Chagas disease in the US: an emerging health threat

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Objectives

- Disease description & overview
  - history, epidemiology, risk factors
  - clinical stages, symptoms
  - testing and keys to diagnosis

- Transmission routes

- Control strategies and treatment options

- Obstacles faced
Chagas Disease - Introduction

- American trypanosomiasis
- Neglected disease
- Discovered by Carlos Chagas in 1909
- DNA evidence dates its existence in man for 9000 years
- Charles Darwin thought to have been infected
History

1855
- Vector identified in GA

1860s/70s
- Vector identified in 6 more states

1909
- Parasite observed in CA

1916
- 1st autochthonous cases of Chagas

1955
- Cluster of 3 transplant cases

1909
- 1st autochthonous cases of Chagas

2001
- FDAs approve 1st ELISA-based screening test

2006-07
- All blood centers test for T. cruzi

2012
- Cluster of 3 transplant cases
Chagas Disease - Epidemiology

- Estimated 8-11 million people infected worldwide
- U.S.: estimated 300,000 persons infected

Bern and Montgomery, Clinical Infectious Diseases 2009; 49:e52–4
Graphic: DNDi
Chagas Disease - Epidemiology

- Caused by protozoan *Trypanosoma cruzi*
- Vector-borne only in Americas
  - endemic areas
  - infected vectors, nonhuman mammals

- Transmission
  - vector
  - congenital
  - transfusions
  - organ transplantation
  - rarely: laboratory accidents, food contamination
Chagas Disease – Vector Transmission

- Triatomine “kissing” bugs:
  - mainly exist in poorly constructed homes
  - take blood meal on host
  - pass *T. cruzi* parasites in their feces, which enter the body through mucous membranes or breaks in the skin
Trypanosoma cruzi lifecycle

Triatomite Bug Stages:

1. Triatomite bug takes a blood meal (passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva).

2. Metacyclic trypomastigotes multiply by binary fission in cells of infected tissues. Amastigotes multiply by binary fission in cells of infected tissues. Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle.

3. Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.

4. Multiply in midgut.

5. Metacyclic trypomastigotes in hindgut.

Human Stages:

1. Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.

2. Amastigotes multiply by binary fission in cells of infected tissues.

3. Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.

4. Multiply in midgut.

5. Metacyclic trypomastigotes in hindgut.

CDC
http://www.dpd.cdc.gov/dpdx
States with documented *Trypanosoma cruzi* mammalian reservoirs and vectors

* Published human vector-associated cases
- Green: Both vectors & reservoir species
- Yellow: Vector species

Legend:
- * Published human vector-associated cases
- ** Double asterisks
Risk of transfusion transmission – U.S.

- 7 transfusion transmission cases reported (US & Canada)
- Components with greatest risk: whole blood and platelets
  - platelets implicated in 4 out of 5 U.S. cases
  - whole blood – 18 days
  - platelets – 5 days
  - FFP - < 24 hrs
- Unpublished transfusion transmission cases
Confirmed Positive Blood Donors – U.S.

N = 1826 as of April 10, 2013
Risk of Congenital Transmission – U.S.

- Occurs in 1–10% of children born to infected mothers
- Estimated between 63–315 babies born with Chagas disease every year
- 2010: 1st documented congenital transmission
  - mother originally from Bolivia
  - baby born with evidence of disease

Bern and Montgomery, Clinical Infectious Diseases 2009; 49:e52–4
CDC MMWR 2012; 61(26)
Risk of Organ Transplant Transmission – U.S.

- 9 cases of transplant transmission documented
- More suspected cases investigated
- Prompt diagnosis and treatment leads to better outcomes

**Chagas in Transplant Working Group Recommendations**
- Targeted screening of potential donors from Mexico, Central/South America
- Systematic monitoring: serial PCR, microscopy
- More studies to address knowledge gaps are needed to guide screening
Chagas Disease – Clinical Evolution

- Exposure
  - Acute Chagas infection
    - Cure with drug
    - Chronic indeterminate
      - Permanent indeterminate
      - Reactivation
      - Immunosuppression
      - Cardiac
      - Digestive
    - Chronic determinate
      - Drug
      - "Cure"
Chagas disease - Clinical diagnosis

- **Acute infection**
  - identifying the parasite in blood smear or buffy coat
  - blood cultures
  - PCR

- **Chronic infection**
  - persistent circulating antibody – ELISA, IFA
  - problems with specificity and sensitivity
  - *no gold standard test for Chagas disease*
Antitrypanosomial Drug Treatment

- **Acute infection**: reduce symptom severity, shorten clinical course and duration of detectable parasitemia
  - 90% serorevert if treated early

- **Indeterminate infection**: reduce progression to cardiac disease (no proven reduction in GI disease)

- **Determinate infection**: benefits unknown
  - BENEFIT trial - randomized double-blind controlled clinical trial investigating the role of benznidazole in patients with chronic Chagas heart disease

BENEFIT: “Benznidazole Evaluation for Interrupting Trypanosomiasis”
Antitrypanosomal Drug Treatment

- **Should ALWAYS be offered:**
  - acute infection
  - congenital infection
  - children (<18 years) with chronic disease
  - reactivation due to immunosuppression

- **Should generally be offered:**
  - reproductive-age women
  - adults (19-50) with indeterminate form, or mild-mod cardiomyopathy

- **Optional:**
  - adults >50 without advanced cardiomyopathy
  - patients w/chagas Gl tract disease, but w/o adv. cardiomyopathy

- **Contraindicated:**
  - during pregnancy; severe renal/hepatic insufficiency

Benznidazole & Nifurtimox

- Similar efficacy
- Not licensed in US; CDC sponsors expanded-access IND
- Oral tablets; age/weight based dosing
- Both are associated with frequent side effects, particularly in adults; high frequency of non-compliance
  - tolerability: benznidazole > nifurtimox
- Better tolerated in children, well tolerated in infants
- Mutagenic?
Nifurtimox

- Manufacturer: Bayer
- Nitrofuran compound
- Metabolism: CYP450 enzyme system
- Elimination: renal (low excretion)
- ADRs:
  - anorexia, weight loss, nausea, vomiting, abdominal discomfort, diarrhea
  - insomnia, tremors, paresthesias, polyneuropathy
  - dizziness, vertigo, mood changes, myalgias
- 90 -120 day course of therapy
**Benznidazole**

- **CDC source:** LAFEPE
- **Nitroimidazole derivative**
- **Elimination:** renal/fecal
- **ADRs:**
  - dermatologic: photosensitivity, rash, exfoliative dermatitis
  - peripheral neuropathy
  - anorexia, weight loss, nausea/vomiting
  - rarely, bone marrow suppression
- **Disulfiram-like reaction possible**
- **Available in easily dispersible tablet for pediatric patients**
- **60 day course of therapy**
New Drug Pipeline?

- Triazoles (ravuconazole and posaconazole) exhibit *in vitro* activity against *T. cruzi* (Phase II trials)
- Cruzipain inhibitors
- Bisphosphonates
- Trypanothione synthesis inhibitors
Challenges

- Complex multidisciplinary approach needed
  - infectious disease, cardiology, gastroenterology, OB/GYN, internal medicine, pediatrics, social services
  - lack of awareness among U.S. physicians
- Reluctance of patients (and providers?) to seek treatment
- Drugs to treat are not FDA-approved
- Lack of definitive diagnostic testing
- Defining the U.S. burden of disease and risk
- Public health system
  - reportable only in AZ, MA, and TN
  - low testing capacity at local / state public health laboratories
Chagas disease, was once entirely confined to Latin America, has now spread to other continents.

Chagas disease is curable if treatment is initiated soon after infection.

Up to 30% of chronically infected people develop cardiac alterations and up to 10% develop digestive, neurological or mixed alterations, for which specific treatment may become necessary.

Blood screening is vital to prevent infection through transfusion and organ transplantation.

Many barriers to treatment exist; much work is needed through research, policy, and partnerships.
Thanks to

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