Important items to address prior to prescribing Benznidazole in the USA

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Determine the phase and form of Chagas disease

- The acute phase consists of the 1-2 months after infection
- Patients then pass into the chronic phase which lasts the rest of the person’s life in the absence of treatment
- The vast majority of patients in the US have long-standing chronic *T. cruzi* infection
- Immunocompromised patients (HIV, organ transplant recipient) with chronic *T. cruzi* infection can have reactivation (similar to the acute phase), which may be life threatening
- How to make the diagnosis depends on the phase and form of the disease

Confirm the diagnosis [1, 2]

- Confirmed diagnosis of chronic *Trypanosoma cruzi* infection requires positive results by 2 distinct assays for IgG antibodies, preferably based on different antigens
- Most US commercial laboratories offer only one IgG assay
- Most IgM assays are not useful for the diagnosis of Chagas disease
- Molecular and parasitological assays are not used for the diagnosis of chronic *T. cruzi* infection, but are useful in the acute phase, congenital *T. cruzi* infection and to monitor for infection or reactivation in immunocompromised hosts [3-5]
- The Centers for Disease Control and Prevention (CDC) offers consultation regarding patients with suspected Chagas disease and, when determined to be appropriate, offers several IgG serologic assays and PCR (Parasitic Diseases Public Inquiries: Tel.: 404-718-4745; email parasites@cdc.gov).
- Acute *T. cruzi* infection and infection in immunocompromised hosts may be life-threatening, and CDC may be contacted directly for rapid diagnostic advice. For suspected chronic *T. cruzi* infection, CDC recommends initial testing in a commercial laboratory, and contacting the appropriate state or local health department prior to contacting CDC.
Baseline clinical evaluation [2]

- Complete history and physical examination focusing on cardiac and gastrointestinal signs and symptoms
- 12-lead electrocardiogram with 30-second rhythm strip
- For patients with cardiac symptoms or ECG abnormalities: additional cardiac evaluation, including referral to cardiologist. 24-hour ambulatory ECG monitoring/holter monitor, echocardiogram and exercise testing
- For patients with signs or symptoms related to esophageal or colonic dysfunction (particularly for patients from Southern Cone countries): appropriate barium studies
- Patients should be counseled not to donate blood
- All children of infected women should be tested for T. cruzi infection

Dose calculation

- The standard dosing regimen is 5 to 7 mg/kg/day P.O. in two divided doses 12 hours apart for 60 days. For adults, most experts aim for 5 mg/kg/day.
- In children <12 years, the daily dose may be up to 75 mg/kg/day. Elimination is fastest in the youngest age groups and decreases with increasing age [8-11].
- Clinical trial data suggest that adverse events are more frequent with higher daily doses than lower ones [12, 13]. In general, we recommend an upper dosing limit of 300 mg per day, and a hard upper limit of 400 mg/day regardless of body weight.
- There is no evidence that beginning with a lower benznidazole dosage and then increasing the dosage alters the likelihood of adverse events. [14, 15]

Consider the strength of evidence for benefit from antitrypanosomal therapy [2]

- Treatment of acute T. cruzi infection, including congenital infection in infants, is always recommended
- For chronic T. cruzi infection, the strength of evidence for efficacy varies for different age groups, with the strongest evidence base for children
- Treatment of reactivation of chronic T. cruzi infection in immunocompromised hosts can be life-saving, but data on efficacy for cure are lacking
- For adults with chronic T. cruzi infection without advanced cardiomyopathy, decisions must take into account the uncertainties about clinical benefit and frequency of adverse effects
- Treatment of women prior to pregnancy significantly decreases the risk of subsequent vertical transmission [6]. Treatment is contraindicated during pregnancy, In general, the younger the patient, the stronger the consensus that he or she should be treated
- Antitrypanosomal treatment has not been shown to alter the course of established cardiomyopathy [7]

Clinical and laboratory monitoring before treatment

- Baseline complete blood count, hepatic and renal function tests prior to initiation of treatment
- Impaired hematologic status, hepatic or renal function are contraindications to treatment
- Benznidazole should be avoided during pregnancy and breastfeeding. Women should be counseled to use effective birth control. However, benznidazole treatment was reported to be life-saving in symptomatic T. cruzi reactivation in an HIV-co-infected woman during the third trimester, and the infant was born healthy [16].

Clinical and laboratory monitoring during treatment

- Patients should be monitored at least every 2 weeks throughout the course of treatment
- Patients should be counseled to return immediately if adverse events occur
- Repeat complete blood count and liver function tests every 2-3 weeks
Gastrointestinal side effects may be ameliorated by timing administration after a meal. Patients should avoid alcohol consumption and sun exposure during treatment.

Adverse events associated with benznidazole treatment [9, 10, 15, 17-20]

- The most frequently reported adverse event is dermatitis, which occurs in 25-50% of adults and 5-25% of children.
- Benznidazole-induced dermatitis is more common in females than males.
- Onset of dermatitis most commonly occurs around day 9 or 10 of treatment, but may occur anytime during the course of treatment.
- Arthralgia or myalgia occurs in 0 to 35% of adults.
- Symptoms of peripheral neuropathy, most commonly paresthesias, occur in 25-50% of adults [9-11].
- Peripheral neuropathy tends to have onset in the second month of treatment [9-11].
- Gastrointestinal side effects, especially anorexia, occur in 15-50% of adults.
- Rare but potentially serious side effects include hepatotoxicity, neutropenia and thrombocytopenia.
- Adverse events are more frequent in adults than in children, and more frequent in children older than 7 years than in those 7 years or younger.
- Treatment interruption due to adverse events is reported in 10-35% of adults, most commonly due to dermatitis.

Management of adverse events

- Advise the patient to seek medical advice immediately if any apparent adverse effects occur.
- Mild dermatitis may be managed with antihistamines and/or topical steroid cream, without interruption of treatment.
- Exfoliative dermatitis, dermatitis with fever or marked angioedema, should prompt immediate suspension of treatment.
- Moderate to severe dermatitis may be managed with oral steroids.
- If oral steroids are prescribed, consider serological testing for Strongyloides stercoralis and/or presumptive treatment with ivermectin. Testing for latent tuberculosis infection should also be considered.
- Peripheral neuropathy, leukopenia or thrombocytopenia should prompt cessation of treatment.
References
