National HIV Curriculum

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

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Treatment of *Toxoplasma* Encephalitis (TE): Outline

- Background
- Clinical Manifestations & Diagnosis
- Treatment
- Medication Side Effects
- Summary

Background

Background: *Toxoplasma* Encephalitis

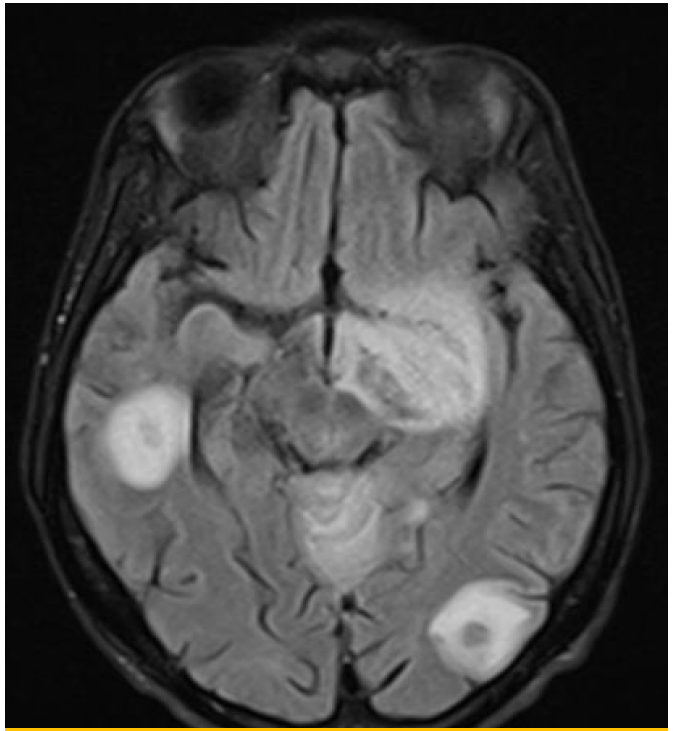
- Etiologic agent is *Toxoplasma gondii*, a protozoal parasite
- Disease in PWH occurs from reactivation of latent organisms when CD4 <100 cells/mm^3
  - Typical clinical presentation is focal encephalitis
  - Atypical manifestations include retinitis, pneumonitis, and disseminated disease
- Rates of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

Source: HHS. Opportunistic Infections Guidelines. Toxoplasma Gondii. January 2023.

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



Brain MRI

Source: HHS. Opportunistic Infections Guidelines. Toxoplasma Gondii encephalitis. January 2023.

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

Source: HHS. Opportunistic Infections Guidelines. Toxoplasma Gondii encephalitis. January 2023.

Treatment

Toxoplasma Encephalitis: Acute Treatment (≥ 6 weeks)

PREFERRED REGIMEN	ALTERNATIVE REGIMENS
Pyrimethamine + Sulfadiazine + Leucovorin (all PO)	TMP-SMX (IV or PO) [a] *or* Pyrimethamine PO + Leucovorin PO + Clindamycin (IV or PO)[bc] *or* Atovaquone + pyrimethamine + leucovorin (all PO) *or* Atovaquone + sulfadiazine (all PO) *or* Atovaquone + pyrimethamine + leucovorin (all PO) *or* Atovaquone PO

NOTES:

[a] If pyrimethamine is not available, TMP-SMX should be used instead of pyrimethamine-sulfadiazine

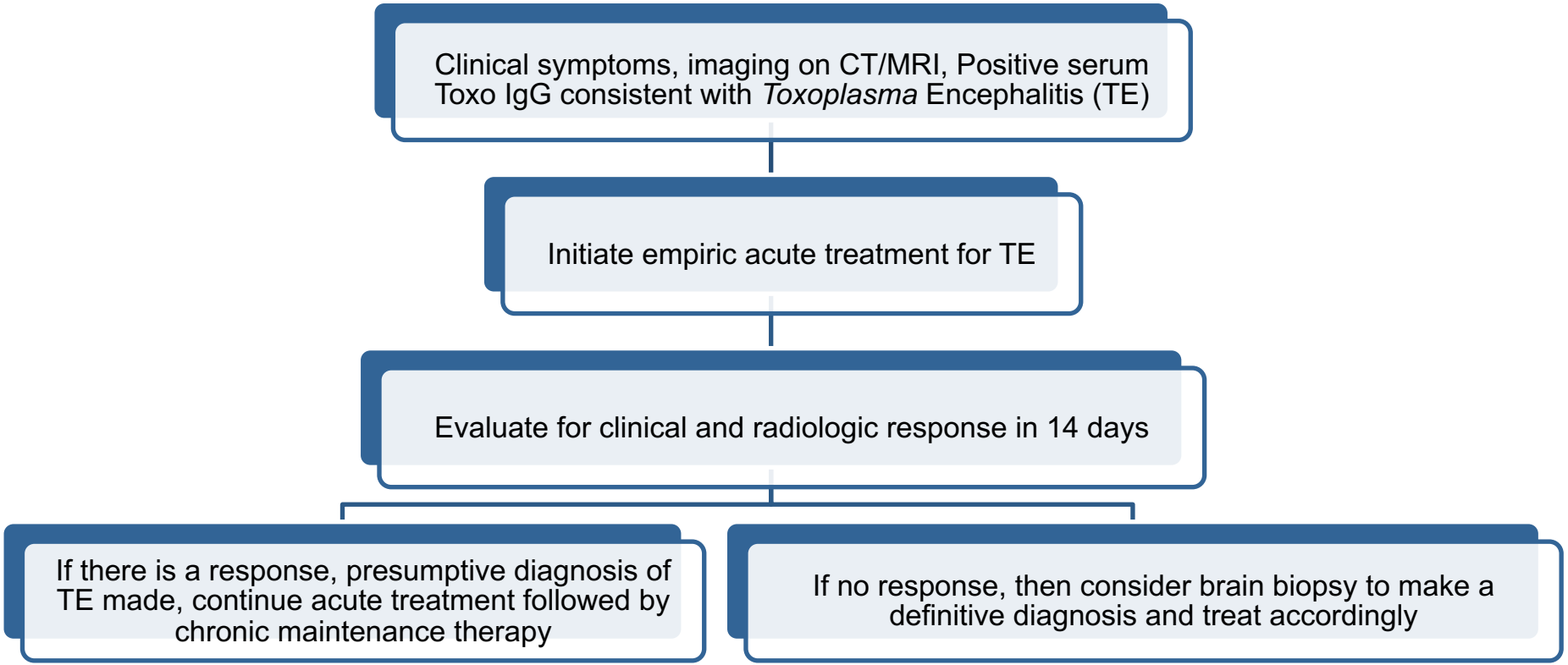
[b] Additional PCP prophylaxis agent must be added to this regimen

[c] Preferred alternative regimen for sulfa-intolerant individuals

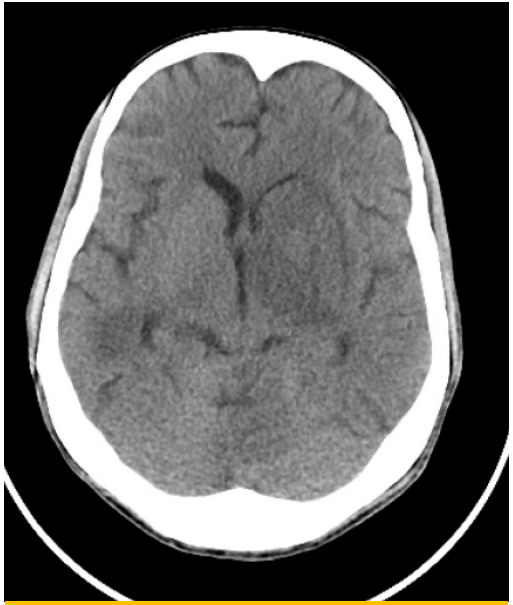
- Consider sulfa-desensitization for individuals with sulfa-allergies especially for those with severe disease
- Acute treatment for Toxoplasma encephalitis should be administered for at least 6 weeks, with longer duration for severe clinical or radiologic disease
- After completion of acute treatment,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

Source: HHS. Opportunistic Infections Guidelines. Toxoplasma Gondii encephalitis. January 2023.

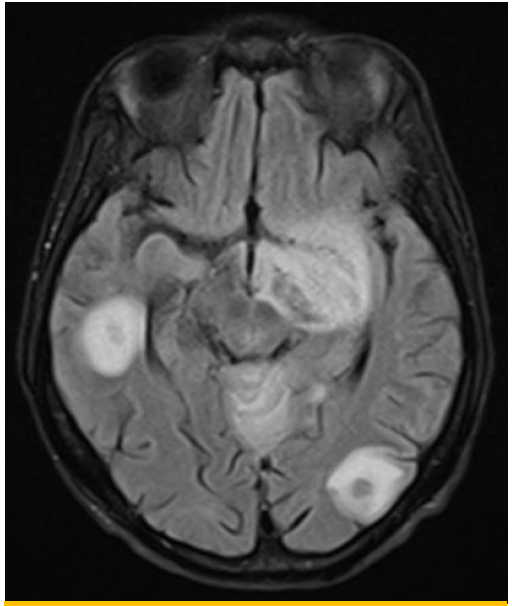
Toxoplasma Encephalitis: Treatment Algorithm



MRI has Enhanced Sensitivity for Detecting TE Lesions

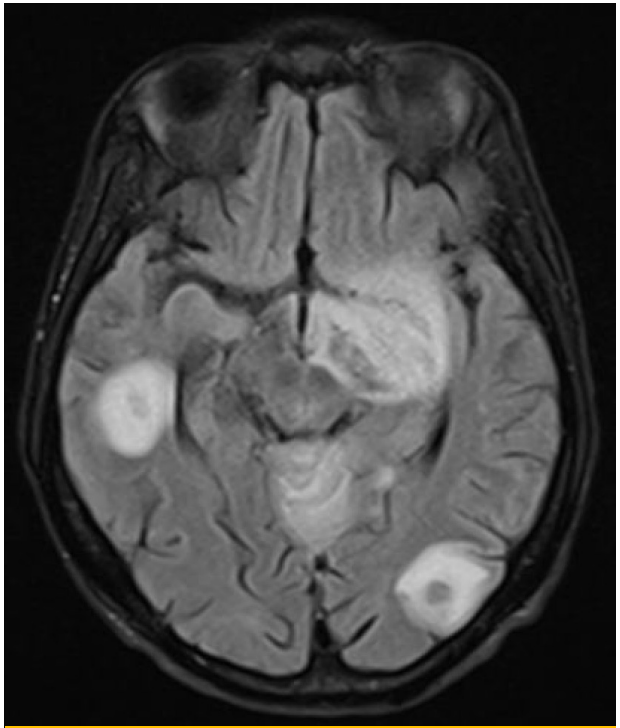


Non-contrast Head CT
At time of TE diagnosis

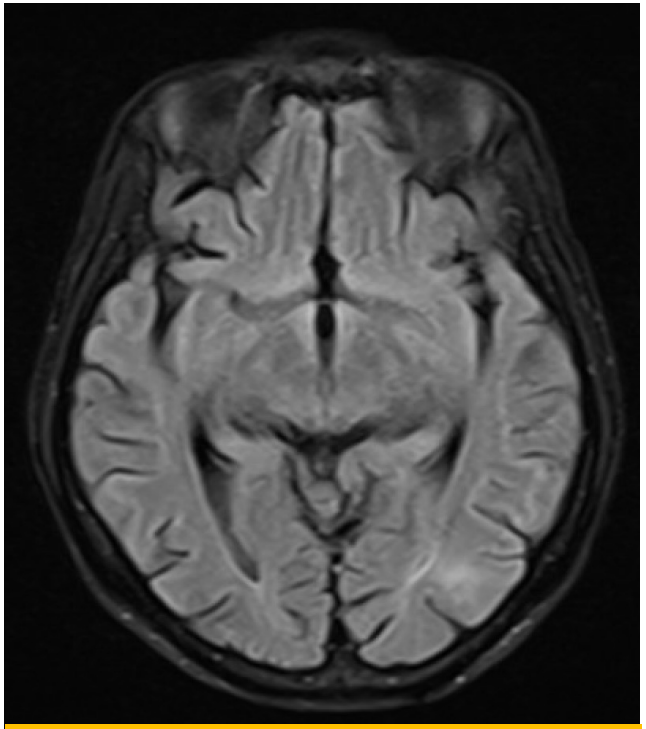


MRI Brain with contrast
At time of TE diagnosis

Image of MRI brain of patient with TE at time of diagnosis and after 2 week TE treatment course

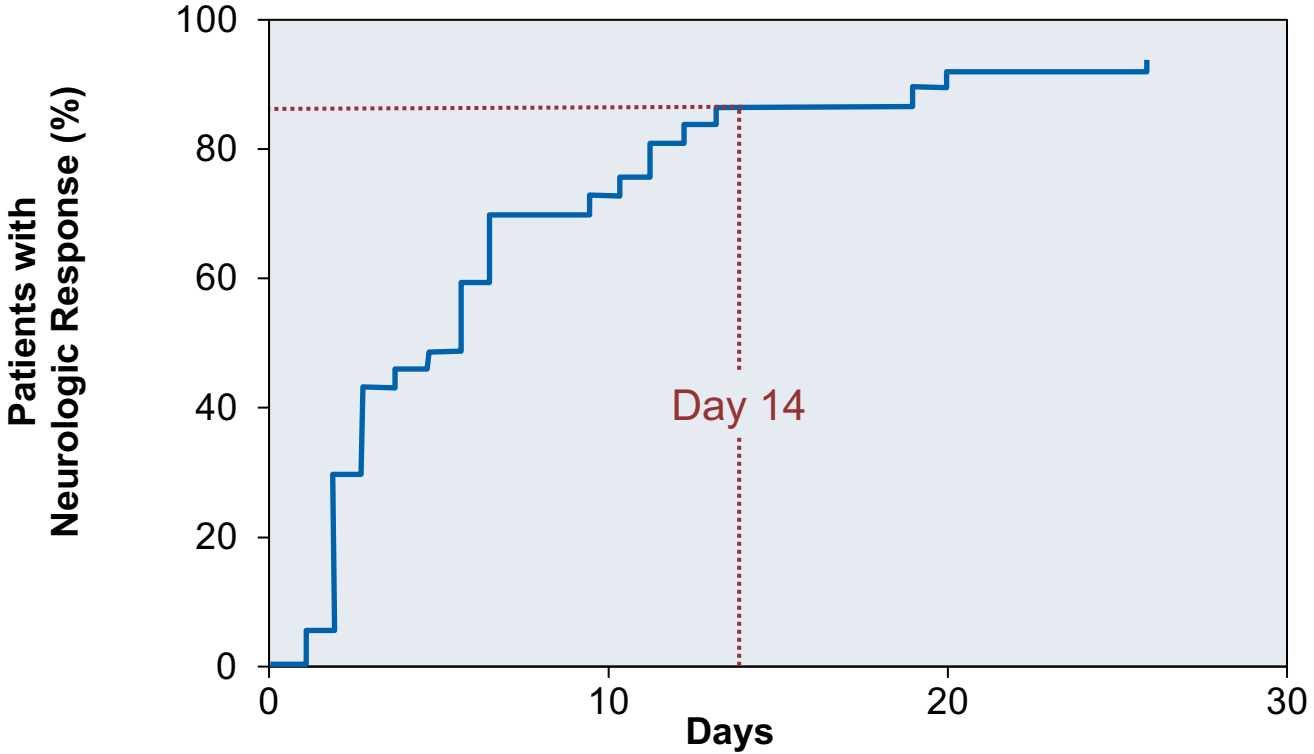


MRI Brain with contrast
At time of TE diagnosis



MRI Brain with contrast
After 2 weeks of empiric TE treatment

Timing of Neurologic Response in Patients with *Toxoplasma* Encephalitis



Toxoplasma Encephalitis: Chronic Maintenance Therapy (PO Regimens)

PREFERRED	ALTERNATIVE
Pyrimethamine + Sulfadiazine + Leucovorin	TMP-SMX [a] *or* Pyrimethamine + Leucovorin + Clindamycin [b] *or* Atovaquone + pyrimethamine + leucovorin *or* Atovaquone + sulfadiazine *or* Atovaquone + pyrimethamine + leucovorin *or* Atovaquone

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

- 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

Source: HHS. Opportunistic Infections Guidelines. Toxoplasma Gondii encephalitis. January 2023.

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

Source: HHS. Opportunistic Infections Guidelines. Toxoplasma Gondii Encephalitis. January 2023.

When to Restart Chronic Maintenance for TE

- Resume secondary prophylaxis if CD4 <200 cells/mm^3

Source: HHS. Opportunistic Infections Guidelines. Pneumocystis pneumonia. January 2023.

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

Source: HHS. Opportunistic Infections Guidelines. Pneumocystis pneumonia. January 2023.

Medication Side Effects

Side Effects of Medications Used for TE Treatment

Medication	Potential Side Effects
TMP-SMX	Renal dysfunction, hyperkalemia, leukopenia, Steven Johnson syndrome, rash, hepatitis
Pyrimethamine	Rash, GI upset, bone marrow suppression (if leucovorin is not co-administered)
Sulfadiazine	Rash, leukopenia, crystalluria
Atovaquone	Tastes bad
Clindamycin	Diarrhea

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

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