33 yo woman who is 14 weeks pregnant has been diagnosed with reactivation of her previously diagnosed ocular toxoplasmosis. Her ophthalmologist insists that her macular active lesions require immediate anti-toxoplasma therapy. She has positive Toxoplasma IgG and negative IgM. Without anti-toxoplasma treatment, what is the risk of transmission of the parasite to her fetus?

A. 100%
B. 75%
C. 50%
D. 25%
E. Essentially zero
Toxoplasma gondii infects over one billion people worldwide

disease burden due to toxoplasmosis

epidemiology update

is there a correlation between parasite strain and clinical manifestations?
during pregnancy

ocular disease

immunocompromised patients


Congenital Toxoplasmosis (CT) in the United States

∼500 to 5000 newborns with CT/∼4.2 million live births per year

ocular disease in 12%-30% of CT children. New lesions in up to 31% of referred children who followed up to a mean age of 10.8 years

intracranial calcifications in 9.5% of infants identified by prenatal screening programs and in 21.7% of infants identified by postnatal programs

hydrocephaly, microcephaly, and psychomotor and mental retardation

∼89% of women of childbearing age are susceptible

Ocular Sequelae of Congenital Toxoplasmosis in Brazil Compared with Europe

Ruth E. Gilbert1, Katherine Freeman2, Eleanor G. Lape2, Lilian M. O. Bahia-Oliveira4, Hoi Kuan Tan4, Maxine Watson5, Wilma Bifulcoso5, Mike R. Stafford6, Cikki Petersen7, for The European Multicenter Study on Congenital Toxoplasmosis (EMSCOT)

Figure 1: Survival analyses showing proportion of children without sequelae according to age in years when acetone-water lesion was detected in Brazil (solid line), and European (dashed line) and prenatal (dotted line).
Toxoplasmosis in immunocompetent patients

Ocular toxoplasmosis affects an estimated 1.26 million persons in the United States alone. Post-natally acquired ocular disease is more common than it was once thought.

*T. gondii* can also cause lymphadenopathy, myocarditis, myositis, hepatitis.

In addition, pneumonia, fever, brain abscesses, and death have been reported in certain geographical areas.

Community outbreak of acute toxoplasmosis in immunocompetent patients

- Unusually severe clinical presentation in otherwise normal individuals
- 8 had severe disseminated disease (including pneumonia and hepatitis) that resulted in three deaths: one adult, one newborn, and one fetus
- Genotype analysis with 8 microsatellite markers revealed that only one strain was responsible for at least 5 of the 11 cases

Demar M et al. Clin Infect Dis 2007;45: e88-95

T. gondii strains

- Type I
- Type II
- Type III

Tachyzoites

Tissue cysts

Oocysts
patients with organ transplants, AIDS, cancer, or those taking immunosuppressive drugs, reactivated and untreated toxoplasmosis has 100% mortality rate.

brain abscesses, diffuse encephalitis without brain-occupying lesions, pneumonitis, fever of unknown origin, myocarditis, hepatosplenomegaly, lymphadenopathy and skin lesions.


Jones JL et al. Clinical Infectious Diseases 2009; 49:878–84
Risk factors associated with acute *T. gondii* infection in the United States

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>aOR</th>
<th>CL</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating raw ground beef</td>
<td>6.67</td>
<td>2.09-21.24</td>
<td>7%</td>
</tr>
<tr>
<td>Eating rare lamb</td>
<td>8.39</td>
<td>3.68-19.16</td>
<td>20%</td>
</tr>
<tr>
<td>Eating locally produced cured, dried, or smoked meat</td>
<td>1.97</td>
<td>1.18-3.28</td>
<td>22%</td>
</tr>
<tr>
<td>Working with meat</td>
<td>3.15</td>
<td>1.09-9.10</td>
<td>5%</td>
</tr>
<tr>
<td>Drinking unpasteurized goat's milk</td>
<td>5.09</td>
<td>1.45-17.80</td>
<td>4%</td>
</tr>
<tr>
<td>Having 3 or more kittens</td>
<td>27.89</td>
<td>5.72-135.86</td>
<td>10%</td>
</tr>
<tr>
<td>Eating raw oysters, clams, or mussels</td>
<td>2.22</td>
<td>1.07-4.61</td>
<td>16%</td>
</tr>
</tbody>
</table>

Risk factors associated with acute *T. gondii* infection in the United States

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>aOR</th>
<th>CL</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking untreated water elevated the risk</td>
<td>3.11</td>
<td>(0.92-10.51)</td>
<td></td>
</tr>
<tr>
<td>Eating frozen ground pork was associated with an increased risk of recent <em>T. gondii</em> infection in pregnant women</td>
<td>2.30</td>
<td>(1.12-4.74); AR= 22 (6-33)</td>
<td></td>
</tr>
<tr>
<td>Not able to explain the risk for 48% of the infections (14 to 49% in Europe)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jones JL et al. Clinical Infectious Diseases 2009; 49:878-84
Risk factors for *T. gondii* infection in 131 mothers of infants with congenital toxoplasmosis

Summary epidemiologic factors of maternal exposure and illness history

<table>
<thead>
<tr>
<th>Factor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any exposure to cats</td>
<td>65</td>
</tr>
<tr>
<td>Any exposure to undercooked or uncooked meat</td>
<td>50</td>
</tr>
<tr>
<td>Any exposure to cats or undercooked or uncooked meat</td>
<td>75</td>
</tr>
<tr>
<td>Specific exposure to cat litter or uncooked meat</td>
<td>39</td>
</tr>
<tr>
<td>Unexplained febrile illness or lymphadenopathy during pregnancy</td>
<td>48</td>
</tr>
<tr>
<td>Exposure to cat litter, uncooked meat, or toxoplasmosis-like illness during pregnancy</td>
<td>48</td>
</tr>
</tbody>
</table>


Toxoplasmosis during pregnancy

Clinical Presentation of Congenital Toxoplasmosis during Pregnancy

• asymptomatic
• abnormal ultrasound
  - hydrocephalus
  - calcifications (brain or hepatic)
  - splenomegaly
  - ascites
• death of the fetus
Clinical Presentation of Congenital Toxoplasmosis in the Newborn and Children

(1) sub-clinical infection
(2) disease (mild or severe) occurring in the first months of life
(3) overt neonatal disease
(4) sequelae or relapse of a previously undiagnosed infection manifested during infancy, childhood or adolescence

Clinical Dictum:

Only those women who acquire toxoplasma infection during pregnancy are at risk for giving birth to a congenitally infected infant

In Women with Prior History of Toxoplasmic Chorioretinitis, What is the Risk of delivering a Congenitally Infected Child?

Garweg JG. Reactivation of ocular toxoplasmosis during pregnancy. BJOG 2005;112:241–2
Demonstration of antibodies in serum

- Differential agglutination (AC/HS)
- IgG avidity

*Antibody may persist for months or a year or more
IgM antibody response during acute and chronic infection

• In patients with recently acquired primary infection, *T. gondii*-specific IgM antibodies are detected initially and in most cases these titers become negative within a few months

• However, *T. gondii*-specific IgM titers may be observed for a year or more after initial infection

• Prolonged persistence of IgM antibodies does not appear to have clinical relevance and these patients should not be considered to have recently acquired infection

• Several kits for detection of IgM may yield relatively high frequency of false positive results (JCM 1997;35:174-8)

Interpretation of a Positive *T. gondii*-Specific IgM antibody

• True positive result in the setting of a recently acquired infection

• True positive result in the setting of an infection acquired in the distant past

• False positive result in the setting of an infection acquired in the distant past
• ~20% of pregnant women will choose abortion when told they have IgM antibody
• ~60% of positive IgM tests reported by outside laboratories are falsely positive; thus, 6 of every 10 aborted fetuses are not infected

Confirmatory Serological Testing for Toxoplasmosis and Abortion in the United States


Initial Serological Screening at Commercial or non-Reference Labs

<table>
<thead>
<tr>
<th>IgG</th>
<th>IgM</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>No evidence of prior exposure</td>
<td>Infected prior to pregnancy*</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td>Confirmatory testing at a Reference Lab</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive or equivocal</td>
<td>Confirmatory testing at a Reference Lab</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Positive or equivocal</td>
<td>Confirmatory testing at a Reference Lab</td>
<td></td>
</tr>
</tbody>
</table>

*Except during third trimester

A - IgM test alone can never be used to diagnose the acute infection (value of toxoplasma serologic profile in pregnancy)

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgE</th>
<th>AC/HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/10*</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/10</td>
<td>8,000</td>
<td>6.9</td>
<td>20</td>
<td>5.0</td>
<td>≥1600/≥3200</td>
</tr>
</tbody>
</table>

Final Interpretation: most consistent with a recently acquired infection. Can not exclude possibility of having acquired the infection during this pregnancy

AC/HS = differential agglutination

*16, 32.5 weeks pregnant on 1/10
Confirmatory Serological Testing during Pregnancy at PAMF-TSL

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgE</th>
<th>AC/HS</th>
<th>AVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/28</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/23*</td>
<td>256</td>
<td>4.0</td>
<td>–</td>
<td>–</td>
<td>50/400</td>
<td>0.631</td>
</tr>
</tbody>
</table>

Final Interpretation: most consistent with a chronic infection acquired prior to this pregnancy

AC/HS = differential agglutination; AVT = avidity
*AP, 10 weeks pregnant on 12/23

---

Confirmatory Serological Testing during Pregnancy at PAMF-TSL

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgE</th>
<th>AC/HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/31*</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/31</td>
<td>4096</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>400&gt;3200</td>
</tr>
</tbody>
</table>

Final interpretation: most consistent with a chronic infection acquired prior to this pregnancy

AC/HS = differential agglutination; NA = Non-Acute
*DT, 18 weeks pregnant on 1/31

---

The Differential Agglutination Test as a Diagnostic Aid in Cases of Toxoplastic Lymphadenitis

IgG avidity interpretation during gestation

High avidity in the first 16 weeks essentially rules out that acute infection occurred during the first 4 months of pregnancy.

Low or equivocal avidity does not mean the patient has a recently acquired infection; low avidity antibodies may persist for more than five months or even one year.

Can we prevent fetal infection by treatment of a mother who acquires infection during pregnancy?

- Spiramycin* (attempt to prevent transmission - controversial)
- Pyrimethamine/Sulfadiazine (after 18-21 weeks gestation)
  - Also treats the fetus
  - Potentially teratogenic

*? 60% effective if given in early gestation

Montoya JG. And Remington JS. Clinical Infectious Diseases 2008; 47: 554-66.
Management of *Toxoplasma gondii* Infection during Pregnancy

Jane M. Montoya and Josh S. Remington

At a major reference laboratory in France

- **SPECIFICITY:** 100%
- **PPV:** 100%
- **SENSITIVITY:** 64%
- **NPV:** 88%

Prenatal diagnosis using PCR on amniotic fluid according to gestational age at maternal infection

unshaded bars = sensitivity
shaded bars = negative predictive value
CI = confidence interval


Ocular Toxoplasmosis

Symptomatic or active
1. discovered at birth in a newborn with CT
2. reactivation of CT
3. in association with acute post-natally acquired infection
4. reactivation of a previous post-natally acquired infection

Asymptomatic scar
Ocular Toxoplasmosis Typical Retinal Lesions

• In the setting of typical appearing lesions and serological test results consistent with toxoplasma infection, invasive procedures are usually not indicated.

Ocular Toxoplasmosis Atypical Retinal Lesions

• In a number of patients, the retinal lesion morphology may be non-diagnostic and/or the response to treatment is suboptimal.

Fundus photography of right eye at initial presentation. There is vitreous opacity and intraretinal whitening in posterior pole. HSV, VZV, CMV, Toxoplasma, Toxocara, Syphilis.
Ocular Toxoplasmosis
Atypical Retinal Lesions

• abnormal Toxoplasma antibody response in ocular fluids (immune load)
• demonstration of the parasite by isolation, histopathology or PCR

"Use Of The Polymerase Chain Reaction for Diagnosis of Ocular Toxoplasmosis"

Table 1. Clinical Findings, Treatment, and Outcome in Seven Patients in Whom Ocular Fluid Infections by Toxoplasma Chlamydia Reactions Were Established by Polymerase Chain Reaction (Table 1): Posterior Retina DNA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Stage</th>
<th>Eye</th>
<th>Treatment</th>
<th>Degree of Clinical Improvement</th>
<th>PCR Result</th>
<th>Medical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>0</td>
<td>1</td>
<td>R</td>
<td>2 of 5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>F</td>
<td>0</td>
<td>2</td>
<td>R</td>
<td>2 of 5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>0</td>
<td>3</td>
<td>R</td>
<td>2 of 5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>0</td>
<td>4</td>
<td>R</td>
<td>2 of 5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>M</td>
<td>0</td>
<td>5</td>
<td>R</td>
<td>2 of 5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>F</td>
<td>0</td>
<td>6</td>
<td>R</td>
<td>2 of 5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>M</td>
<td>0</td>
<td>7</td>
<td>R</td>
<td>2 of 5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Appearance of right eye 3½ weeks after initiation of anti-Toxoplasma Rx. Macular lesion is more circumscribed, and there is now surrounding chorioretinal atrophy.


atypical-appearing lesions: multiple foci of active retinitis, retinitis resembling virally induced retinal necrosis syndrome (vitreitis, peripheral retinitis, retinal vasculitis), significant intraretinal hemorrhage, absence of ophthalmoscopically visible chorioretinal scarring.

Immunocompetent 10 yo girl with unilateral retinitis (right eye)
District of Columbia

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgE</th>
<th>AC/HS*</th>
<th>Avidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/15/08</td>
<td>8,000</td>
<td>&gt;10.0</td>
<td>0.0</td>
<td>2.8</td>
<td>800/800</td>
<td>low pattern</td>
</tr>
</tbody>
</table>

Final Interpretation:
Consistent with a recently acquired infection. If eye lesion(s) is consistent with toxoplasmosic chorioretinitis, these serologic test results support an acute infection rather than reactivation of a congenital infection as the mechanism for this patient's eye disease. Treatment with anti-toxoplastic drugs may be indicated.

*AC/HS = differential agglutination
57 yo man with unilateral diffuse retinitis  
(HIV negative)  
Connecticut

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgE</th>
<th>AC/HS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/09</td>
<td>512</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>&lt;50/800 non acute pattern</td>
</tr>
</tbody>
</table>

PCR on vitreous fluid positive

Final Interpretation:  
Consistent with an infection acquired in the distant past, thus eye disease is most likely the result of reactivation of a latent infection rather than of a recently acquired infection. We recommend that, unless there is a contraindication, the patient be treated with anti-toxoplasma medications.

*AC/HS = differential agglutination

HIV - 49 yo man with diffuse white exudates on the retina. History of travel to South America. Ophthalmologist suspected VZV. Lesion involves the macula  
North Carolina

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/08</td>
<td>1,024</td>
<td>0.0</td>
</tr>
</tbody>
</table>

PCR on vitreous fluid positive

Final Interpretation:  
The positive PCR result from the vitreous fluid suggests that T. gondii is the etiologic agent. Anti-toxoplasmonic therapy is indicated.

8 yo girl with unilateral lesion, morphology suggestive of toxo chorioretinitis  
California

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgE</th>
<th>AC/HS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>1/11/08</td>
<td>64</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Child</td>
<td>1/22/08</td>
<td>512</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Final Interpretation:  
These serologic test results consistent with a chronic infection suggesting eye disease is the result of reactivation of latent infection rather than of an acute infection, most likely congenital.

*AC/HS = differential agglutination
Toxoplasmosis in Immunocompromised Patients

Immunocompromised patients can develop toxoplasmosis as a result of their acute/primary infection... although primary infection tends to be asymptomatic, it may in some patients result in the following clinical manifestations (alone or in combination):
- lymphadenopathy
- chorioretinitis
- fever
- headache
- general malaise
- hepatitis
- myositis
- myocarditis

...or reactivation of their latent infection if they have already been exposed to the parasite
- brain abscesses
- diffuse encephalitis without brain-occupying lesions
- pneumonia
- fever of unknown origin
- myocarditis
- hepatosplenomegaly
- lymphadenopathy
- skin lesions
Laboratory Diagnosis of Toxoplasmosis in the Immunocompromised Patient

serologies

PCR

histological examination with hematoxylin and eosin (H&E) or Wright Giemsa stains, immunohistochemistry with T. gondii-specific immunoperoxidase

isolation of the parasite

<table>
<thead>
<tr>
<th>Table 1. Drugs used in toxoplasmosis in the setting of acute infection or reactivation* (primary therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfamethoxazole (PO)</strong></td>
</tr>
<tr>
<td>200 mg loading dose</td>
</tr>
<tr>
<td>Followed by 50 mg (PO) once daily</td>
</tr>
<tr>
<td>150 mg (PO) daily (up to 50 mg)</td>
</tr>
<tr>
<td>(during and 1 week after therapy with pyrimethamine)</td>
</tr>
<tr>
<td><strong>Folic acid</strong> (PO)**</td>
</tr>
<tr>
<td>5 mg (PO)</td>
</tr>
<tr>
<td><strong>Sulfadiazine (PO)</strong></td>
</tr>
<tr>
<td>100 mg (PO) (up to 1500 mg (PO) every 6 hours)</td>
</tr>
<tr>
<td><strong>Chloramphenicol (PO or IV)</strong></td>
</tr>
<tr>
<td>480 mg every 6 hours (up to 1200 mg every 6 hours)</td>
</tr>
<tr>
<td><strong>Trimethoprim/Sulfamethoxazole (PO or IV)</strong></td>
</tr>
<tr>
<td>10 mg/kg/day (trimethoprim component) divided in two to three doses (doses as high as 15 - 20 mg/kg/day have been used)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preferred regimen: pyrimethamine/sulfadiazine/folic acid or trimethoprim/sulfamethoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Folic acid</strong> = leucovorin. Folic acid should not be used as a substitute for folic acid.</td>
</tr>
<tr>
<td><strong>After the successful use of a combination regimen during the acute/primary therapy phase,</strong>**</td>
</tr>
<tr>
<td>**** agents at half-doses are usually used for maintenance or secondary prophylaxis.****</td>
</tr>
</tbody>
</table>

* Maintenance may be continued after the acute phase for several weeks. ** Preferred regimen varies depending on the patient's condition and the type of toxoplasmosis. *** Maintenance may include a lower dose of the original regimen or a different combination of drugs. **** Maintenance may include the use of lower doses of the original regimen or the addition of a new drug.
33 yo woman who is 14 weeks pregnant has been diagnosed with reactivation of her previously diagnosed ocular toxoplasmosis. Her ophthalmologist insists that her macular active lesions require immediate anti-toxoplasma therapy. She has positive Toxoplasma IgG and negative IgM. Without anti-toxoplasma treatment, what is the risk of transmission of the parasite to her fetus?

A. 100%
B. 75%
C. 50%
D. 25%
E. Essentially zero