Treatment of *Toxoplasma* Encephalitis

Aley Kalapila, MD, PhD  
Associate Editor, National HIV Curriculum  
Associate Professor of Medicine  
Division of Infectious Diseases  
Emory University School of Medicine & Grady Health System

Last Updated: January 22, 2024
Dr. Kalapila has no financial conflicts of interest or disclosures.
Treatment of *Toxoplasma* Encephalitis (TE): Outline

- Background
- Clinical Manifestations & Diagnosis
- Treatment
- Medication Side Effects
- Summary
Background
Background: *Toxoplasma* Encephalitis

- Etiologic agent is *Toxoplasma gondii*, a protozoal parasite
- Disease in PWH occurs from reactivation of latent organisms when CD4 <100 cells/mm$^3$
  - Typical clinical presentation is focal encephalitis
  - Atypical manifestations include retinitis, pneumonitis, and disseminated disease
- Rates of disease have decreased with wider use of ART and TMP-SMX for prophylaxis

Clinical Manifestations and Diagnosis
Clinical Manifestations of *Toxoplasma* Encephalitis

- Common symptoms include fever, headache, seizures, encephalitis
- Extracerebral disease is less common
- CT / MRI of brain shows ring enhancing lesions in brain parenchyma
- MRI (with contrast) is more sensitive than CT
- MRI should be obtained in patients with equivocal or negative brain CT

Diagnosis of *Toxoplasma* Encephalitis

- Presumptive diagnosis is made based on presentation, symptoms, CT/MRI brain imaging, and positive serum Toxoplasma Ab

- Initial work up should include head imaging and lumbar puncture (if feasible), with CSF studies including *T. gondii* PCR and other relevant infectious work up

- *T. gondii* PCR on CSF fluid is specific but not sensitive

- Gold standard for definitive diagnosis is detection of *T. gondii* on pathology via brain biopsy

- TE diagnosis is almost always presumptive and brain biopsy is not usually required

Treatment
### Toxoplasma Encephalitis: Acute Treatment (≥ 6 weeks)

<table>
<thead>
<tr>
<th>PREFERRED REGIMEN</th>
<th>ALTERNATIVE REGIMENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimethamine + Sulfadiazine + Leucovorin (all PO)</td>
<td>TMP-SMX (IV or PO) a or</td>
</tr>
<tr>
<td></td>
<td>Pyrimethamine PO + Leucovorin PO + Clindamycin (IV or PO)bc or</td>
</tr>
<tr>
<td></td>
<td>Atovaquone + pyrimethamine + leucovorin (all PO) or</td>
</tr>
<tr>
<td></td>
<td>Atovaquone + sulfadiazine (all PO) or</td>
</tr>
<tr>
<td></td>
<td>Atovaquone + pyrimethamine + leucovorin (all PO) or</td>
</tr>
<tr>
<td></td>
<td>Atovaquone PO</td>
</tr>
</tbody>
</table>

**NOTES:**
- a If pyrimethamine is not available, TMP-SMX should be used instead of pyrimethamine-sulfadiazine
- b Additional PCP prophylaxis agent must be added to this regimen
- c Preferred alternative regimen for sulfa-intolerant individuals

- Consider sulfa-desensitization for individuals with sulfa-allergies especially for those with severe disease
- Acute treatment for Toxoplasma encephalitis should be administered for at least 6 weeks, with longer duration for severe clinical or radiologic disease
- After completion of acute treatment, all patients should be continued on chronic maintenance therapy

Toxoplasma Encephalitis: Treatment Algorithm

Clinical symptoms, imaging on CT/MRI, Positive serum Toxo IgG consistent with Toxoplasma Encephalitis (TE)

Initiate empiric acute treatment for TE

Evaluate for clinical and radiologic response in 14 days

If there is a response, presumptive diagnosis of TE made, continue acute treatment followed by chronic maintenance therapy

If no response, then consider brain biopsy to make a definitive diagnosis and treat accordingly
MRI has Enhanced Sensitivity for Detecting TE Lesions

Non-contrast Head CT
At time of TE diagnosis

MRI Brain with contrast
At time of TE diagnosis
Image of MRI brain of patient with TE at time of diagnosis and after 2 week TE treatment course
Timing of Neurologic Response in Patients with Toxoplasma Encephalitis

# Toxoplasma Encephalitis: Chronic Maintenance Therapy (PO Regimens)

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>ALTERNATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimethamine + Sulfadiazine + Leucovorin</td>
<td>TMP-SMX (^{a}) or</td>
</tr>
<tr>
<td></td>
<td>Pyrimethamine + Leucovorin + Clindamycin (^{b}) or</td>
</tr>
<tr>
<td></td>
<td>Atovaquone + pyrimethamine + leucovorin (or)</td>
</tr>
<tr>
<td></td>
<td>Atovaquone + sulfadiazine (or)</td>
</tr>
<tr>
<td></td>
<td>Atovaquone + pyrimethamine + leucovorin (or)</td>
</tr>
<tr>
<td></td>
<td>Atovaquone</td>
</tr>
</tbody>
</table>

**NOTES:**

- If pyrimethamine is not available, TMP-SMX should be used instead of pyrimethamine-sulfadiazine
- Additional PCP prophylaxis agent must be added to this regimen

- Discontinue chronic maintenance when patient is asymptomatic and has CD4 > 200 cells/mm\(^3\) on combination ART for > 6 months
- Resume secondary prophylaxis / chronic maintenance therapy when CD4 < 200 cells/mm\(^3\)
Discontinuation of Chronic Maintenance Therapy for TE

- Successful completion of initial therapy for TE
- No signs or symptoms of TE
- Increase in CD4 >200 cells/mm$^3$ for >6 months on ART
- Some experts also recommend full resolution of brain lesions

When to Restart Chronic Maintenance for TE

- Resume secondary prophylaxis if CD4 <200 cells/mm$^3$
When to Initiate Antiretroviral Therapy

- Optimal timing is unknown
- Typically within 2-3 weeks of the diagnosis of TE
- IRIS with treatment of TE rare

Medication Side Effects
## Side Effects of Medications Used for TE Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX</td>
<td>Renal dysfunction, hyperkalemia, leukopenia, Steven Johnson syndrome, rash, hepatitis</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>Rash, GI upset, bone marrow suppression (if leucovorin is not co-administered)</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>Rash, leukopenia, crystalluria</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Tastes bad</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>
Summary
Toxoplasma Encephalitis: Summary

• TE occurs from reactivation of latent cysts when CD4 <100 cells/mm$^3$

• Acute treatment is empiric based on clinical symptoms, characteristic brain lesions on CT/MRI imaging, and positive serum Toxo IgG

• Preferred acute treatment is pyrimethamine with sulfadiazine and leucovorin

• Cost of pyrimethamine often makes preferred regimen less feasible, in which case TMP/SMX should be used

• If no clinical improvement after 14 days, consider brain biopsy for definitive diagnosis

• After acute treatment, continue with chronic maintenance therapy until the patient has immune reconstitution on ART

• ART can be initiated within 2-3 weeks of TE diagnosis
Acknowledgments

The production of this **National HIV Curriculum** Mini-Lecture was supported by Grant U1OHA32104 from the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS). Its contents are solely the responsibility of the University of Washington IDEA Program and do not necessarily represent the official views of HRSA or HHS.