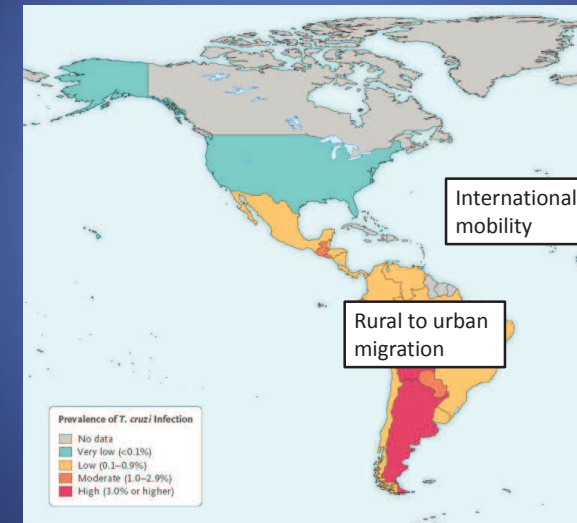


# Maladie de Chagas, une histoire globale et locale

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 Institut de Santé Globale – UNIGE  
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## Pre-2000 era



## 1990-...



IOM 2010

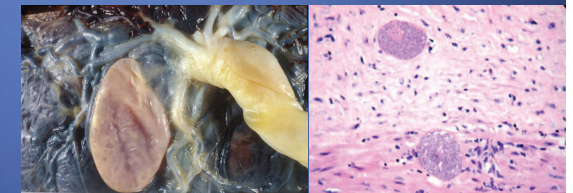
## Genève

- 1996: 1<sup>er</sup> cas  
 Femme 55 ans, Bolivie, insuffisance cardiaque NYHA 3, BBD, BAVIII  
 Dx: IF positive, cardiomyopathie chagastique  
 Tt: pacemaker, Ø médic. antiparasitaire

Sztajzel, Eur Heart J. 1996;17(8):1289

- 2001-2005  
 2 infections congénitales

- 2005-...  
 De plus en plus de cas adultes  
 (25% cardiopathie)



Jackson, EID 2009;15(4):601-3

## Prevalence

### Pregnant Latin American women – Geneva 2007 N=72

	n/N	%
All	7/72	9.7
Bolivian	5/30	16.6

### Adult Latin American immigrants – Geneva 2008 N=1012

	n/N	% (95% CI)
All	130/1012	12.8 (10.8-14.9)
Bolivian	127/485	26.2 (22.3-30.1)
Cardiopathy	14/130	11.3 (6.2-18.2)
Infected blood donors	22/130	16.9 (10.9-24.5)

Jackson Y et al. *Emerg Inf Dis* 2009;15(4):601-4  
 Jackson Y et al. *PLOS Neglect Trop Dis* 2010;4(2):e592

## Facteurs associés à l'infection

	Prevalence of CD, n (%)	Unadjusted OR for CD (95%CI)	Adjusted OR for CD* (95%CI)	Adjusted OR for CD* (95%CI)
<b>Age (years)</b>				
≤35	37/494 (7.5%)			
>35	93/518 (18.0%)	2.7 (1.8;4.0)	3.6 (2.3;5.6)	6.1 (2.2;16.7)
<b>Gender</b>				
Women	108/835 (12.9%)	1.04 (0.6;1.7)	0.85 (0.5;1.5)	1.04 (0.3;3.4)
Men	22/177 (12.4%)			
<b>Origin</b>				
Bolivia	127/486 (26.1%)	61.7 (19.5;195.3)	71.2 (22.4;226.4)	31.7 (7.2;139.5)
Other	3/528 (0.6%)			
Mother with <i>T. cruzi</i> infection	26/78 (33.3%)	5.9 (3.4;10.3)		6.5 (1.9;22.8)
Mother without <i>T. cruzi</i> infection	47/604 (7.8%)			
Previous triatomine bite	35/113 (31.0%)	7.1 (3.9;12.0)		1.8 (0.7;4.6)
No previous triatomine bite	20/336 (6.0%)			

Jackson et al. *PLoS Negl Trop Dis* 2010; 4(2): e592 6

## Children

- 45 cases in Spain and Switzerland
  - 2 acute
  - 43 chronic phase
    - 1 megaesophage
- 41 received treatment
  - 13 (31.7%) with AE
  - 2 (4.9%) treatment interruptions
- 29 followed-up at 2 years
  - 5 (17.2%) cured

Guerineau et al. *Ped Inf Dis* 2014

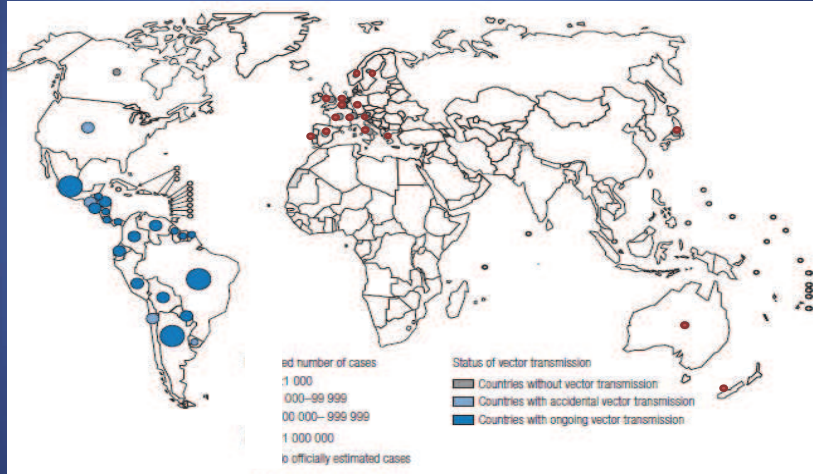
## Transmission

- Congénitale: 6/36 (16.7%)
- Sanguine: 1 donneur infecté (HUG)

	Latin American migrants (n = 1012) N (%)	Bolivian migrants (n = 486) N (%)	Migrants with Chagas disease (n = 130) N (%)
<b>History of blood donation</b>			
	247* (24.4)	109 (22.4)	22 (16.9)
in Latin America	208 (84.2)	96 (88.1)	22 (100)
in Europe	17 (6.9)	1 (0.9)	0
not stated	27 (10.9)	13 (11.9)	0
<b>Intention to give blood outside Latin America</b>	206 (20.4)	70 (14.4)	24 (18.5)
<b>History of organ donation</b>			
	0	0	0
<b>Intention to give organ</b>	360 (35.6)	149 (30.7)	34 (26.2)

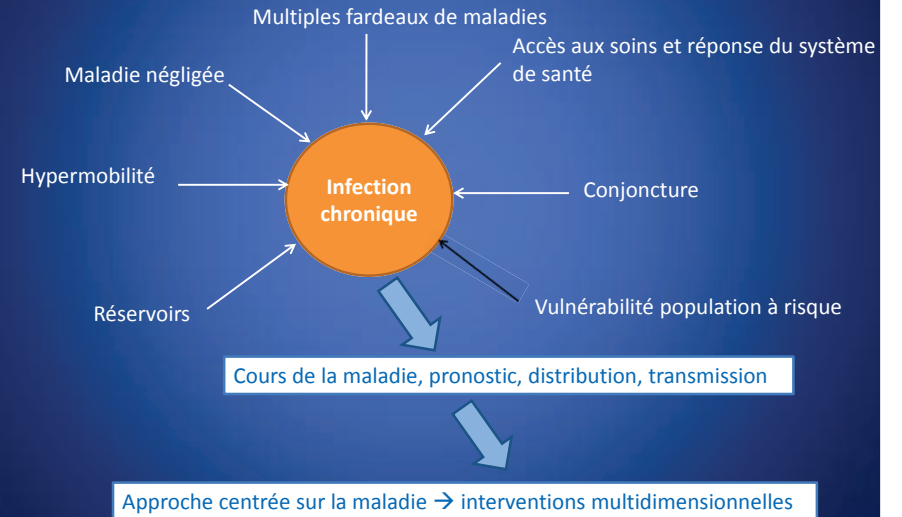
Rodriguez Guerineau et al. *Ped Inf Dis J* 2014;33(5):458-62  
 Pizzi Bosman et al. *Blood Transf* 2011; 9(suppl 1)  
 Jackson et al. *PLoS Negl Trop Dis* 2010; 4(2): e592 8





WHO TDR NTD report 2010

## Défis de santé publique

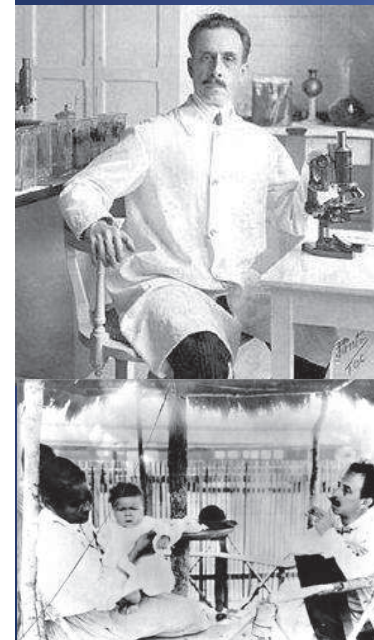


## Asswisschagas

- Community involvement
- Information, education
- Advocacy



## Carlos Chagas 1879-1934

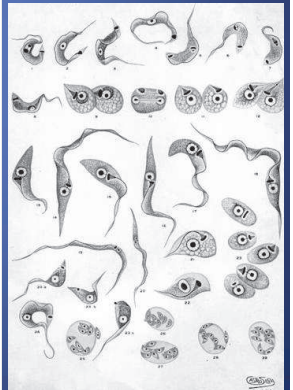


*Trypanosoma bangsi*  
 Nova espécie humana,  
 em ocorrência pelo trypano-  
 some Chagasi.

Trabalho realizado sob a  
 direção de Sr. Corral  
 em São Paulo -  
 Sr. Carlos Chagas -  
 chefe de serviço de  
 Instituto Corral de São  
 Paulo.

Síndrome:  
 Schizotrypanose - Hiper-  
 ite paratuberculosa.

Descrição:  
 A *trypanosoma bangsi*  
 é uma espécie de ameba  
 que apresenta as seguintes  
 características: corpo  
 oval, com dois flagelos  
 agudos, e um ou mais  
 de evolução humana,  
 grosseira e tuberculosa,  
 mas com características  
 muito semelhantes  
 à *trypanosoma*.  
 Ela é encontrada nos  
 5-10 mil de...



# Neglected Tropical Diseases

- Dengue
- Rabies
- Trachoma
- Buruli ulcer (*Mycobacterium ulcerans* infection)
- Endemic treponematoses
- Leprosy (Hansen disease)
- Chagas disease (American trypanosomiasis)
- Human African trypanosomiasis (sleeping sickness)
- Leishmaniasis
- Cysticercosis
- Dracunculiasis (guinea-worm disease)
- Echinococcosis
- Foodborne trematode infections
- Lymphatic filariasis
- Onchocerciasis (river blindness)
- Schistosomiasis (bilharziasis)
- Soil-transmitted helminthiases

**Working to overcome  
the global impact of  
neglected tropical diseases**

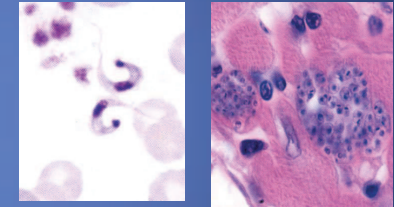
First WHO report on neglected tropical diseases



WHO, TDR 2010

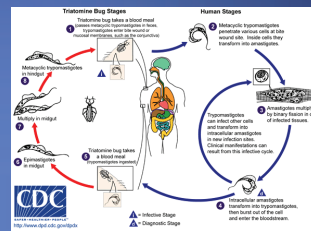
# Trypanosoma cruzi infection

- Zoonosis: wildlife, peri-domestic animals, cats, dogs, ...
- Flagellated protozoa
  - Circulating trypomastigotes
  - Tissue amastigotes
- Vector
  - Blood-sucking triatoma

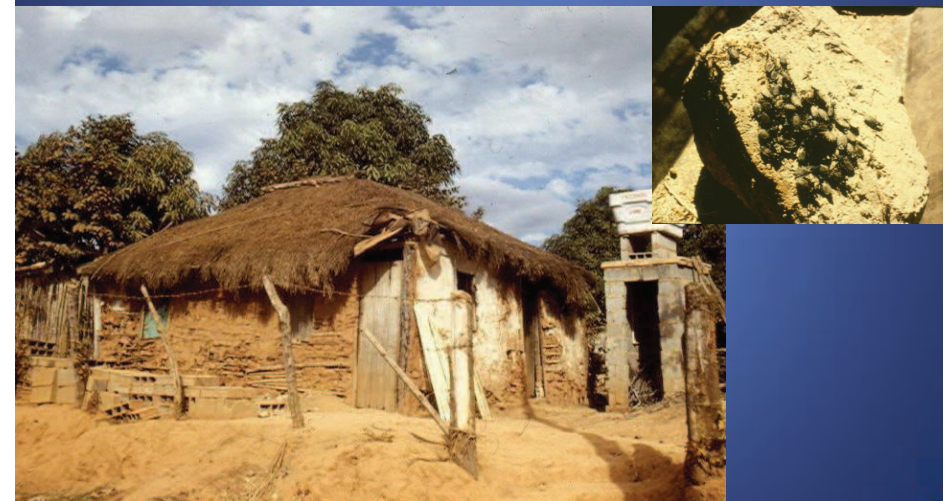


# Transmission

- Vectors
  - Predominant route
  - Americas only



# Vectorial transmission

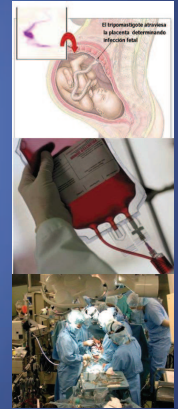






## Other routes of infection

- Congenital (5-10%)
- Transfusion (10-20%)
- Organ transplant
- Food-borne
- Laboratory



**Non-endemic countries**

## Burden of disease

At risk: 70 mio

Prevalence: 5.7 mio

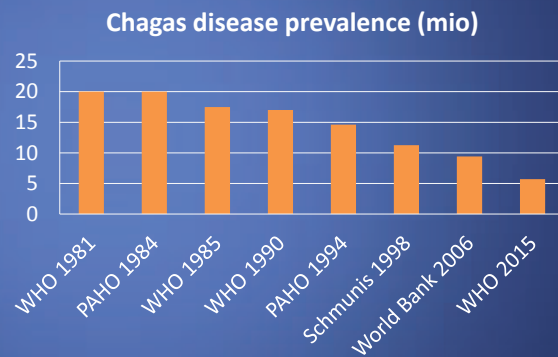
Cardiomyopathy: 1.2 mio

Incidence: ~40'000

Mortality: ~ 14'000 (=dengue)

DALYs: 806'000

Costs (US\$): 7.2 bn



WHO 2015  
Wkly Epidemiol Rec 2015; 90: 33-43  
Lee B. et al. Lancet Infect Dis 2013;13(4):342-8

## Endemic countries Blood donors

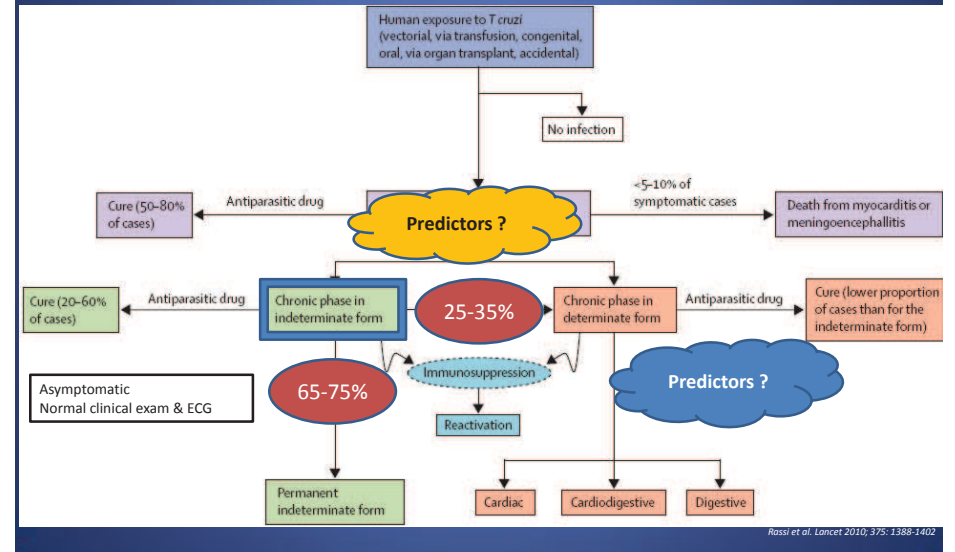
Prevalence	Countries
Unknown	Belize, Guyana, Suriname, French Guiana, Canada
<0.1%	Cuba, Dominican Rep., USA
0.1-1.0	Brazil, Uruguay, Ecuador, Nicaragua
1.0-5.0	Chile, Colombia, CR, Peru, Venezuela Honduras, El Salvador, Panama, Guatemala, Mexico
5.0-10.0	Argentina, Paraguay
>10.0	Bolivia



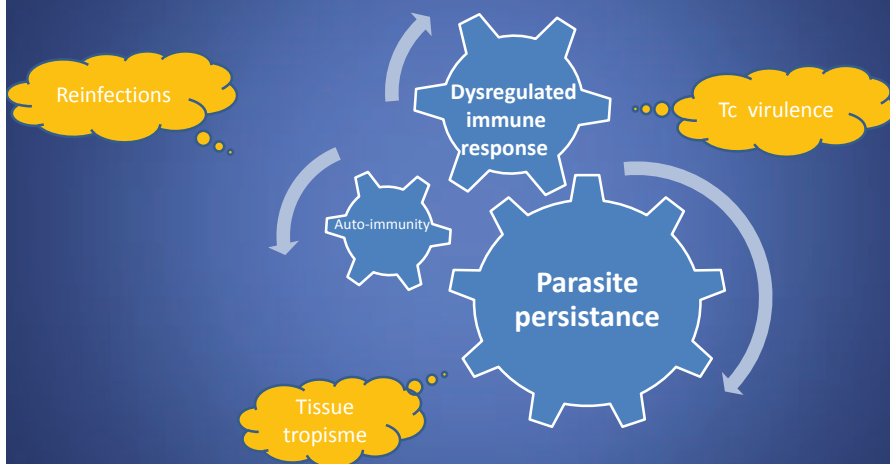
PAHO 2006

# Clinical presentation

## Infection → disease



## Pathogenesis



## Acute infection

- 90% asymptomatic
  - Chagoma, fever, polyadenopathy, hepatosplenomegaly
  - Myocarditis
  - Encephalitis
- 10% mortality**



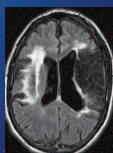
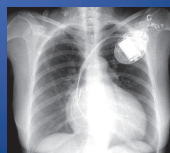
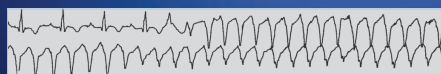
## Cardiac forms

Arrhythmia

Cardiomyopathy

Thromboembolism

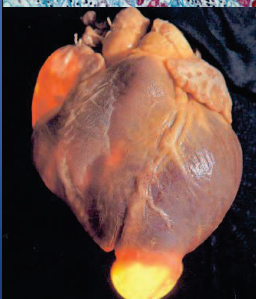
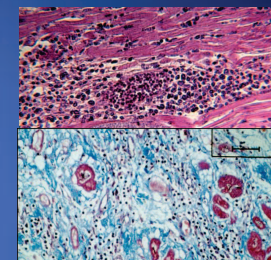
Death



:375: 1388-1402

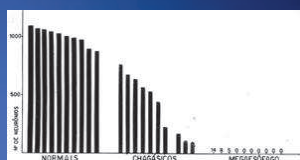
## Cardiomyopathy

- Acute / chronic inflammatory process
- Segmentar (apical, postero-inferior)
- Fibrosis and dilatation
- Apical aneurysm
- Microvascular abnormalities
- Asymptomatic, atypical chest pain, palpitation, syncope



## Digestive form

- Neural cells destruction  
→ progressive dismotility
- Mega Syndrome
  - megaesophagus (achalasia-like)
  - megacolon (Hirschprung-like)
- Dysphagia, regurgitation, constipation

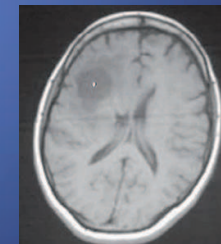


De Rezende et al. Rev Bras Gastroenterol 1960;12:247-62.

## Immunosuppression

*T. cruzi* reactivation: ↑↑ circulating trypomastigotes

- Drug induced (post transplant) erythema nodosum / panniculitis myocarditis
- HIV (<200 CD4/mm<sup>3</sup>) Toxoplasmosis-like (meningo-) encephalitis myocarditis



DíazGranado C et al. Lancet Infect Dis 2009;9:324-30



## Management

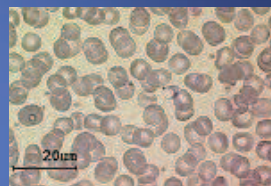
## Clinical work-out

1. Confirm the diagnosis
2. Define the clinical stage
3. Assess the cardiac damages
4. Look for comorbidities/co-infections
5. Evaluate need for treatment

## Diagnosis

- **Acute phase** (<1 month)

	Se (%)	Sp (%)
– Microscopy	80-95	100
– PCR	>95	100



- **Chronic phase**

– Serology (2 tests)	98-99	98-100
– Rapid tests	95-98	99
– PCR	50-75	100
– Microscopy	10-30	99



Chappuis et al. J Clin Microb 2010; 48(8):2948-52

Rassi A. et al. Lancet 2010; 375: 1388-1402

Urbina J. Acta Tropica 2008,doi:10.1016/j.actatropica.2009.10.023.

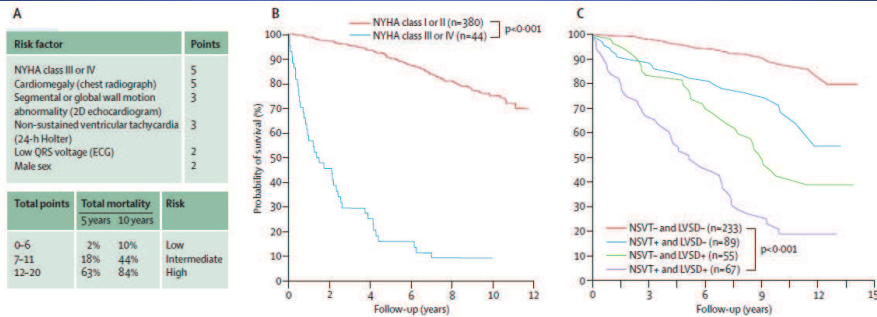
## Staging

- History (chest pain, palpitation, syncope, dysphagia, constipation)
- 12-lead ECG (+ 30 sec. DII strip)
  - Echocardiogram / MRI
  - 24-Hours Holter test
- Barium studies if digestive symptoms





# Prognosis



Rassi A. et al. Lancet 2010; 375: 1388-1402

# Associated risk factors

- Immunosuppression
- Co-infections: Strongyloides (anguillulosis): 20%
- Cardiovascular risk factors

	n (%)	95% confidence interval
Excessive waist circumference	87 (63.5)	55.3-71.7
Overweight or obesity	102 (74.5)	67-81.8
Obesity	35 (25.5)	18.2-32.9
High blood pressure	24 (17.5)	11.1-24
High serum cholesterol	22 (16.1)	9.8-22.3
Impaired fasting glucose	32 (23.4)	16.2-30.5
Diabetes	4 (2.9)	0.6-5.8
Metabolic syndrome	23 (16.8)	10.5-23.1
Depression	39 (28.5)	20.8-36.1
Anxiety	80 (58.4)	50-66.8

Jackson Y et al. TMIH 2012;17(5):595-603

# Treatment

Figure 2. Kaplan-Meier curves of cumulative percentage of patients who changed clinical group.

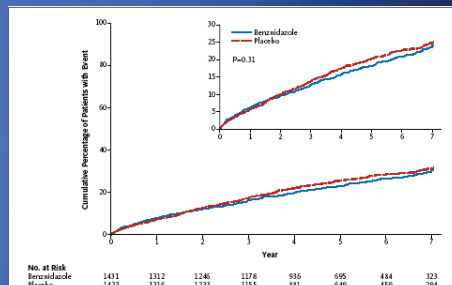
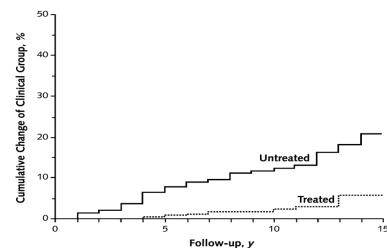


Figure 1. Primary Composite Outcome during 7 Years of Follow-up. Shows is the rate of the primary composite outcome (death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of a pacemaker or implantable cardioverter-defibrillator, cardiac transplantation, new heart failure, stroke or transient ischemic attack, or other thromboembolic event) among patients in the benzadazole group and the placebo group during a 7-year period (hazard ratio in the benzadazole group, 0.93; 95% CI 0.81 to 1.07; P=0.31 by the log-rank test). The inset shows the same data on an enlarged y axis.

Viotti R. Ann Intern Med 2006;144:724-734  
Morillo, N Engl J Med. 2015;373(14):1295-306

## Antitrypanosomal Drug Treatment by Chagas Disease Phase, Form, and Demographic Group

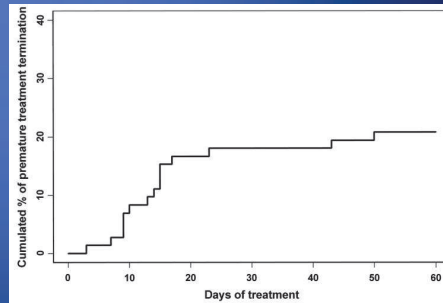
Antitrypanosomal Drug Treatment by Chagas Disease Phase, Form, and Demographic Group	Strength of Recommendation and Quality of Supporting Evidence <sup>a</sup>
Should always be offered	
Acute <i>Trypanosoma cruzi</i> infection	AII
Early congenital <i>T. cruzi</i> infection	AII
Children aged ≤12 y with chronic <i>T. cruzi</i> infection	AI
Children aged 13-18 y with chronic <i>T. cruzi</i> infection	AIII
Reactivated <i>T. cruzi</i> infection in patient with HIV/AIDS or other immunosuppression	AII
Should generally be offered	
Reproductive-age women	BIII
Adults aged 19-50 y with indeterminate form, or mild to moderate cardiomyopathy (Kuschnir grades 0, I, or II)	BII
Impending immunosuppression <sup>b</sup>	BII
Optional	
Adults aged >50 y without advanced cardiomyopathy (Kuschnir grades 0, I, or II)	CIII
Patients with Chagas gastrointestinal tract disease but without advanced cardiomyopathy <sup>c</sup>	CIII
Should generally not be offered	
Advanced chagasic cardiomyopathy with congestive heart failure (Kuschnir grade III)	DIII
Megaesophagus with significant impairment of swallowing	DIII
Should never be offered	
During pregnancy	EIII
Severe renal or hepatic insufficiency	EIII

Bern C. JAMA. 2007; 298(18):2171-81

## Treatment

Drug	Dosage mg/kg/d	Dose max	First used
Benznidazol	5 -7.5	300 mg/d	1969
Nifurtimox	10-15	-	1972

- 60 days
- Similar efficacy
  - >90% acute phase
  - 30-60% chronic phase
- Poor tolerance in adults N>B
- Limited availability (WHO)



Jackson Y et al. Clin Inf Dis 2010;15;51(10):e69-75

## Assessing cure

- Acute stage: parasite clearance (microscopy, PCR) and serology
- Chronic stage: serology ?

### BUT

- Takes decades
- Loss to follow-up
- Proteomic markers ?

Jackson et al. BMC Inf Dis 2013, 13:85

## Recommandations

## Screening

- All Latin American (Mexico to Chile) with
  - Cardiac symptoms
  - Abnormal ECG
  - Dysphagie/severe constipation
- Born or lived in Bolivia
- Family history of Chagas disease
- Blood transfusion in Latin America
- Immunosuppression

! Do not omit adopted children, naturalized, binationals !

## Family-centered approach

- Screen the whole family around index case
- Use index case as community informant
  - Awareness
  - Prevention (visiting friends and relatives)

*Zulantay et al. PLoS Negl Trop Dis 2013;7(2): e1959.*

## Take home messages

- Emerging infection in Switzerland and Europe
- Screening by serology in groups at risk
- Consider it as a cardio-vascular risk factor
- Look for comorbidities including infectious