AAFP GLOBAL HEALTH SUMMIT
Primary Health Care and Family Medicine: Health Equity for All

Chagas Disease in the United States: Who to Screen, How to Treat

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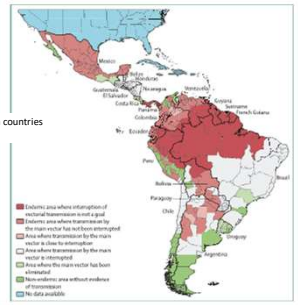
Transmission of Chagas Disease by the Main Vector Triatome

Endemic in 21 Latin American countries



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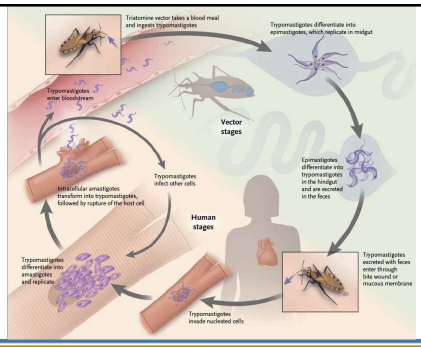
Chagas Disease

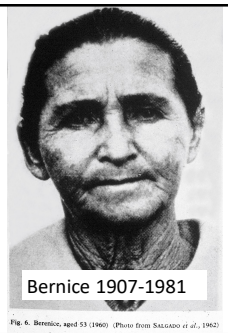
- Caused by protozoan parasite *Trypanosoma cruzi*
- Zoonotic disease, many animal reservoirs
- > 5 million people infected in Mexico, Central and South America
- Estimated 300,000 living with Chagas disease in the United States
- Two phases of infection, acute and chronic
- 20 – 40% of chronically infected develop cardiac disease, fewer develop gastrointestinal disease

Bern & Montgomery. *Clin Infect Dis* 2009; 49:e52
Manne-Goehler J, Umeh CA, et al. Plos Negl Trop Dis 2016 Nov 7.

Fig. 5. Chagas examining Berenice, aged 2 (1909). (Photo from Bacellar, "Brazil's Contributions to Tropical Medicine and Malaria", Rio de Janeiro, 1963 in Kean, 1977.)



N Engl J Med 2015;373:456-66.



Bernice 1907-1981

Fig. 6. Berenice, aged 53 (1960) (Photo from Salgado *et al.*, 1962)

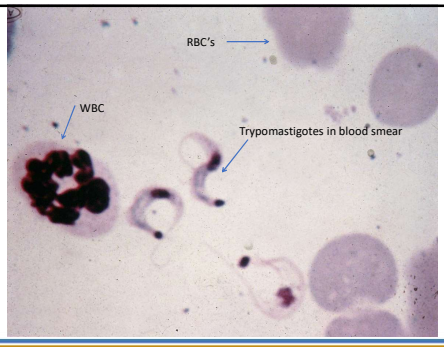
Classic Chagas Disease Transmission Cycle

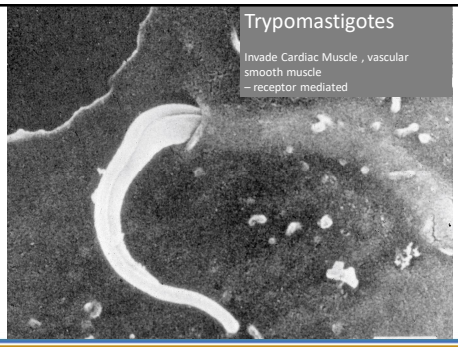
Other modes of transmission:
- Blood transfusion
- Organ transplantation
- Laboratory accident
- Congenital
- Oral transmission (contaminated food/drink)

Trypanasoma cruzi

Mammalian Hosts

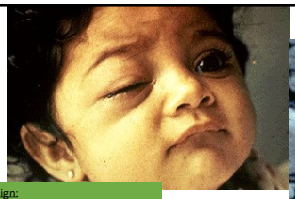
Triatome Vectors



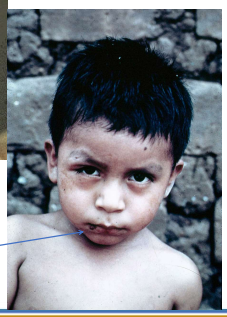


Trypomastigotes

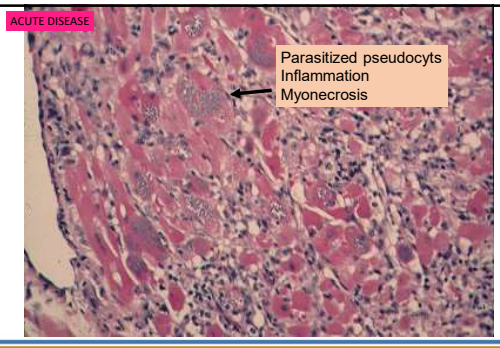
Invade Cardiac Muscle , vascular smooth muscle
– receptor mediated



Romaña's sign:
Nonpainful unilateral edema of the upper
And lower eyelids
Lasts for several weeks

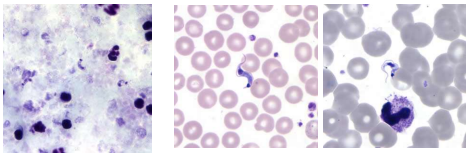


Chagoma



Acute phase infection: Morphological identification

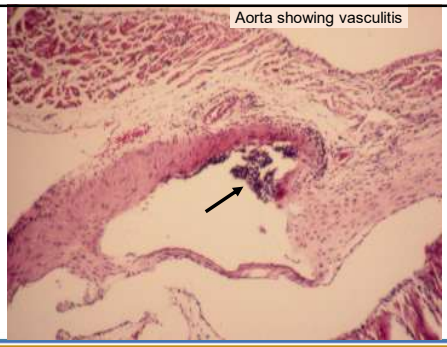
- **Giemsa stained blood smears**



Giemsa stained thick blood smear

Giemsa stained thin blood smears

Courtesy of Susan Montgomery



Acute phase infection: Molecular detection (PCR)

- **Higher sensitivity than morphological identification methods**
  Extraction methods for sample preparation can increase sensitivity—e.g., testing buffy coat vs. whole blood specimens
- **Presence of detectable DNA does not necessarily mean circulating parasites**
- **PCR performed at CDC**

Schijman AG, Bisio M, Orellana L, Sued M, Duffy T, et al. (2011) International study to evaluate PCR methods for detection of *Trypanosoma cruzi* DNA in blood samples from Chagas disease patients. PLoS Negl Trop Dis 5: e931.

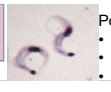
Qvarnstrom Y, Schijman AG, Veron V, Aznar C, et al. (2112) Sensitive and specific detection of *Trypanosoma cruzi* DNA in clinical specimens using a multi-target real-time PCR approach. PLoS Negl Trop Dis 2012;7:e1689.

Acute phase of Chagas disease

1-2weeks*

- < 1% diagnosed, most mild
- May have signs at portal of entry
- High parasitemia: visible on microscopy of fresh specimen, culture, PCR sensitivity high
- Fever, systemic symptoms, hepatosplenomegaly (last up to 3 mo.), atypical lymphocytosis
- EKG abnl common, acute meningoencephalitis and myocarditis rare, but associated with high mortality

Acute Phase of Chagas Disease



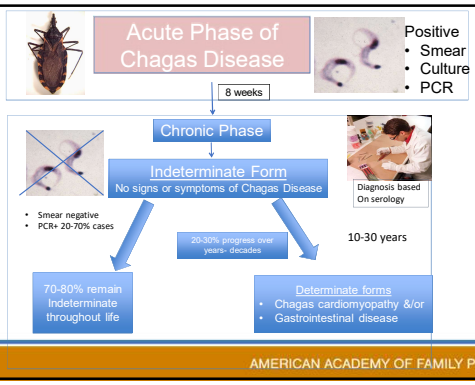
Positive
- Smear
- Culture
- PCR

8 weeks

Chronic Phase

Indeterminate Form
No signs or symptoms of Chagas Disease

Normal ECG and CXR
May have subtle changes on autonomic testing or echocardiogram, unclear if these have prognostic value
≥ 70% remain asymptomatic life-long
Most infected blood donors



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What is Chagas Cardiomyopathy, and why does the diagnosis matter?

Diagnosis of chronic phase infection

- **Detecting presence of *T. cruzi* specific antibody in peripheral blood**
- **Antibody levels persist for life in absence of treatment**
- **Growing evidence that antibody levels may decrease/sero-revert with successful treatment but timing dependent on duration of infection**

Alvarez MG, Bertocchi GL, Cooley G, Albareda MC, et al. (2016) Treatment success in Trypanosoma cruzi infection is predicted by early changes in serially monitored parasite-specific T and B cell responses. PLoS Negl Trop Dis 10:e0004657.

46 year old man with chest pain and shortness of breath

46 year old El Salvadorian immigrant who has multiple prior ER visits over past 3 years for CP and shortness of breath.

Has had physical exam findings c/w CHF,

ECG shows sinus rhythm with a bifascicular block,

Echo moderate LV dysfunction with scar in the inferolateral wall.

Given rx of ACE, BB, diuretic which he takes sporadically as he is uninsured.

Chronic phase infection: Serologic testing

- **Serological methods but no gold standard test**
  - **3 FDA-cleared diagnostic ELISA kits***
    - **All ELISAs but different antigen preparations**
  - **Laboratory developed tests**
    - **Immunofluorescence assays (IFA)**
    - **Immunoblots (e.g., TESA)***
  - **Commercial diagnostic labs offer serologic testing**
    - **Change kits without notice**
    - **Offer testing with only one assay**
- **Problems with specificity and sensitivity of all tests**

Standard for diagnosis: positive results on two or more different format assays, different antigen preparations

***CDC performs FDA-cleared ELISA kits/ immunoblot in parallel**

Current presentation

- BP 105/70, HR 90, 95% RA
- Elevated JVP, crackles, S1 S2, S3, S4, 3/6 holosystolic murmur
- Troponin I 1.2 ng/ml, BNP 800 pg/ml
- ECG NSR with bifascicular block
- A diagnostic procedure was performed
- **Trypanosoma Cruzi IgG Hemagen ELISA positive, confirmed by CDC with Weiner ELISA and TESA blot**

Chronic Chagas Cardiomyopathy

- 20-30% of infected patients will progress to this stage, unclear who will progress.
- Defined as an abnormal ECG in the setting of confirmed positive serology.
- More serious pathology in approx. 30% of those with abnormal ECGs, including CHF, stroke, arrhythmia.

So your patient is confirmed positive by the CDC….what do you do next?

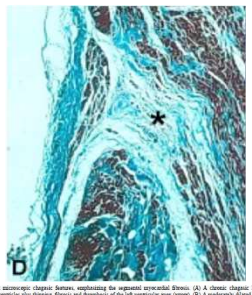


Fig. 3. Macroscopic and microscopic chagasic features, emphasizing the segmental myocardial fibrosis. (A) A chronic chagasic heart exhibits severe dilation of left and right ventricles plus thinning fibrosis and thrombosis of the left ventricular apex (arrow). (B) A moderately dilated and hypertrophic left ventricle showing segmental fibrosis on the apex (arrow), considered to be a pathognomonic lesion of Chagas heart disease. (C) Fibrotic thinning of the myocardium adjacent to the mitral valve at the posterior wall of the left ventricle (arrow). (D) Microscopic view of the bifurcation of the His bundle showing segmental fibrosis (asterisk) at the origin of the right bundle branch (Masson trichrome, objective magnification: 2.5×).

ECG with 30 second rhythm strip

PLoS Negl Trop Dis 12 June 13, 2018(6): e0006567

- The main diagnostic criteria for chronic phase

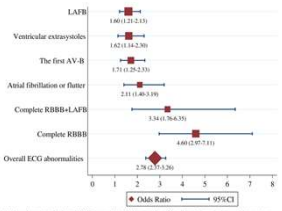


Fig 3. Prevalence of overall and specified ECG abnormalities in CD in compared non-CD participants. Forrester determined the association between overall and specified ECG abnormalities with CD in compared Non-CD participants. Abbreviations: CD=Chagas disease; RBBB=Right bundle branch block; LAFB=Left anterior fascicular block; AV B=Atrioventricular block.

Symptoms of Chronic Phase: Cardiac

- Angina-like CP, from microvascular disease
- Exertional intolerance: chronotropic incompetence
- Palpitations/Syncope: autonomic issues/brady/tachyarrhythmias
- CHF: LV/RV dysfunction
- Stroke: apical aneurysm even without or mild LV impairment, afib

Cause of death:
SCD: @50%
CHF: @40%
Embolic event @10%

If you look for Chagas in patients with these ECG findings from Latin America…..

- Data from Olive View Medical Center CECD
- 5% of all bundle branch blocks had Chagas
- 17.9% of bifascicular block had Chagas
- 7.5% of patients with pacemakers had Chagas

What else do I need to do for my patient with Chagas?

Stroke in Chagas

- Can be the first presentation
- Associated with lower EF, ***BUT*** also with apical aneurysm even with normal EF.
- NB: Look carefully for aneurysm in stroke patients!
- May also be due to higher rates of afib.

Echo in Chagas

- **A**: Normal in Indeterminate: low risk VT/CVA: strain
- **B/C**: Regional WMA, posterolateral particularly affected.
- **B/C**: Apical aneurysm, with thrombus
- **C/D**: Dilated cardiomyopathy with scar

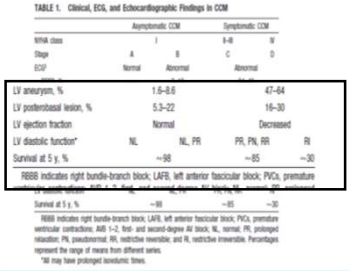


TABLE 1. Clinical, ECG, and Echocardiographic Findings in CCM

	Asymptomatic CCM		Symptomatic CCM	
NYHA class	I		II–III	IV
Stage	A	B	C	D
ECG*	Normal	Abnormal	Abnormal	
LV aneurysm, %	1.6–8.6		47–64	
LV posterobasal lesion, %	5.3–22		16–30	
LV ejection fraction	Normal		Decreased	
LV diastolic function*	NL	NL, PR	PR, PN, RR	RI
Survival at 5 y, %	~98		~85	~30

RBBB indicates right bundle-branch block; LAFB, left anterior fascicular block; PVCs, premature ventricular contractions; AVB 1–2, first- and second-degree AV block; NL, normal; PR, prolonged relaxation; PN, pseudonormal; RR, restrictive reversible; and RI, restrictive irreversible. Percentages represent the range of means from different series.
*All may have prolonged isovolumic times.

Sudden Death in Chagas

- Can be the first presentation
- Usually from tachyarrhythmia from scar, the more scar, the higher the risk
- Associated with lower EF, but can occur in near normal EFs

Clinical syndromes c/w Chagas

Heart Failure in Chagas

- The diagnosis is not usually considered
- BENEFIT trial: no benefit to antiparasitic therapy if heart disease present.
- GDMT is appropriate, but even in this setting prognosis is worse than other cardiomyopathies.
- Chagas patients do well with transplant; reactivation is possible, responds well to antiparasitic therapy.

How likely am I to make the diagnosis in a heart failure patient?

- Meymandi et al @ CEDC: 19% of non-ischemic CHF patients from endemic regions had Chagas
- Mount Sinai in NYC: 13% of non-ischemic patients had Chagas

Carlos Chagas (1879-1934)

Bern, Montgomery et al. Current Opinion Infect Dis 2008 476-82

Screening for Chagas

Blood donor screening in the United States

- **FDA approved first screening test in Dec 2006**
- **Many but not all blood centers started screening early 2007**
- **Second test approved April 2010 (different manufacturer, different assays ELISA or ChLIA)**
- **FDA approved 'confirmatory' test same antigens as ChLIA screening test**
- **Screening tests approved for serum or plasma from living donors of blood or organs and of cadaveric specimens**
- **Recommended for screening Hematopoietic stem cell transplantation donors and recipients**

A 28 year old woman born in rural El Salvador donates blood. She came to the United States when she was 18 years old and has not been back to her home country. She receives a letter telling her that she has tested positive for Chagas disease which instructs her to see her doctor. She is now in your office with her letter. She has no symptoms. Her physical examination is normal. What is the NEXT best step in the management of this patient?

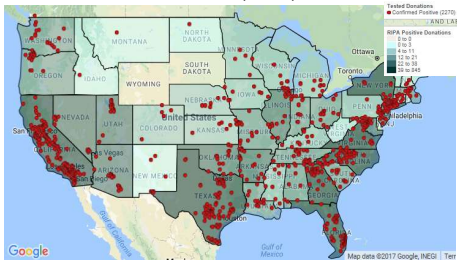
A. **Treat with antiparasitic agents (benznidazole)**
B. **Obtain a second confirmatory ELISA test**
C. **Obtain a PCR on the patient's serum**
D. **Obtain an Echocardiogram**

Blood donor screening in the United States

- **FDA guidance issued Dec 2010, all centers expected to screen by end of 2011**
  Screen all donors initially, if negative no need to test future donations
- **Donors deferred on basis of positive screening test (repeatedly positive) regardless of confirmatory test results**

FDA Guidance for industry: use of serologic tests to reduce the risk of transmission of Trypanosoma cruzi infection in whole blood and blood components intended for transfusion
https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm235855.htm

Confirmed positive blood donors
2007 – 2017*, n = 2,270



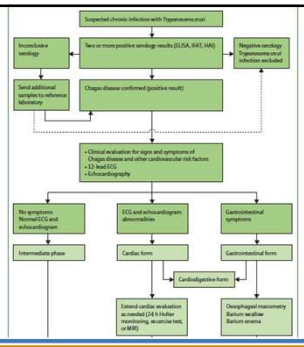
Patient with new diagnosis of Chagas disease

- Confirm diagnosis with diagnostic laboratory testing
- Obtain complete medical history
- Perform physical examination, complete review of systems
- 12-lead EKG with 30 sec rhythm strip
- If cardiac or gastrointestinal signs/ symptoms are present, further work-up as indicated
  - Barium studies, etc.
  - Echocardiogram, Holter, etc.

What blood donor screening results tell us

- **> 2,200 cases of chronic Chagas disease among blood donors since introduction of screening in 2007***
  - Screening test positive, either of two tests
  - Supplemental test positive
  - Blood centers do not record country of birth, only age, sex, zip code of residence
  - A few of these donors have domestically acquired infections
- **Where people with Chagas disease are living**

Source: AABB Chagas Biovigilance program, as of September 8, 2017



Molina et al. Lancet 2018:391:82-94

How to interpret blood donor testing results

- **Many patients' infections first identified by blood donor screening**
- **FDA approved blood donor screening ≠ diagnostic testing**
- **False positives happen, risk history of donor/patient is important**
- **Blood donor testing not sufficient for diagnosis**
  - Using a very sensitive test in a low prevalence population
  - One manufacturer's screening test uses the same antigens as the same manufacturer's supplemental test
- **Positive blood donor needs diagnostic testing, with two different assays using different antigen preparations**

A 32 year old woman born in rural El Salvador donates blood. She came to the United States when she was 18 years old and has not been back to her home country. receives a letter telling her that she has tested positive for Chagas disease and instructs her to see her doctor. She is now in your office with her letter. She has no symptoms. Her physical examination is normal. What is the NEXT best step in the management of this patient?

A. **Treat with antiparasitic agents (benznidazole)**
B. **Obtain a second confirmatory ELISA test ✔**
C. **Obtain a PCR on the patient's serum**
D. **Obtain an Echocardiogram**

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Chagas Disease in the United States: Who to Screen, How to Treat

Congenital Chagas Disease

Factors Enhancing or Possibly Increasing Transmission

- High maternal parasitic load
- Genotype: There are several genetic lineages of *T. cruzi* parasites. The role of lineage on transmission is not well characterized
- HIV co-infection: Increases the risk for transmission
- *T. cruzi* can "cluster" in families but there is no defined genetic predilection
- Maternal age: Increasing maternal age could enhance transmission

Beukens et al. Mat Child Health 2008; 12:283.

Congenital Chagas Disease

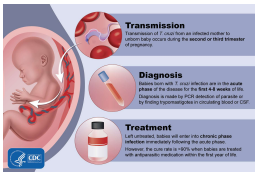
- An estimated 40,000 infected women of childbearing age live in the US; an estimated 63-315 infected infants are born each year*
- Most congenitally infected infants appear at healthy at birth; untreated, they are at risk for developing life-threatening cardiac or GI disease decades later
- 10% to 40% of infants are symptomatic at birth with findings that can include prematurity, hepatosplenomegaly, jaundice, anemia and thrombocytopenia; fetal hydrops, myocarditis or meningoencephalitis can occur but are less common; none of the findings is specific for Chagas disease

Bern & Montgomery. *Clin Infect Dis* 2009; 49:e52.
Beukens et al. Mat Child Health 2008; 12:283.

Challenges to Identifying Infants with Congenital Chagas Disease

- Many infants with congenital infection are asymptomatic at birth and symptoms, when present, are non-specific
- Chagas disease in infants likely occurs more frequently than recognized; even when infants are symptomatic, the diagnosis is often not considered
- Identifying maternal infection is key to identifying infants at risk but maternal screening is not routine
- The prevalence of infection among women of child-bearing age in the US is not known

Mother-to-Child Transmission of *T. cruzi*



- Transmission occurs transplacentally in the 2nd or 3rd trimester of gestation
- There is little evidence to suggest intrapartum or postpartum transmission
- Mothers usually asymptomatic
- Mother-to-infant transmission rates are 1% to 10%
- Transmission rates are higher (5%) in countries where *T. cruzi* is endemic than in those where it is not (3%)*

Edwards et al. JPIDS 2019; doi: 10.1093/jpids/piz018
*Howard et al. *BJOG* 2014; 121:22.

Chagas Disease in Southern Texas

- Cord blood or residual maternal blood obtained from 4,000 of 4,016 infants born consecutively at a single hospital in Houston (2011-2012) had serologic testing for Chagas disease performed at CDC
- >75% of mothers were born in Mexico, Central America or South America
- Samples from 28 of 4,000 women (0.7%) were screen positive by Chagatest ELISA
- Additional testing by IFA and/or TESA immunoblot confirmed Chagas disease in 10 women (0.25%)

Edwards et al. *J Ped Infect Dis* 2015; 4:67.

Comparison of Features for Pregnant Women Based on *T. cruzi* Serology

Maternal feature	*Trypanosoma cruzi* Serologic Status[a] Positive (n = 10)	Negative (n = 3990)	*P* Value
Mean years of age (range)	33.8 (25–41)[b]	28.3 (13–46)	.007
Hispanic ethnicity	10 (100)	3376 (84.6)	NS
Birthplace			
Mexico	3 (30)	2001[c] (50.2)	NS
El Salvador	5 (50)	447 (11.2)	<.001
Honduras	2 (20)	357 (8.9)	NS
Guatemala	0	258 (6.5)	NS
Nicaragua	0	17 (0.4)	NS
Live birth (%)	10 (100)	3880 (97.2)	NS

Edwards et al. *J Ped Infect Dis* 2015; 4:67.

Screening Pregnant Women and their Infants for Chagas Disease

- Chagas disease screening is optimally performed during pregnancy
- Women at risk are those who have migrated from an endemic region
  - Risk is enhanced by having lived in a rural region
  - Risk is also enhanced by having lived in a mud or thatched-roof home
- Women who have visited and lived in an endemic region for 6 months or longer are at risk and should undergo *T. cruzi* screening
- Neonates born to at-risk women who were not tested during pregnancy should be screened for *T. cruzi*

Maternal Interviews and Infant Evaluation

- 8 of 10 chronically infected mothers were interviewed
  - None had heard of Chagas disease
  - None knew of relatives with heart or GI problems
- None had known heart disease or arrhythmia; 1 had a year-long history of constipation
- All had lived in rural areas of Mexico or Central America
  - 6 had lived as children in a mud or adobe home
  - Several had lived in homes with thatched roofs
- 7 infants were term, 1 was a 25-week preterm infant; all had negative serologic tests by age 7 months

Edwards et al. *J Ped Infect Dis* 2015; 4:67.

How to Screen Pregnant Women for Chagas Disease

- Screening can be performed during any trimester of pregnancy
- A commercially-available ELISA should be ordered to test for *T. cruzi* IgG
- Chagas disease screening is a send-out test from most hospital laboratories. Results are available within days
- Cost (~$45) may be covered as an add-on to routine maternal screening
- It is not necessary or appropriate to screen for *T. cruzi* IgM

Triatomine Bug Infestation of a House in Mexico

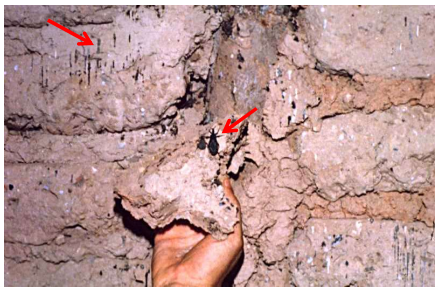


Photo from WHO at: http://www.who.int/chagas/resources/photo_gallery/en/

How to Screen At-Risk Infants and Children for Chagas Disease

- Perform *T. cruzi* IgG antibody screening using a commercially available serologic test
  - Cost of testing is ~$45
  - It is not necessary or appropriate to order *T. cruzi* IgM
- Send screen positive serum to CDC via the State Health Services Laboratory for confirmatory testing. Tests will include:
  - ELISA
  - Trypomastigote excreted antigen immunoblot (TESA)
- Chagas disease is reportable in some states, including Arizona, Arkansas, Louisiana, Mississippi, Tennessee, Texas and Utah

Case Study

An 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

Do you think this infant is at risk for Chagas disease? What additional information would be helpful?

What testing is indicated?

MMWR 2012; 61:477

AMERICAN ACADEMY OF FAMILY PHYSICIANS

Treatment of Chagas Disease

- Treatment is always indicated for congenital Chagas disease. Treatment early in life kills the parasite and prevents long-term complications from heart and intestinal disease; cure rates exceed 90%*
- If a woman is diagnosed with Chagas disease, her other children should also be tested; treatment is always indicated for children <18 years of age
- Treatment is always indicated for women in the childbearing years**, both for the health of the woman and for the sake of her children
- Infection can be transmitted congenitally in sequential pregnancies among women chronically infected with *T. cruzi*

MMWR 2012; 61:477-9. **Bern C. Antitrypanosomal therapy for chronic Chagas' disease. *N Engl J Med* 2011; 364:2527.

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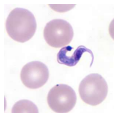
Testing for Suspected Congenital Chagas Disease



- Direct detection: Diagnostic if positive; less sensitive than PCR
- PCR: The most sensitive test for early diagnosis
  - PCR for *T. cruzi* is available at the CDC laboratory; testing is under CLIA
  - Initial negative must be repeated at 1 month of age as parasites multiply in the first weeks of life
- Maternal Serology: Order *T. cruzi* IgG if not performed during pregnancy
- Infant Serology: If PCR is negative and maternal serology is positive, follow infant's *T. cruzi* IgG. Negative serology at 9-12 months of age excludes congenital infection

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Treatment of Acute/Indeterminate/Reactivation Phase

- Offer treatment to all acutely infected patients, or patients with reactivation disease
- Offer treatment to patients ages 18-49 y.o.

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Case Study Outcome

An 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.

Do you think this infant is at risk for Chagas disease? What additional information would be helpful?
His mother had moved to the United States from Bolivia. During the infant's second week of life, she recalled she had been told she had Chagas disease.

What testing is indicated?
Blood smear revealed T. cruzi trypomastigotes and T. cruzi PCR was strongly positive; serologic tests for T. cruzi antibodies were positive. The infant received benznidazole for 60 days and was cured.

*CDC. Congenital transmission of Chagas disease-Virginia, 2010. *MMWR* 2012; 61:477.

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Chagas Disease Treatment

- Treatment is administered orally
- Two medications are available:
  - Benznidazole is commercially available
  - Nifurtimox is approved by FDA for distribution by CDC
- Duration: 60 days (benznidazole) or 90 days (nifurtimox)
- Treatment is best undertaken in consultation with an infectious diseases specialist

Photo from CDC at http://www.cdc.gov/parasites/cme/chagas/index.html

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Prevention of Congenital Chagas Disease

Chagas disease fact sheets for the public are available on-line in English and Spanish through CDC

Other printable resources include, "Help protect mothers and their children from Chagas disease" and, "Chagas disease in the Americas"

www.cdc.gov/parasites/chagas/printedresources.html

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Additional Information and Resources for Chagas Disease Screening and Treatment

https://www.cdc.gov/parasites/chagas/index.html

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