"Risk of Toxoplasma Infection in the United States"

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Toxoplasma gondii infects over one billion people worldwide

life cycle and epidemiology update
disease burden due to toxoplasmosis
is there a correlation between parasite strain and clinical manifestations?
during pregnancy
ocular disease
immunocompromised patients


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

IgG  IgM  IgA  IgE  AC/HS*  Avidity
8,000  >10.0  0.0  2.8  800/800  acute pattern  3.9  low

Final Interpretation:
Consistent with a recently acquired infection. If eye lesion(s) is consistent with toxoplasmic 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

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57 yo man with unilateral diffuse retinitis (HIV negative)
Connecticut

IgG  IgM  IgA  IgE  AC/HS*
512  0.0  0.0  0.0  <50/800  non acute pattern

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-toxoplastic medications.

*AC/HS = differential agglutination

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78 yo woman with panuveitis and chorioretinitis
North Carolina

IgG  IgM  IgA  IgE  AC/HS*  Avidity
16,000  4.1  4.6  1.1  400/3200  Equivocal Pattern  40 0  high

Final Interpretation:
Serological testing at our lab suggests that infection has been present for at least 4 months. A positive dye test at any titer is potentially significant in persons with retinochoroiditis, and toxoplasmosis should be considered among the possible etiologies in such patients.

*AC/HS = differential agglutination

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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

IgG  IgM
1,024  0.0

PCR on vitreous fluid positive

Final Interpretation:
The positive PCR result from the vitreous fluid suggests that T. gondii is the etiologic agent. Anti-toxoplastic therapy is indicated.
8 yo girl with unilateral lesion, morphology suggestive of toxo chorioretinitis

<table>
<thead>
<tr>
<th></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>64</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
<td>&lt;50/200</td>
</tr>
<tr>
<td>Child</td>
<td>512</td>
<td>0.0</td>
<td></td>
<td></td>
<td>Non acute</td>
</tr>
</tbody>
</table>

Mother 64 0.3 0.0 0.0 <50/200 pattern Non acute

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

Clinical implications of research findings in the biology and molecular biology of the parasite
Risk factors for Toxoplasma gondii infection in the United States


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


Model 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50 vs 18-25</td>
<td>2.42 (0.84, 6.95)</td>
</tr>
<tr>
<td>Age 30-49 vs 18-25</td>
<td>1.14 (0.43, 3.21)</td>
</tr>
<tr>
<td>Region Midwest vs West</td>
<td>4.29 (1.96, 9.36)</td>
</tr>
<tr>
<td>Northeast vs West</td>
<td>2.48 (1.87, 2.59)</td>
</tr>
<tr>
<td>South vs West</td>
<td>1.42 (1.06, 1.93)</td>
</tr>
<tr>
<td>Having letters</td>
<td>72.74 (1.70, 322.69)</td>
</tr>
<tr>
<td>Ear locally produced, cured, or smoked meat vs no</td>
<td>2.80 (1.45, 5.39)</td>
</tr>
<tr>
<td>Ear lamb vs no</td>
<td>10.27 (4.05, 26.01)</td>
</tr>
<tr>
<td>Ear ground beef vs no</td>
<td>5.04 (2.35, 10.83)</td>
</tr>
<tr>
<td>Microscopic mite vs no</td>
<td>4.11 (2.57, 6.52)</td>
</tr>
<tr>
<td>Drink unpasteurized goat’s milk, yes vs no</td>
<td>3.17 (1.53, 6.59)</td>
</tr>
<tr>
<td>Work with meat</td>
<td>3.15 (1.09, 9.10)</td>
</tr>
</tbody>
</table>

Model 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Eating raw ground beef</td>
<td>6.67 (2.09-21.24)</td>
</tr>
<tr>
<td>Eating raw lamb</td>
<td>8.39 (3.68-19.16)</td>
</tr>
<tr>
<td>Eating locally produced cured, dried, or smoked meat</td>
<td>1.97 (0.30-11.53)</td>
</tr>
<tr>
<td>Working with meat</td>
<td>3.15 (1.09-9.10)</td>
</tr>
</tbody>
</table>

Model 3

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<th>Parameter</th>
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Risk factors associated with acute T. gondii infection in the United States

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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>aOR</th>
<th>CI</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<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>

Jones JL et al. Clinical Infectious Diseases 2009; 49:878-84

### Examples of decreasing prevalence of *T. gondii* antibodies in different geographical locations

<table>
<thead>
<tr>
<th>Country, city or region</th>
<th>Year</th>
<th>Seroprevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Switzerland, Geneva</td>
<td>1973</td>
<td>87%</td>
</tr>
<tr>
<td>France, Paris</td>
<td>1987</td>
<td>47%</td>
</tr>
<tr>
<td>UK, South Yorkshire</td>
<td>1995</td>
<td>54%</td>
</tr>
<tr>
<td>Sweden, Stockholm</td>
<td>1990</td>
<td>8%</td>
</tr>
<tr>
<td>Greece, Northern region</td>
<td>1984</td>
<td>37%</td>
</tr>
<tr>
<td>Poland, Lodz</td>
<td>1998</td>
<td>45.4%</td>
</tr>
<tr>
<td>US, Palo Alto</td>
<td>2003</td>
<td>39.4%</td>
</tr>
<tr>
<td>US recruits</td>
<td>2003</td>
<td>9%</td>
</tr>
<tr>
<td>Costa Rica, Central Valley</td>
<td>2003</td>
<td>58%</td>
</tr>
</tbody>
</table>

Rosso F. et al. AJTMH 2008; 78: 504-508

### Toxoplasma gondii infects over one billion people worldwide

- *Toxoplasmosis*
  - Immunocompetent patient
    - Lymphadenopathy
    - Ocular disease
    - Fever
    - Hepatitis
    - Schizophrenia?
  - During pregnancy
  - Congenital disease
  - Localized and disseminated disease in 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


Toxoplasmosis in immunocompromised patients

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,
pneumonia, fever of unknown origin, myocarditis, hepatosplenomegaly,
lymphadenopathy and skin lesions

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

Toxoplasmosis during pregnancy


Demar M et al. Clin Infect Dis 2007;45: e88-95
Pregnant women at risk for congenital toxoplasmosis

• women who acquire their primary toxoplasma infection during pregnancy
• chronically infected women who become severely immunosuppressed during pregnancy
• chronically infected women who become infected with a different (possibly more virulent) strain of the parasite


Congenital toxoplasmosis has a wide clinical spectrum

• apparently normal fetus or baby (asymptomatic)
• eye inflammation (chorioretinitis)
  hydrocephalus
  brain calcifications
  hearing loss
• death of the fetus or newborn

Initial Serological Screening at Commercial or non-Reference Labs

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

*Except during third trimester

Demonstration of antibodies in serum

IgG, IgM, IgA, IgE

Differential agglutination (AC/HS)

IgG avidity

*Antibody may persist for months or a year or more

Management of Toxoplasma gondii Infection during Pregnancy

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

Prenatal diagnosis

- PCR in amniotic fluid (18 weeks)
- Ultrasonography

Montoya JG. And Remington JS Clinical Infectious Diseases 2008; 47: 554–66

Fundus photography of right eye at initial presentation. There is vitreous opacity and retinal whitening in posterior pole.

HSV, VZV, CMV, Toxoplasma, Toxocara, Syphilis

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>serologies</td>
<td>PCR histological examination with hematoxylin and eosin (H&amp;E) or Wright Giemsa stains, immunohistochemistry with T. gondii-specific immunoperoxidase isolation of the parasite</td>
</tr>
</tbody>
</table>

Table 1: Drugs used in immunocompromised patients with toxoplasmosis in the setting of acute infection or reactivation (primary therapy)

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimethamine (PO)</td>
<td>25 mg loading dose; followed by 50 mg/day; 75 mg (75 mg/kg/day) for 7 days; 10 mg orally (PO) daily (in 1 week after therapy is stopped)</td>
</tr>
<tr>
<td>Folic acid** (PO)</td>
<td>10 mg/day (PO); 10 mg/day (oral or IV) (for 1 week after therapy is stopped)</td>
</tr>
<tr>
<td>Pyrimethamine (PO)</td>
<td>25 mg loading dose; followed by 50 mg/day; 75 mg (75 mg/kg/day) for 7 days; 10 mg orally (PO) daily (in 1 week after therapy is stopped)</td>
</tr>
<tr>
<td>Sulfadiazine (PO)</td>
<td>1000 mg (640 mg/kg) in 1500 mg (300 mg/kg) in 6 hours; 1500 mg every 6 hours</td>
</tr>
<tr>
<td>Ciprofloxacin (PO or IV)</td>
<td>600 mg every 6 hours; 1200 mg every 6 hours</td>
</tr>
<tr>
<td>Pyrimethamine (PO)</td>
<td>1500 mg orally; 500 mg orally</td>
</tr>
</tbody>
</table>

** Folic acid = leucovorin. Folic acid should not be used as a substitute for folic acid.
*** After the successful use of a combination regimen during the acute/primary therapy phase, maintenance at half-doses are usually used for maintenance or secondary prophylaxis.