Congenital Chagas Disease

Rebecca J. Chancey[a], M.D., D.T.M.H., Morven S. Edwards[b], M.D., Susan P. Montgomery[a], D.V.M., M.P.H.

[a]Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia; and [b]Baylor College of Medicine, Houston, Texas

Pediatrics in Review
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

MOC

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Congenital Chagas Disease: Introduction

- Chagas disease is an infection caused by the protozoan parasite *Trypanosoma cruzi.*
- It is a zoonotic disease with animal reservoirs.
- *T. cruzi* can be transmitted from mother to infant during gestation.
- Rates of maternal-to-infant transmission of *T. cruzi* in the United States are estimated to range from 1% to 5%.
- Without treatment, Chagas disease is a lifelong infection. Recognition and treatment of Chagas disease in the first year of life is usually curative.
- Early treatment of Chagas disease prevents the development, after years or decades, of end-organ complications, including cardiomyopathy and/or digestive system mega-syndromes.

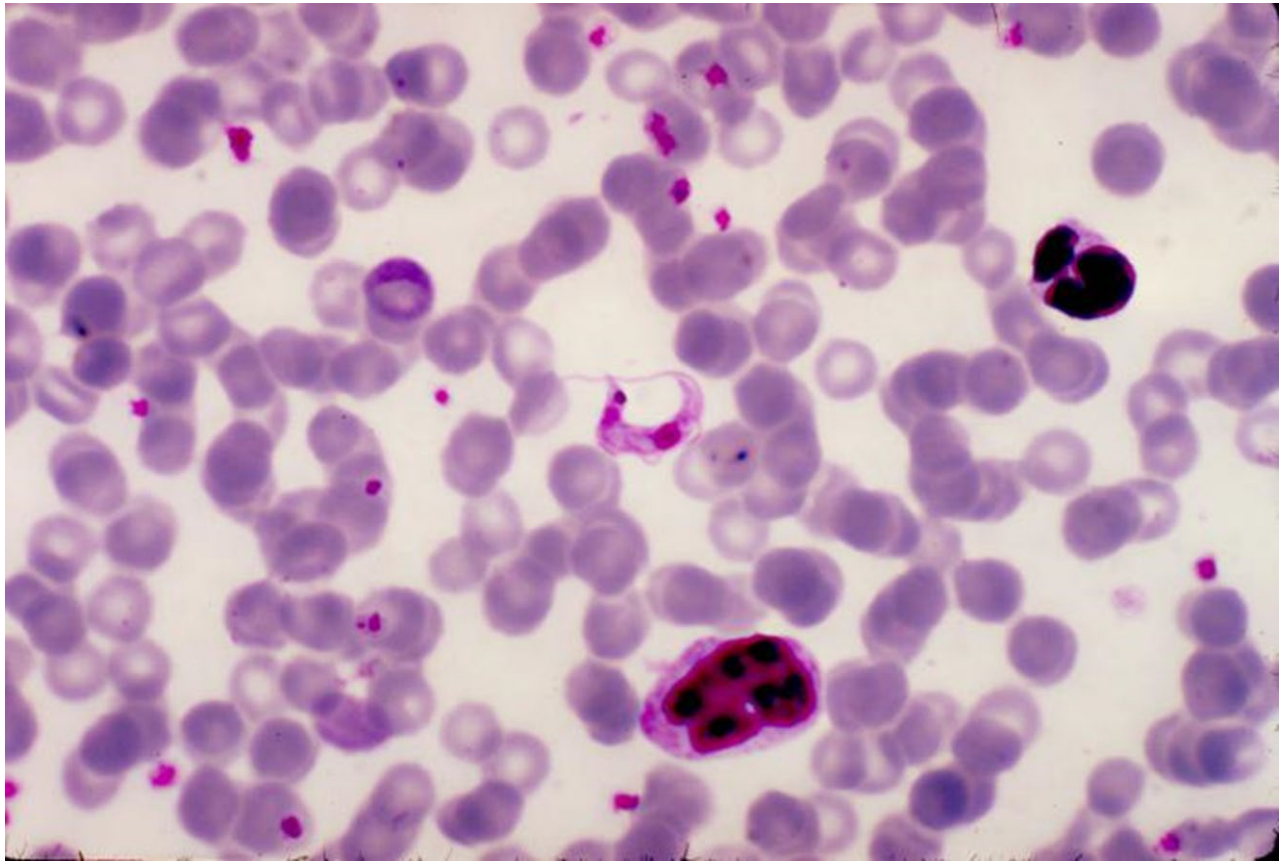
Congenital Chagas Disease: Introduction

- Maternal acquisition of Chagas disease usually occurs in *T. cruzi*-endemic regions of Mexico, Central America and South America.
- Signs of congenital Chagas disease, when present, can mimic other infectious and noninfectious conditions.
- Diagnosis of congenital Chagas disease would be optimized by routine pregnancy-based screening of at-risk pregnant women.
- Aims: Equip healthcare providers to: (1) identify infants at risk for Chagas disease, (2) recognize clinical signs of congenital Chagas disease, (3) confirm the diagnosis of and (4) initiate treatment for congenital Chagas disease.

Congenital Chagas Disease: Epidemiology

- Chagas disease is endemic in many South American and Central American countries and in Mexico.
- Parasites are transmitted in feces of infected triatomine bugs. The bug defecates after taking a blood meal.
- Inoculation occurs when insect feces containing *T. cruzi* trypomastigotes are rubbed into the bite site, another break in the skin, or the mucous membranes of the eye.
- The vector bugs and mammals infected with the parasite are found in many U.S. states but fewer than 100 Chagas disease cases acquired in the United States due to vector-borne transmission are reported.

Bern C. *N Engl J Med* 2015; 373:456.
Lynn MK et al. *Acta Trop* 2020; 205:105361.

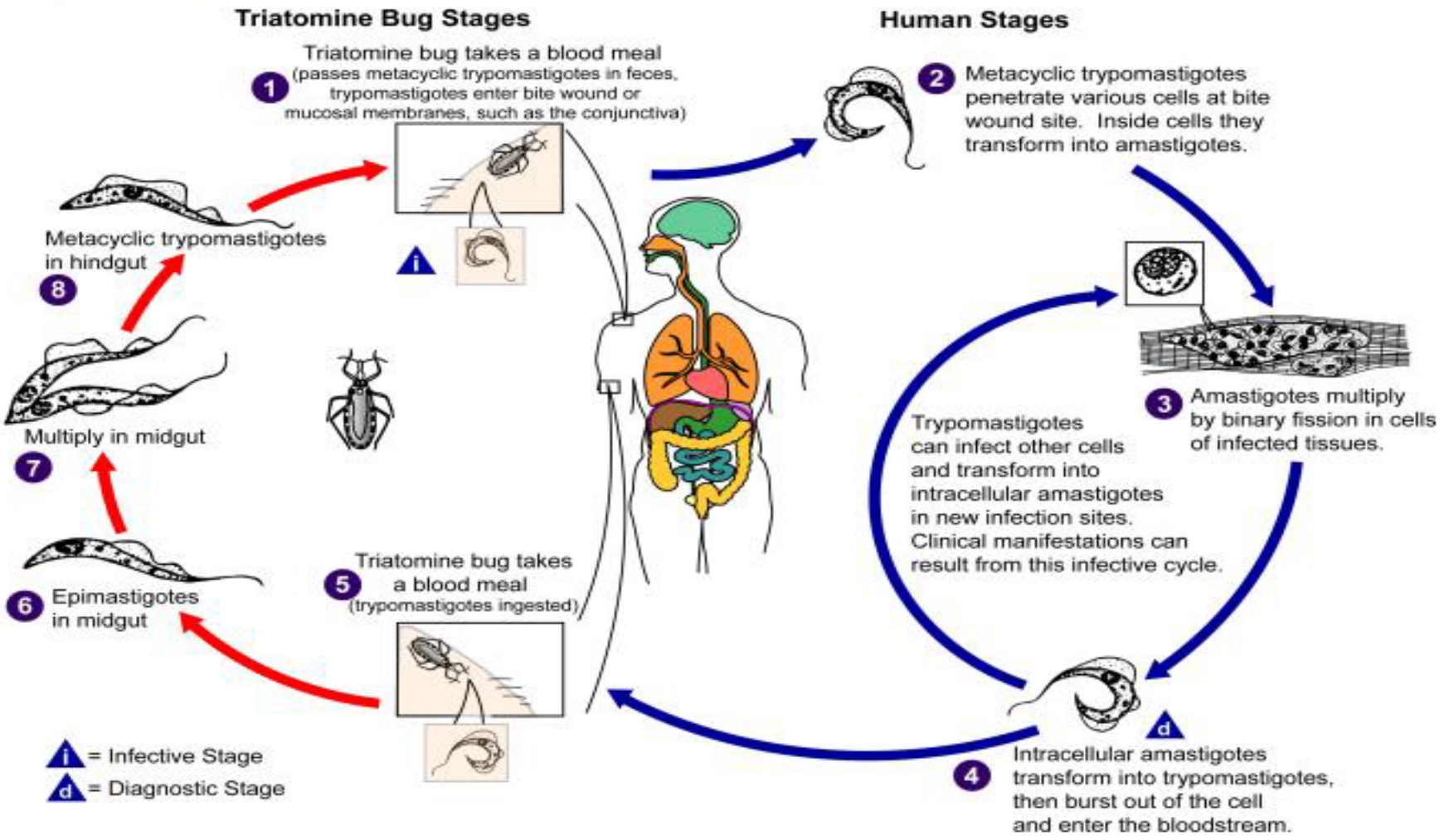


Under a magnification of 1000X, this photomicrograph of a Giemsa-stained blood smear specimen revealed the presence of a parasitic *Trypanosoma cruzi* protozoan, the causative agent for Chagas disease.

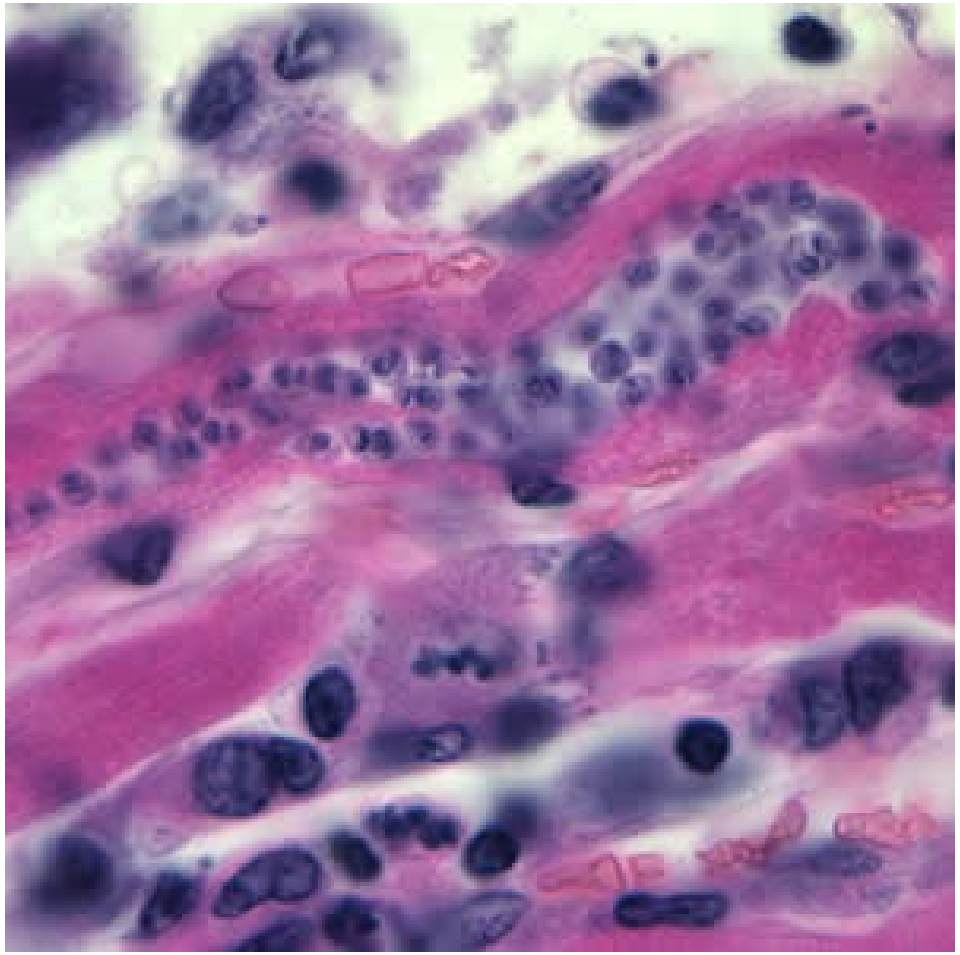
CDC Public Health Image Library

Trypanosomiasis, American (Chagas disease)

(Trypanosoma cruzi)



https://www.cdc.gov>parasites>chagas>biology (Accessed 8/16/22)



Trypanosoma cruzi amastigotes in heart tissue. The section is stained with hematoxylin and eosin (H&E).

CDC DPDx-Laboratory Identification of Parasites of Public Health Concern. Available at: https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html

Congenital Chagas Disease Epidemiology

- The largest cohort of people with Chagas disease living in the United States are immigrants from Mexico, El Salvador, Guatemala and Honduras.
- An estimated 288,000 to 300,167 *T. cruzi*-infected persons live in the United States.
- An estimated 43,000 women of childbearing age who have chronic Chagas disease live in the United States.
- Between 22 and 315 infants with congenital Chagas disease are born yearly in the United States.

Bern C, Montgomery SP. *Clin Infect Dis* 2009; 49:e52.
Irish A et al. *Emerg Infect Dis* 2022; 28:1313.

Congenital Chagas Disease Pathogenesis

- An estimated 22.5% of *T. cruzi* infections now occur through congenital transmission.
- *T. cruzi* transmission can occur during acute or chronic infection and throughout the reproductive years.
- Mother-to-infant transmission occurs during the second or third trimester and can occur near delivery if placental tears occur.
- Congenital Chagas disease is not associated with congenital malformations, since transmission occurs after organogenesis is complete.

World Health Organization. *Wkly Epidemiol Rec* 2015; 90:33.
Carlier Y et al. *Acta Trop* 2015; 151:103.

Congenital Chagas Disease Pathogenesis

- Each pregnancy carries the same risk of maternal to fetal *T. cruzi* transmission, so infants born in subsequent pregnancies can also be infected.
- Maternal parasite load is the strongest predictor of fetal risk.
- Coinfection with human immunodeficiency virus enhances risk for mother-to-infant transmission of *T. cruzi.*
- Postnatal transmission of *T. cruzi* occurs rarely, if ever.

Bern C et al. *Clin Infect Dis* 2009; 49:1667.
Oliveira I et al. *Expert Rev Anti Infect Ther* 2010; 8:945.

Chagas Disease and Breastfeeding

- Transmission of Chagas disease through breast milk has not been reported.
- Mothers with chronic Chagas disease can safely nurse their infants.
- Mothers with acute Chagas disease or reactivation of Chagas disease from immunosuppression can have a high parasite load and should not breastfeed.
- Breastfeeding should be withheld if there is bleeding around the nipples until this has resolved.

Norman FF, López-Vélez R. *Emerg Infect Dis* 2013; 19:1561.

Congenital Chagas Disease

- Congenital Chagas disease in the United States was first reported in a boy born in Virginia in 2010. His mother had moved recently to the United States from Bolivia.
- The infant was born at 29 weeks of gestation by C-section for fetal hydrops. His birth weight was 1,840 g. APGAR scores were 6 at 1 and 9 at 5 minutes. He had ascites and pleural and pericardial effusions.
- Blood smear in week 2 of life revealed *T. cruzi* trypomastigotes and *T. cruzi* PCR was strongly positive; serologic tests for anti-*T. cruzi* antibodies were positive.
- He received benznidazole for 60 days and was cured.

Centers for Disease Control and Prevention. *MMWR* 2012; 61:477.

Congenital Chagas Disease Clinical Aspects

- Ten percent to 40% of infants with congenital Chagas disease have signs of infection at birth or within the first weeks of life.
- Infants with congenital Chagas disease who appear clinically normal at birth are at risk for later development of cardiac and other end-organ damage.
- Untreated, congenital Chagas disease is a lifelong infection.
- Infants with untreated congenital Chagas disease have an estimated 30% likelihood of developing potentially fatal cardiomyopathy or GI megasyndromes years or decades after birth.

Edwards MS et al. *J Pediatr Infect Dis Soc* 2019; 8:461.

Congenital Chagas Disease Clinical Aspects

- Clinical manifestations of congenital Chagas disease present in at least one-fourth of affected infants with signs of infection include:
  - -Low birth weight or prematurity
  - -Hepatomegaly
  - -Splenomegaly
  - -Respiratory distress
- Respiratory distress is usually associated with prematurity rather than parasitic involvement of the lung.

Edwards MS et al. J Pediatr Infect Dis Soc 2019; 8:461.

Congenital Chagas Disease Clinical Aspects

- Findings in 10% to 25% of affected infants with signs of infection include:
  - -Petechiae
  - -Sepsis
  - -Neurologic signs
  - -Cardiomegaly or congestive heart failure
  - -Myocarditis
  - -Cardiac arrhythmias
  - -Meningoencephalitis
  - -Edema or anasarca

Edwards MS et al. *J Pediatr Infect Dis Soc* 2019; 8:461.

Congenital Chagas Disease Clinical Aspects

- Congenital Chagas disease can mimic congenital infections such as those caused by syphilis, cytomegalovirus, toxoplasmosis, Zika virus and viral meningoencephalitis.
- Prematurity or low birth weight, hepatosplenomegaly and petechiae are common in infants with congenital syphilis or cytomegalovirus.
- Congenital Chagas disease can mimic noninfectious disorders including congestive heart failure, respiratory distress syndrome and nonimmune hydrops fetalis.

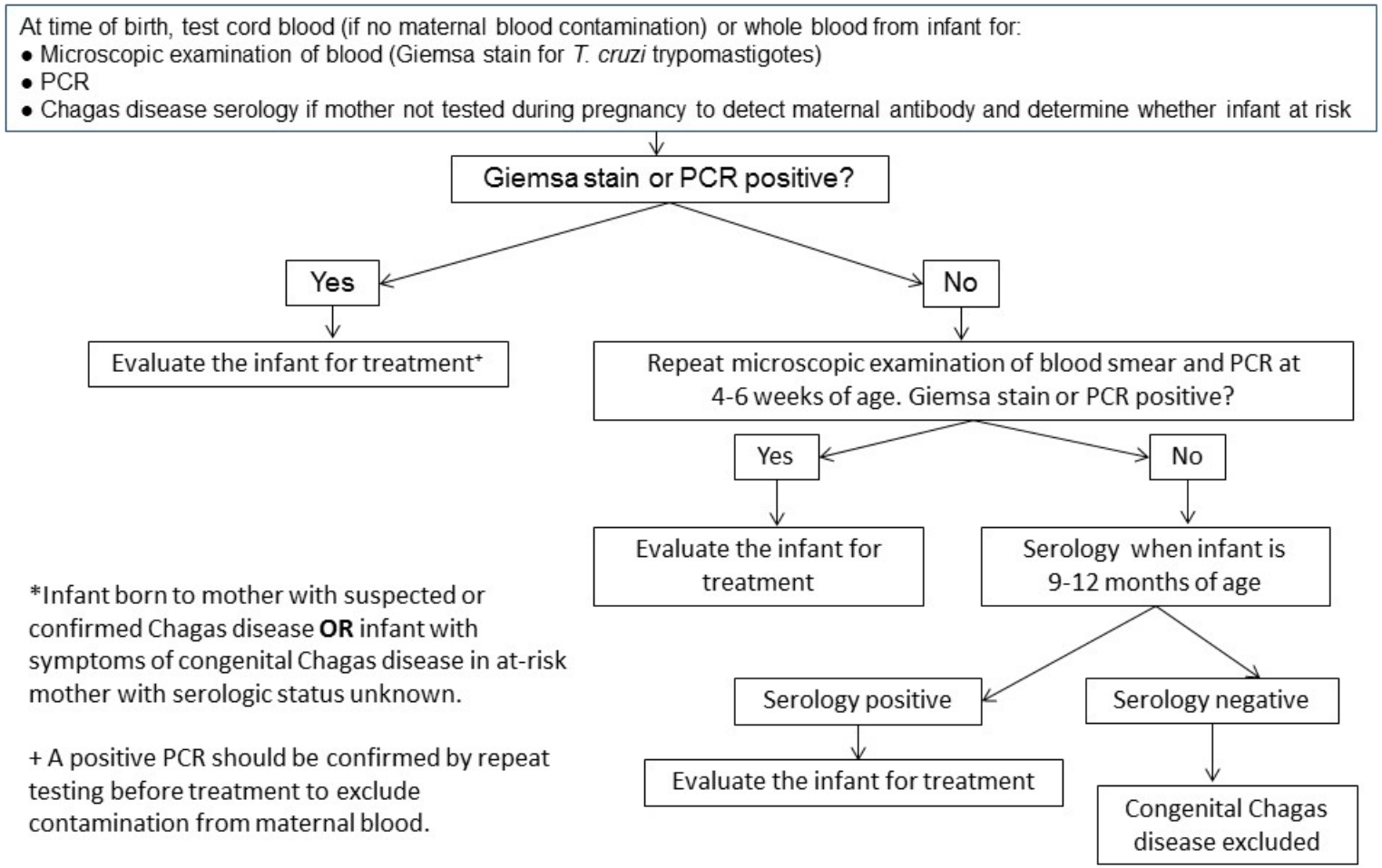
Congenital Chagas Disease Diagnosis

- Infants with signs suggesting congenital Chagas disease born to at-risk mothers with unknown *T. cruzi* serologic status should have *T. cruzi* serologic screening as an initial diagnostic test.
- Detection of *T. cruzi* IgG in infant serum reflects the maternal serological status.
- Commercially-available tests for Chagas serologic screening are the Wiener Chagatest Recombinante v.3.0 ELISA (Wiener Laboratories, Rosario, Argentina) and the Hemagen Chagas' kit ELISA (Hemagen Diagnostics, Inc., Columbia, MD).
- If the test result is positive, additional testing at CDC using an assay with a different antigen preparation is indicated to confirm the mother's serologic status.
- Testing the newborn for parasites could be triggered after a single positive serologic test if an infant was born to a mother at a relatively high risk for Chagas disease, for example, an immigrant from an endemic region.

Congenital Chagas Disease Diagnosis

- Infants born to mothers known to have *T. cruzi* infection should undergo diagnostic testing as soon as possible after birth.
- Fresh anticoagulated infant blood or cord blood, if free from maternal blood contamination, should be examined for detection of motile trypomastigotes and for *T. cruzi* by PCR. When positive, either of these tests is diagnostic of congenital Chagas disease.
- Testing is available through the CDC Division of Parasitic Diseases and Malaria at parasites@cdc.gov or by phone at (404) 718-4745. After hours and on weekends, the CDC Emergency Operator is available at (770) 488-7100.

Algorithm for Evaluation of Congenital Chagas Disease: Infant Younger than 3 Months of Age*



https://www.cdc.gov/parasites/chagas/health_professionals/congenital_chagas.html

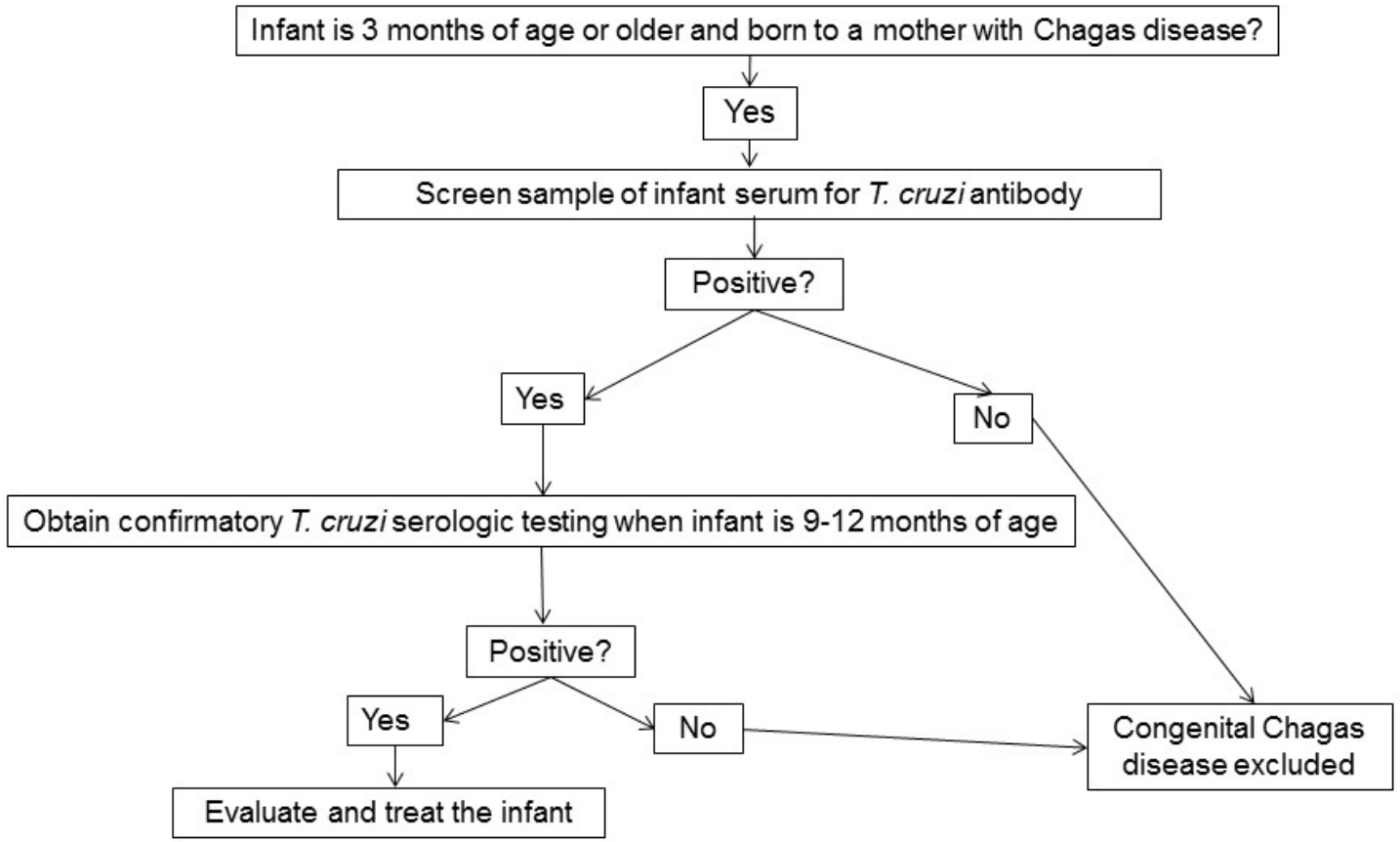
Congenital Chagas Disease Diagnosis Caveats

- A positive PCR for Chagas disease in the first weeks of life can reflect maternal contamination and should be repeated; if both are positive, the diagnosis is confirmed.
- A negative PCR for Chagas disease in first weeks of life can miss congenital infection since parasitemia increases after birth; repeat PCR at 4-6 weeks of age, if positive, confirms the diagnosis.
- Congenital Chagas disease is an acute infection. Signs resolve without treatment in most infants. PCR is not appropriate for evaluation after 3 months of age because, after the acute phase of infection, most parasites are intracellular.
- After the acute phase, infected infants are chronically infected and will be for life if not treated.

Congenital Chagas Disease Diagnosis

- If an infant is 3 months or age or older when concern for congenital Chagas disease arises, the diagnosis is best established serologically.
- Serologic testing at 9 to 12 months of age, when maternally derived IgG should be no longer detectable, will confirm or exclude the diagnosis.
- Persistence of antibody to *T. cruzi* beyond age 12 months is expected to represent an infant's response and confirms a diagnosis of congenital Chagas disease.
- Serologic testing is also appropriate if concern for congenital Chagas disease arises in an older infant or child.

Algorithm for Evaluation of Congenital Chagas Disease for Infants 3 Months of Age or Older



https://www.cdc.gov/parasites/chagas/health_professionals/congenital_chagas.html

Congenital Chagas Disease Management

- Antiparasitic treatment for congenital Chagas disease has a cure rate exceeding 90% during the first year of life.
- Treatment is indicated in any infant with congenital Chagas disease and for all children <18 years of age with chronic Chagas disease.
- Childbearing-aged women with chronic Chagas disease should receive treatment after delivery and completion of breastfeeding for their benefit. Treatment can prevent congenital *T. cruzi* transmission in subsequent pregnancies.
- Consultation with an expert in Chagas disease management is advised before initiating antiparasitic drug treatment.

Murcia L et al. *J Infect Dis* 2017; 215:1452.

Congenital Chagas Disease Management

- The two drugs available for treatment of *T. cruzi* infection are benznidazole and nifurtimox.
- Nifurtimox has approval from the U.S. Food and Drug Administration (FDA) and is commercially available for treatment of pediatric patients from birth, as long as the weight is at least 2.5 kg, and for children younger than 18 years of age.
- Use of nifurtimox to treat a patient outside of the FDA-approved age range is based on clinical diagnosis and decision by a treating physician under practice of medicine.
- The dose is 10-20 mg/kg per day orally in 3 divided doses for 60 days for children weighing less than 41 kg and 8-10 mg/kg per day orally in 3 divided doses for those with body weight of 41 kg or greater.

Chagas disease treatment. Available at: https://www.cdc.gov/parasites/chagas/health_professionals/tx.html

Congenital Chagas Disease Management

- Benznidazole is FDA-approved for the treatment of Chagas disease in pediatric patients 2 to 12 years of age.
- Benznidazole is available from www.benznidazoletablets.com
- Use of benznidazole to treat a patient outside of the FDA-approved age range is based on clinical diagnosis and decision by a treating physician under practice of medicine.
- The treatment dose for children 2-12 years of age is 5-8 mg/kg per day orally in 2 divided doses for 60 days.
- Benznidazole is considered first-line treatment based upon a more favorable adverse effect profile and accumulated clinical experience.

Chagas disease treatment. Available at: https://www.cdc.gov/parasites/chagas/health_professionals/tx.html

Congenital Chagas Disease Management

Drug	Age group	Dosage and duration
Benznidazole	2–12 years of age	5–8 mg/kg per day orally in 2 divided doses for 60 days
Lampit® (nifurtimox)	Birth to younger than 18 years of age, weighing at least 2.5 kg	Body weight greater than or equal to 41 kg: 8–10 mg/kg per day orally in 3 divided doses for 60 days
		Body weight less than 41 kg: 10–20 mg/kg per day orally in 3 divided doses for 60 days

Chagas disease treatment. Available at: https://www.cdc.gov/parasites/chagas/health_professionals/tx.html

Congenital Chagas Disease Management

- Adverse events are common with nifurtimox and benznidazole but both medications are well tolerated in neonates and infants.
- Adverse events after the use of nifurtimox include:

  -Gastrointestinal (anorexia, nausea, abdominal pain, vomiting)

  -Neurologic (headache, memory loss, peripheral neuropathy)

  -Weight loss

  -Psychiatric (anxiety, insomnia)

  -Musculoskeletal (arthralgia, myalgia)

Abbott A et al. *MMWR* 2022; 71:371.
Altcheh J et al. *Pediatrics* 2011; 127:e212.

Congenital Chagas Disease Management

- Adverse events are common with nifurtimox and benznidazole but both medications are well tolerated in neonates and infants.
- Adverse events after the use of benznidazole include:

  -Allergic dermatitis (rash, pruritis)

  -Gastrointestinal (anorexia, nausea, abdominal pain)

  -Psychiatric (insomnia)

  -Neurologic (headache, peripheral neuropathy)

Jackson Y et al. *J Antimicrob Chemother* 2020; 75:690.

Congenital Chagas Disease Prevention

- At least 40,000 U.S. women of childbearing age have chronic Chagas disease acquired, in most, while living in an endemic region.
- Pregnancy-based screening has the advantage that the results are available at delivery, optimizing the opportunity to identify Chagas disease for both mother and infant.
- Systematic pregnancy-based *T. cruzi* screening in at-risk women living in non-endemic regions can identify congenital Chagas disease with or without signs of infection. Such programs also illustrate the feasibility of screening at-risk family members.

Basile L et al. *Euro Surveill* 2019; 24:1900011.

Congenital Chagas Disease Prevention

- Serologic testing family members of an infant with congenital Chagas disease should include:

  -Each of the infant's siblings

  -The infant's mother

  -The infant's maternal grandmother

  -The mother's siblings

- Screening of siblings of index infants diagnosed with Chagas disease in one report found that 7.8% of 178 siblings tested were positive for *T. cruzi.*

Basile L et al. *Euro Surveill* 2019; 24:1900011.

Congenital Chagas Disease Prevention

- Targeted or universal maternal screening with infant testing and maternal and infant treatment for confirmed Chagas disease would be cost saving in the United States.
- At current testing costs, maternal screening, infant testing and treatment are cost-saving for maternal prevalence as low as 0.057% and for mother-to-infant transmission probability as low as 0.001%.
- Targeted screening and treatment with benznidazole would result in savings of $1,314 per birth and $670 million in lifetime savings per birth-year cohort.

Perez-Zetune V et al. *Am J Trop Med Hyg* 2020; 102:1086.

Congenital Chagas Disease Summary

- On the basis of strong evidence from research, a majority of persons in the United States with Chagas disease have chronic *T. cruzi* infection acquired in an endemic region of Mexico, Central America or South America. Infants born to women with chronic Chagas disease are at risk for congenital Chagas disease.

- On the basis of strong evidence from research, maternal parasite load is the strongest predictor of fetal risk of *T. cruzi* transmission during gestation and PCR is the optimal method for early detection of infection. Rates of maternal-to-infant transmission of *T. cruzi* in the United States are estimated to range from 1% to 5%.

Congenital Chagas Disease Summary

- On the basis of evidence from research, 10% to 40% of infants with congenital Chagas disease have signs of infection at birth or in the first weeks of life. When present, these signs can suggest but are not diagnostic of a congenital infection.

- On the basis of evidence from research, mothers with chronic Chagas disease may breastfeed their infants unless there are cracked and bleeding nipples.

Congenital Chagas Disease Summary

- On the basis of strong evidence from research, treatment of congenital Chagas disease in the first year of life is almost uniformly curative.

- On the basis of strong evidence from research, targeted or universal maternal serologic screening for *T. cruzi* infection during pregnancy with infant testing and maternal and infant treatment for confirmed Chagas disease would be cost saving in the United States.