, other diagnostic procedures used in neonates are cranial and abdominal ultrasonography (or magnetic resonance imaging) and ophthalmological examination.
Ocular toxoplasmosis represents a relative indication for treatment: therapy should be initiated in particular when the optic nerve or macula is threatened, when the patient has reduced visual acuity due to vitreous inflammation, or when the lesions are large (>1 disk diameter) (16). The main targets of drug treatment are the tachyzoite metabolic pathways of folic acid and protein synthesis; to date the tissue cysts containing bradyzoites remain virtually impregnable. The drugs most often used are spiramycin, pyrimethamine, sulfadiazine, clindamycin, and sometimes atovaquone (Table). To minimize unwanted effects, folic acid (not folic acid) is also given. During pregnancy, folic acid antagonists should be used only from the 16th gestational week onwards; before this, spiramycin can be given in the attempt to prevent placental transmission. The priority is rapid initiation of combination therapy. In cases where treatment was started within 4 weeks after maternal infection, the rate of clinical manifestations in infected children was reduced from 70% to less than 20% (35). A recent prospective randomized study also found indications that combination treatment with pyrimethamine plus sulfadiazine plus folic acid was superior to spiramycin in terms of clinical manifestations in infected newborns (37). This is especially the case when treatment is started early, within 3 weeks after maternal seroconversion during pregnancy. For ocular toxoplasmosis, in addition to the drugs already mentioned, cotrimoxazole is increasingly being used and has proved valuable for long-term prevention of recurrence (<12 months) in at-risk patients (e25, e26).

Prevention
Public health institutions in Germany have stated that greater awareness of preventive measures is needed to reduce the risk of infection (6, e27–e29). The main preventive measures relate to reducing the pathogen burden in the food chain; improving food hygiene; public education, especially of women of child-bearing age; and various precautions in immunosuppressed persons (including in transplantation medicine). Specific goals and interventions include the following:

● From the point of view of disease prevention, the goal should be to keep farm animals destined for human consumption free of *T. gondii* (e27). Veterinary data show that this can be achieved by controlling rodent pests and keeping cats out of animal sheds (38).

● Developing vaccines against the excretion of oocysts by infected cats could reduce exposure to oocysts. Live vaccines (Toxovax) are currently being used in sheep to reduce the development of tissue cysts (e30).

● Physicians and health authorities (especially in the eastern federal states of Germany, because of the higher rates of infection there) should be made more aware of the toxoplasmosis issue. Educational prevention programs (adequate cooking of meat and thorough washing of fruit and vegetables [e28, e29]) can only reduce the rate of new infections, however, not eliminate existing cases of infection (e31).

● Screening for *T. gondii* antibodies during pregnancy, as carried out for example in France and Austria, is not currently performed in Germany (e32). However, antenatal care under the prevailing German guidelines (*Mutterschafts-Richtlinien*) does include serological tests when there are grounds for suspecting toxoplasmosis (39). In one retrospective study of 685 pregnant women, early diagnosis and treatment of acute infection in the mother led to a sharp reduction in the disease burden of newborns (35). Since recent data do not support the assumption hitherto that screening prevents only a small number of cases (5), these two facts suggest that the value of a screening program needs to be reassessed (40, e33).

● In transplantation medicine, especially allogeic hematopoietic stem cell transplantation, the preventive measures recommended by the professional societies should be observed: these include screening of donors and recipients, drug prophylaxis, and instructions regarding hygiene (27).

Conflict of interest statement
Professor Gross has received fees for the preparation of scientific conferences and reimbursement of travel and accommodation costs from MSD. The remaining authors declare that no conflict of interest exists.

Manuscript received on 15 November 2018, revised version accepted on 23 May 2019

Dedication
We dedicate this article to the memory of our valued colleague and researcher into toxoplasmosis, Ermanno Candolfi (Strasbourg), who was taken from us much too soon.

Translated from the original German by Kersti Wagstaff.

References


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Supplementary material: For eReferences please refer to: www.aerzteblatt-international.de/ref2519
eFigures, eTables: www.aerzteblatt-international.de/l19m0435
CME credit for this unit can be obtained via cme.aerzteblatt.de until 15 September 2019. Only one answer is possible per question. Please select the answer that is most appropriate.

**Question 1**
To which group of pathogens does *Toxoplasma gondii* belong?
- a) Bacteria
- b) Viruses
- c) Prions
- d) Nematodes
- e) Protozoa

**Question 2**
Which treatment regimen is used in a patient with retinochoroiditis?
- a) Tetracycline + folic acid
- b) Pyrimethamine + sulfadiazine + folic acid
- c) Vancomycin + fluconazole
- d) Amoxicillin + fluconazole + atovaquone
- e) Spiramycin + atovaquone

**Question 3**
By what percentage does seroprevalence rise with every year of age in Germany from 18 onwards?
- a) 0.1%
- b) 0.5%
- c) 1%
- d) 2%
- e) 5%

**Question 4**
How is *T. gondii* probably most frequently transmitted in Germany?
- a) By the eating or handling of undercooked meat
- b) By contaminated blood products
- c) By contaminated drinking water
- d) By mother-to-child transmission
- e) By aerosols

**Question 5**
Which animals are definitive hosts of *T. gondii* and a possible source of infection for human beings?
- a) Dogs
- b) Foxes
- c) Hares
- d) Cats
- e) Pigeons

**Question 6**
In which federal states in Germany are most cases of *T. gondii* infection diagnosed?
- a) Schleswig-Holstein + Bavaria
- b) Lower Saxony + North Rhine-Westphalia
- c) Berlin + Brandenburg
- d) Baden-Württemberg + Hesse
- e) Rhineland-Palatinate + Saarland

**Question 7**
In which organ does *T. gondii* most frequently persist?
- a) Liver
- b) Pancreas
- c) Spleen
- d) Kidney
- e) Brain

**Question 8**
Which of the following is a typical malformation found in a child whose mother was infected by *T. gondii* during the second trimester of pregnancy?
- a) Horseshoe kidney
- b) Hypoplasia of the liver
- c) Hydrocephalus
- d) Spina bifida
- e) Macrosomia

**Question 9**
Which of the following is an indication for treatment of a *T. gondii* infection?
- a) Demonstration of IgG in a patient with acute conjunctivitis
- b) Interstitial pneumonia in an immunocompetent patient
- c) Lymphadenitis in a patient with acute infection
- d) Seronegative patient who has received a liver transplant
- e) Seroconverted pregnant woman with a markedly raised *T. gondii*-specific IgM titer

**Question 10**
What is the mortality rate in transplant recipients who develop toxoplasmosis?
- a) 3% to 20%
- b) 23% to 40%
- c) 43% to 60%
- d) 63% to 80%
- e) 83% to 100%

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- Participation in the CME certification program is possible only via the Internet: cme.aerzteblatt.de. This unit can be accessed until 15 September 2019. Submissions by letter, e-mail or fax cannot be considered.
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  - „Hearing Impairment in Old Age—Detection, Treatment, and Associated Risks“ (issue 17/2019) until 21 July 2019;
- This article has been certified by the North Rhine Academy for Continuing Medical Education. Participants in the CME program can manage their CME points with their 15-digit “uniform CME number” (einheitliche Fortbildungszahl, EFN), which is found on the CME card (8027XXXXXXXXXX). The EFN must be stated during registration on www.aerzteblatt.de (”Mein DA“) or else entered in “Meine Daten,” and the participant must agree to communication of the results.
Supplementary material to:

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e17. Demarco AL, Rodrigues Mde L, Figueiredo JF, et al.: Susceptibility to toxoplasmosis retinochoroiditis is associated with HLA alleles reported to be implicated with rapid progression to AIDS. Dis Markers 2012; 33: 309–12.


e39. Takakura A, Tessier HH, Goldstein DA, et al.: Viral retinitis following intraocular or periciliar corticosteroid administration: a case series
**Simplified representation of dissemination and immune response in T. gondii infection.** Once oral infection has occurred, T. gondii penetrates the intestinal epithelium and becomes disseminated, in part intracellularly, in dendritic cells and macrophages in the host and infects many organs. In the gut, macrophages and dendritic cells recognize intracellular tachyzoites and/or conserved structural features of the parasite (e.g., glycosylphosphatidylinositol, parasitic DNA and RNA) by means of toll-like receptors (TLR9) and other pattern-associated recognition receptors. The activated macrophages and dendritic cells produce IL-12, which induces interferon-γ production of natural killer (NK) cells and type 1 innate lymphoid cells. Alongside this activation of the innate immune system, parasite-specific CD4^+ and CD8^+ T cells develop, which also produce IFN-γ and are activated by dendritic cells and/or macrophages. IFN-γ induces antiparasitic effector mechanisms in infected cells, such as production of GTPases and indoleamine-2,3-dioxygenase. Likewise, the cytotoxic effect of NK and CD8^+ T cells contributes to the elimination of infected cells. Through the production of IL-4, T cells activate B cells, which contribute to protection by producing T. gondii-specific antibodies.
**eTABLE 1**

**Risk factors affecting the course of a T. gondii infection**

<table>
<thead>
<tr>
<th>Infection route and clinical manifestation</th>
<th>T. gondii-specific risk factors</th>
<th>Quantitative measurement</th>
<th>Reference/source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genotype I versus genotypes II + III with severe clinical course</td>
<td>86.9 versus 72.9%; OR 2.47, 95% CI [1.1; 5.4])</td>
<td>(9)</td>
</tr>
<tr>
<td><strong>Postnatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral toxoplasmosis</td>
<td>Increased incidence of genotype II</td>
<td>Descriptive case series; no concrete data available</td>
<td>(10)</td>
</tr>
<tr>
<td>Ocular toxoplasmosis</td>
<td>Increased severity of retinitis with genotypes I, III, or atypical pathogens Atypical genotypes may lead more often than type II to ocular toxoplasmosis and more frequent recurrences</td>
<td>Descriptive case series; no concrete data available OR 10.0, 95% CI [3.4; 40.8]; (p &lt;0.0001) (p = 0.037)</td>
<td>(7, 11) (e18, e34, e35)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infection route and clinical manifestation</strong></td>
<td><strong>Host-specific factors</strong></td>
<td><strong>Quantitative measurement</strong></td>
<td><strong>Reference/source</strong></td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>NALP1 gene polymorphisms are associated with congenital toxoplasmosis</td>
<td>NALP1 rs801261 (p &lt;0.00268) NALP1 rs11652907 (p &lt;0.02)</td>
<td>(e36, e37)</td>
</tr>
<tr>
<td>Ocular toxoplasmosis</td>
<td>HLA-B62 increases susceptibility to bilateral eye involvement</td>
<td>OR 2.8 (p = 0.006)</td>
<td>(12)</td>
</tr>
<tr>
<td></td>
<td>Retina-specific ABCA4 transporter increases susceptibility to congenital eye involvement</td>
<td>OR 2.06, 95% CI [1.14; 3.73] (p = 0.017)</td>
<td>(e38)</td>
</tr>
<tr>
<td></td>
<td>Alpha-1 type II collagen COL2A1 increases susceptibility to congenital eye involvement</td>
<td>OR 1.79, 95% CI [1.06; 3.04] (p = 0.031)</td>
<td>(e38)</td>
</tr>
<tr>
<td>Cerebral toxoplasmosis (reactivated T. gondii encephalitis)</td>
<td>High risk of reactivation in CD4+ T cells &lt;100/μL (e.g., after heart or stem cell transplantation)</td>
<td>OR 26.8, 95% CI [1.5; 16.9] (p = 0.001)</td>
<td>(13)</td>
</tr>
<tr>
<td><strong>Postnatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular toxoplasmosis</td>
<td>Age &lt;21 years and male sex show higher tendency to recurrence</td>
<td>Descriptive case series showing increased recurrence in patients below 21 years of age (p &lt;0.05)</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td>Age &gt;50 years: larger/atypical retinal lesions</td>
<td>Descriptive case series</td>
<td>(e39)</td>
</tr>
<tr>
<td></td>
<td>Intraocular overproduction of proinflammatory cytokines (IL-17)</td>
<td>Descriptive case series</td>
<td>(e40, e41)</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility to ocular toxoplasmosis in the presence of gene polymorphisms for these cytokines:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interferon-γ (A/T + T/T allele)</td>
<td>OR 2.62, 95% CI [1.1; 6.19] (p = 0.014) OR 3.3, 95% CI [1.604; 6.835] (p = 0.0014) OR 4.2, 95% CI [2.48; 7.12] (p = 0.003) OR 2.55, 95% CI [1.11; 5.55] (p = 0.01) OR 5.27, 95% CI [3.18; 8.74] (p = 0.001) OR 6.62 (95% CI not provided) (p = 0.01) OR 5.46 (95% CI not provided) (p = 0.02)</td>
<td>(e42)</td>
</tr>
<tr>
<td></td>
<td>Interferon-γ (GG rs2069718)</td>
<td></td>
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<tr>
<td></td>
<td>Interferon-γ (874T/A)</td>
<td></td>
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<tr>
<td></td>
<td>IL-10 (1082A/ AA+AG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-10 (1082 G/G)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-1A (889 C/T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toll-like receptor 9</td>
<td>OR 4.23, 95% CI [1.6; 30.8] (p &lt;0.001)</td>
<td>(e48)</td>
</tr>
<tr>
<td></td>
<td>Chemokine receptor CCR5</td>
<td>OR 2.98 (95% CI not provided) (p = 0.018)</td>
<td>(e49)</td>
</tr>
<tr>
<td></td>
<td>Protective effect for ocular toxoplasmosis Purinergic receptor P2X7</td>
<td>OR 0.27, 95% CI [0.09; 0.80] (p &lt;0.01)</td>
<td>(e50)</td>
</tr>
</tbody>
</table>
The following distinctions are made:

<table>
<thead>
<tr>
<th>Infection route and clinical manifestation</th>
<th>T. gondii-specific risk factors</th>
<th>Quantitative measurement</th>
<th>Reference/source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HLA B35 (in AIDS patients) increased risk of reactivation</td>
<td>OR 3.04 (95% CI not provided) ( p = 0.01 )</td>
<td>(e17)</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval; OR, odds ratio

Data on frequency distribution and risks are taken from the original publications.
### eTABLE 2

**Risk pattern and prophylactic measures for T. gondii infection in transplantation medicine**

<table>
<thead>
<tr>
<th>Organ or tissue transplantation</th>
<th>Risk of transmission</th>
<th>Risk of reactivation</th>
<th>Onset of symptoms</th>
<th>Measures/prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart or heart–lung</td>
<td>High for mismatch D+,R-</td>
<td>Low in R+</td>
<td>25–195 days</td>
<td>Cotrimoxazole for prevention</td>
</tr>
<tr>
<td>Liver</td>
<td>Low for mismatch D+,R-</td>
<td>Low in R+</td>
<td>Median 24 days</td>
<td>Cotrimoxazole for prevention</td>
</tr>
<tr>
<td>Kidney</td>
<td>Low for mismatch D+,R-</td>
<td>Low in R+</td>
<td>Median 19 days</td>
<td>Not known</td>
</tr>
<tr>
<td>Bowel</td>
<td>Low for mismatch D+,R-</td>
<td>Not known</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Cornea</td>
<td>No risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stem cell transplantation**

| Autologous                     | No risk               | Very low in R+       | 9–120 days        | Not known |
| Allogeneic                     | Low                   | High in R+, independent of donor serology | Median 62 days | Cotrimoxazole for prevention (already used for *Pneumocystis* prophylaxis)  
Alternatively, pyrimethamine–sulfadoxine from month 1 to month 6 after stem cell transplantation 
Continued or initiated anew if GVHD or long-term immunosuppression occurs |

*Adapted from (e19)*

D, donor; GVHD, graft-versus-host disease; R, recipient; +, T. gondii seropositive; –, T. gondii seronegative