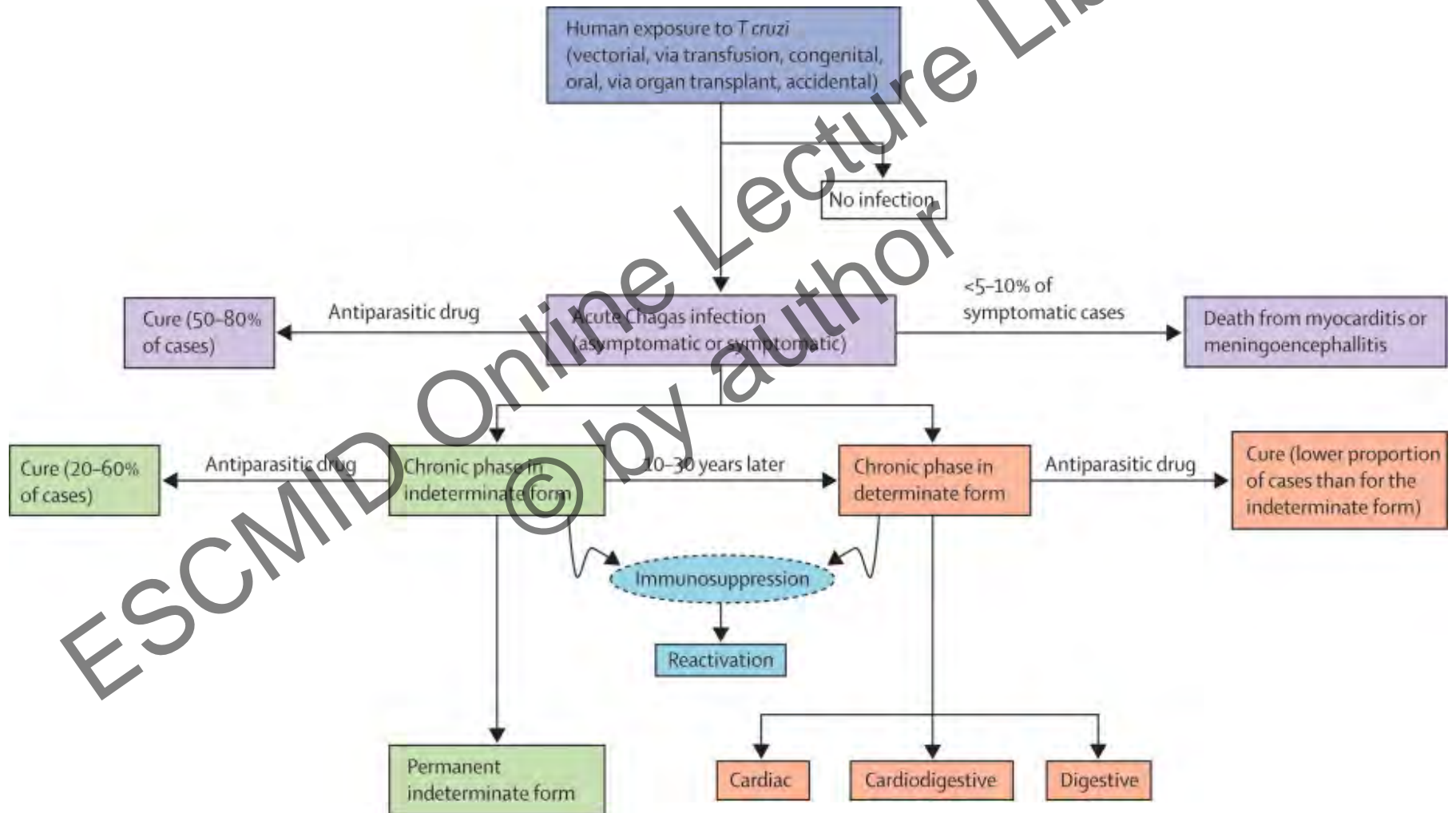


Natural history of Chagas disease



Acute Chagas disease

Incubation period: 7-14 days

Clinical manifestations:

Asymptomatic: most cases

Mild fever: 10-20%

Severe disease: <5% (more frequent in young individuals)

- Acute heart failure
- ECG modifications
- Myocarditis
- Heart blockages
- Meningoencephalitis

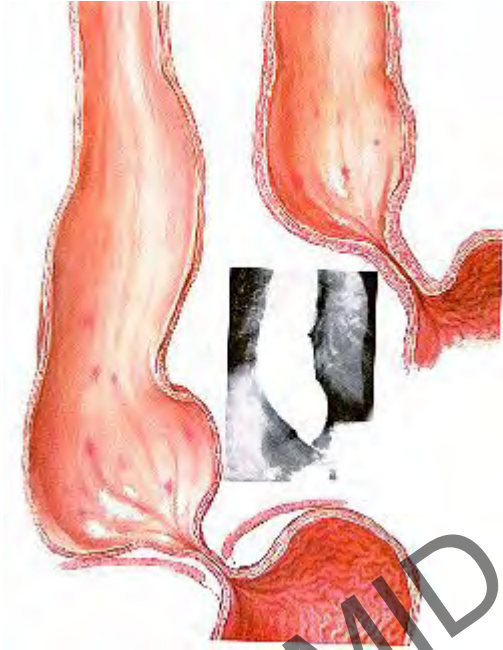


Duration of acute disease: 4-8 weeks

Indeterminate Chagas disease

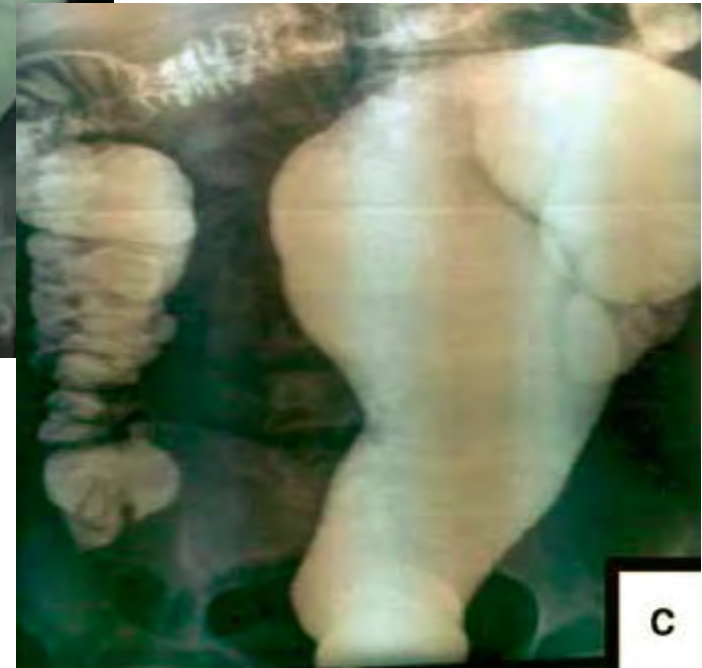
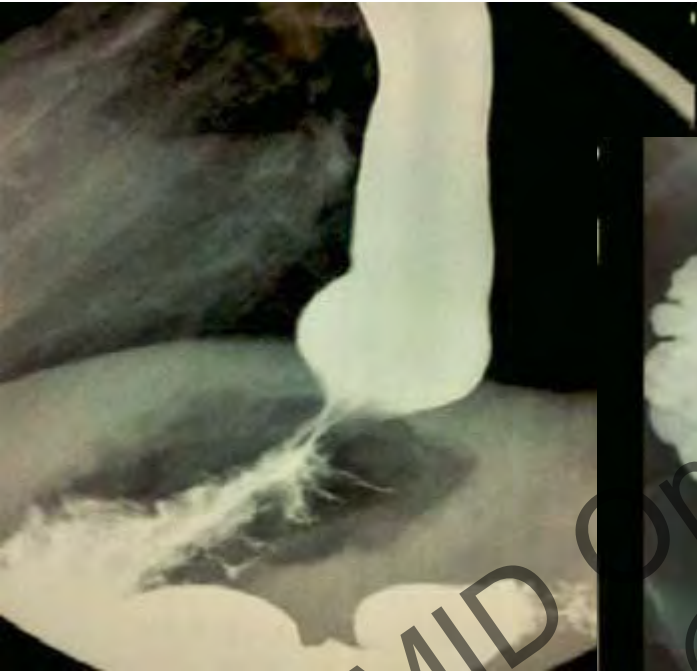
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Chronic Chagas disease

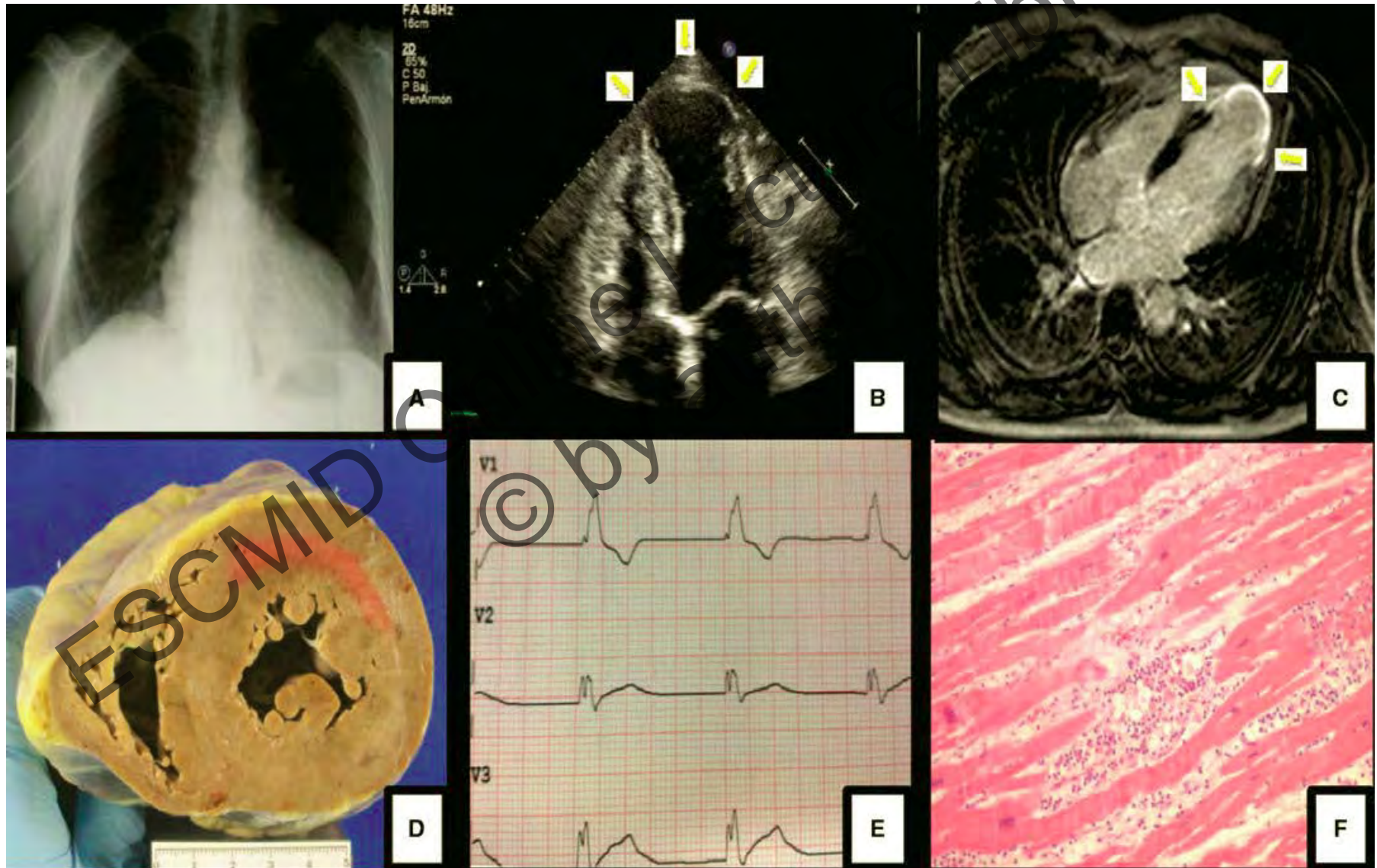


- Megaoesophagus
- Cardiomyopathy
- Megacolon

Chronic Chagas disease: digestive form



Chronic Chagas disease: cardiac form



Congenital Chagas disease

- **Most** infected infants are **asymptomatic** with normal weight and vital signs.
- Some newborns (especially the prematures - 17% in Bolivia) may show a **broad spectrum of clinical features**:
 - Low birthweight (27% in Bolivia)
 - Jaundice, anaemia, hepatosplenomegaly, CNS and heart involvement ...
 - Apgar < 7 (18% in Bolivia)
 - Critical general status
- At least 1 symptom in 47% of cases
- Severe symptoms in 27% of cases, with poor prognosis
- Case-fatality rate: **10% in the first 48h**

Congenital Chagas disease

Respiratory distress

Fever

Anasarca

Jaundice

Seizures

Tachycardia

Muscle hypotonia

Hepatosplenomegaly

Heart failure

Meningoencephalitis



Outline

1. The disease

- Etiology
- Transmission
- Clinical features

2. **Epidemiology**

- Chagas disease in endemic countries
- Imported Chagas disease in Europe

3. Diagnosis of Chagas disease in the mother/newborn

4. Treatment of Chagas disease in the mother/newborn

Geographic distribution of *T. cruzi*



Trends in the reduction of the incidence of infection

	1980-85		2005	
	Infected individuals	Individuals at risk of infection	Infected individuals	Individuals at risk of infection
Southern Cone Initiative (launched in 1991)				
Argentina	2 640 000 (10.0%)	23%	1 600 000 (4.1%)	19%
Bolivia	1 300 000 (24.0%)	32%	620 000 (6.8%)	35%
Brazil	6 180 000 (4.2%)	32%	1 900 000 (1.0%)	12%
Chile	1 460 000 (18.9%)	63%	160 200 (1.0%)	5%
Paraguay	350 000 (2.4%)	31%	150 000 (2.5%)	58%
Uruguay	37 000 (3.4%)	33%	21 700 (0.7%)	19%
Andean Pact Initiative (launched in 1997)				
Colombia	900 000 (20.0%)	11%	436 000 (1.0%)	11%
Ecuador	30 000 (10.7%)*	41%	230 000 (1.7%)	47%
Peru	6 210 000 (9.8%)	39%	1 920 000 (0.7%)	12%
Venezuela	1 200 000 (3.0%)	72%	310 000 (1.2%)	18%
Central America Initiative (launched in 1997)				
Belize	2000 (0.7%)	50%
Costa Rica	130 000 (11.7%)	45%	23 000 (0.5%)	23%
El Salvador	900 000 (20.0%)	45%	232 000 (3.4%)	39%
Guatemala	1 100 000 (16.6%)	54%	250 000 (2.0%)	17%
Honduras	300 000 (15.2%)	47%	220 000 (3.1%)	49%
Nicaragua	58 600 (1.1%)	25%
Panama	200 000 (17.7%)	47%	21 000 (0.01%)	31%
Mexico	1 100 000 (1.0%)	28%
Total	17 395 000 (4.3%)	25%	7 694 500 (1.4%)†	20%

..-data not available. *Prevalence of infected individuals was underestimated. †Includes about 150 000 infected individuals living in the USA and 18 000 in the Guianas, but data for these regions are not shown in the table.

Table 1: Prevalence of *Trypanosoma cruzi* infection in Latin American countries in 1980-85²⁹ and 2005,¹⁸ and effect of initiatives to control or eliminate Chagas disease

The burden of Chagas disease

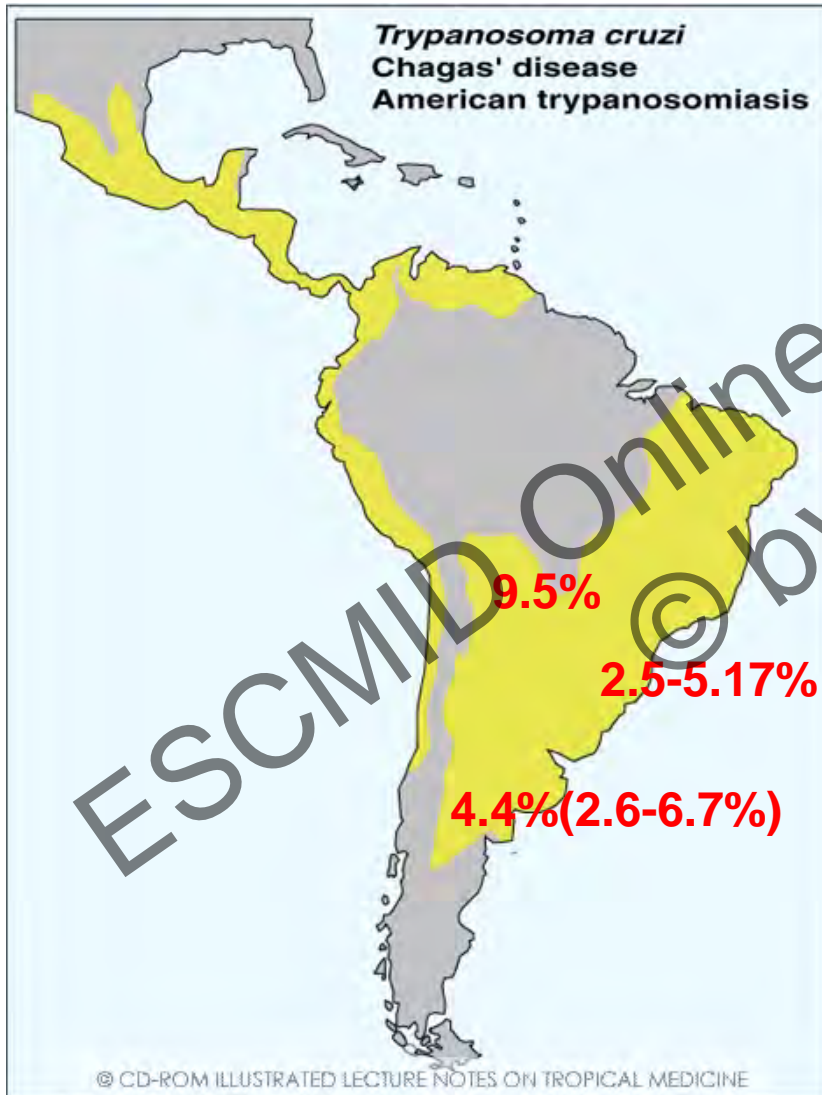


- Endemic in 21 countries
- 16-18 millions people infected
- 100 millions people at risk
- Wide inter-country variations
- Migration

Epidemiology of maternal Chagas disease

- Seroprevalence in pregnant women:
 - in Latin America: **4-52%**
 - in Bolivia (Cochabamba, Tarija, Chuquisaca): **15-40%**
- WHO 2006: **2 million pregnant women infected**
- Most infected pregnant women are asymptomatic (10% RB blockade)

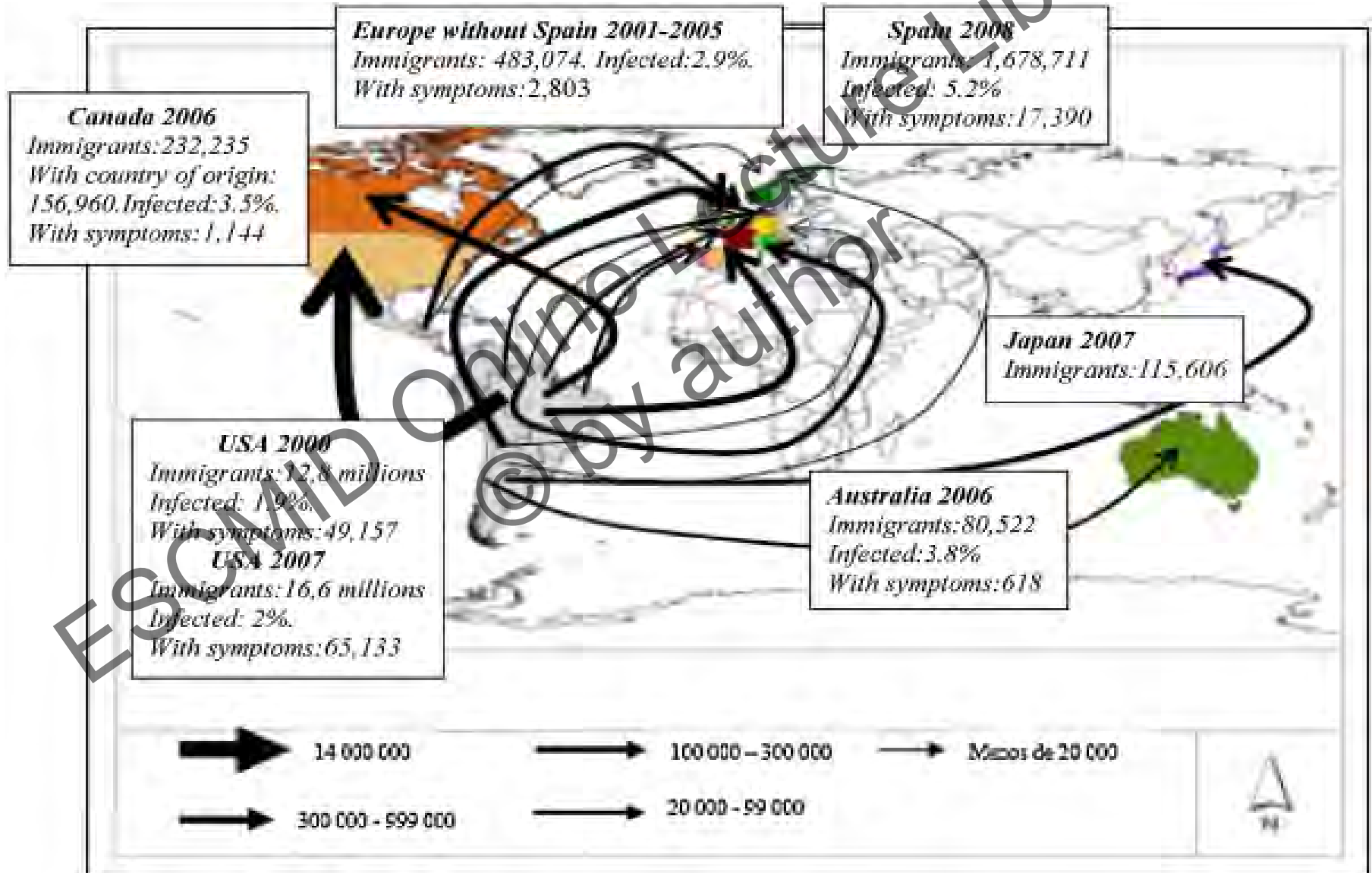
Epidemiology of congenital Chagas disease



Incidence:

- 0,1-12%
- 15.000 new cases/year
- in Bolivia (Cochabamba, Tarija, Chuquisaca): 2,3-5.9% = 2700 new cases/year

Chagas disease and Migration



Imported Chagas disease in Europe (WHO, 2009)

Map A3. Distribution of cases of *Trypanosoma cruzi* infection in Europe by country, and reported transmission (autochthonous, transfusional or congenital transmission of infection acquired among European travellers to disease-endemic areas) among the European population (data reported to WHO as of December 2009)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2009. All rights reserved.

0 275 550 1 100 1 650 2 200 Kilometers



Estimates of LA migrants in Europe and births to mothers from CD endemic countries, 2009

Country	Resident immigrants								Annual births	
	Regular population		Estimated undocumented (min-max)		Adoptions		Total (min-max)			
	Nb	%	Nb	% ^a	Nb	%	Nb	% ^a	Nb	%
Belgium	28,880	1	14,440	1	490	1	43,810	1	722	1
France	97,981	4	51,500	5	19,389	51	168,870	5	5,545	10
Germany	85,313	4	Not reported	-	Not reported	-	85,313	3	Not reported	-
Italy	260,864	12	112,000-120,000	11	6,784	18	379,648-387,648	12	3,351	6
The Netherlands	220,172	10	17,400	2	Not reported	-	237,572	7	Not reported	-
Portugal	110,113	5	11,011	1	Not reported	-	121,124	4	3,950	7
Spain	1,263,342	56	484,509	47	6,354	17	1,754,205	53	35,525	67
Switzerland	35,761	2	38,000-42,000	4	4,994	13	78,755-82,755	2	375	1
United Kingdom	162,517	7	250,000-335,000	28	Not reported	-	412,517-497,517	14	3,433	6
Total	2,264,943	101^b	978,860-1,075,860	99^b	38,011	100	3,281,814-3,378,814	101^b	52,901	98^b

^a In the case of minimum and maximum values, the percentage refers to the average value.

^b The deviation is due to rounding.

Trend in migration from LA to Italy 2006-2010

Year	N°	Males %	N° Municipalities	Change from previous year
2006	261.659	35,9%	6.251	
2007	276.101	36,6%	6.270	5,5%
2008	298.860	37,2%	6.289	8,2%
2009	324.917	37,5%	6.388	8,7%
2010	354.186	37,3%	6.463	9,0%

Estimated number of *T. cruzi*-infected LA immigrants in Italy, 2008-2009

COUNTRIES	LEGAL+ILLEGAL	PREVALENCE OF T. CRUZI INFECTION	ESTIMATED NUMBER OF INFECTED IMMIGRANTS
Argentina	16294	4,9%	798
Bolivia	18-26000	14,8%	2664-3848
Brasile	150000	0,8%	1200
Cile	4372	1,2%	52
Colombia	19832	1,2%	238
Costarica	446	n.d.	n.d.
Cuba	17638	n.d.	n.d.
Rep. Dominicana	21756	n.d.	n.d.
Ecuador	73235-80000	0,2%	146-160
El Salvador	6096	1,5%	91
Guatemala	532	n.d.	n.d.
Honduras	632	n.d.	n.d.
Messico	5724	0,5-6,8%	29-389
Nicaragua	373	n.d.	n.d.
Panama	384	n.d.	n.d.
Paraguay	1246	4,5%	56
Peru'	76406-78000	0,2%	153-156
Uruguay	1956	0,6%	12
Venezuela	6235	1,3%	81
Others	144	n.d.	n.d.
TOTAL	417493-438656	-	5520-7081

Seroprevalence of T.cruzi infection in LA migrants

Arch Gynecol Obstet. 2012 Apr;285(4):919-23.

CHAGAS DISEASE IN LATIN AMERICAN PREGNANT IMMIGRANTS: EXPERIENCE IN A NON-ENDEMIC COUNTRY.

Ramos JM, Milla A, Rodríguez JC, López-Chejade P, Flores M, Rodríguez JM, Gutiérrez F.

PURPOSE:

Chagas disease is a systemic chronic parasitic infection by *Trypanosoma cruzi* endemic in Latin America. Migration of women of childbearing age from Latin America to developed countries may spread the disease to non-endemic areas through vertical transmission.

METHODS:

Prospective study of seroprevalence of *T. cruzi* infection in immigrant Latin American pregnant women during a 5-year period (from 2006 to 2010) in Spain.

RESULTS:

Seven out of 545 participants were seropositive for *T. cruzi* [prevalence 1.28%, 95% confidence interval (CI) 0.06-2.56]. Four (57%) were from Bolivia and three (43%) from Paraguay. The seroprevalence in pregnant women from Bolivia was 10.26% (95% CI 4.06-23.58) and in participants from Paraguay was 6.52% (95% CI 2.24-17.5). No congenital transmission occurred.

CONCLUSIONS:

Seroprevalence of *T. cruzi* infection in Latin American pregnant women coming from Bolivia and Paraguay is high. Those women should be screened for *T. cruzi* to control mother-to-child transmission in non-endemic areas.

Congenital transmission of *T. cruzi* in Europe

Otero S, Sulleiro E, Molina I, Espiau M, Suy A, Martin-Nalda A, Figueras C., *Congenital transmission of Trypanosoma cruzi in non-endemic areas: evaluation of a screening program in a tertiary care hospital in Barcelona, Spain.* Am J Trop Med Hyg. 2012 Nov;87(5):832-6. doi: 10.4269/ajtmh.2012.12-0152. Epub 2012 Sep 17.

Flores-Chavez MD, Merino FJ, Garcia-Bujalance S, Martin-Rabadan P, Merino P, Garcia-Bermejo I, Delgado A, Cuadros J; Working Group on Chagas Disease of Autonomous Community of Madrid. *Surveillance of Chagas disease in pregnant women in Madrid, Spain, from 2008 to 2010.* Euro Surveill. 2011 Sep 22;16(38). doi:pii: 19974.

Jackson Y, Myers C, Diana A, Marti HP, Wolff H, Chappuis F, Loutan L, Gervaix A. *Congenital transmission of Chagas disease in Latin American immigrants in Switzerland.* Emerg Infect Dis. 2009 Apr;15(4):601-3. doi: 10.3201/eid1504.080438.

Child-bearing age LA women infected with *T. cruzi*

Acta Trop. 2009 Nov;112(2):228-30.

PREVALENCE OF CHAGAS DISEASE IN THE LATIN AMERICAN IMMIGRANT POPULATION IN A PRIMARY HEALTH CENTRE IN BARCELONA (SPAIN).

Soriano Arandes A, Muñoz Gutierrez J, Vergés Navarro M, Castells Doménech C, Portús Vinyeta M, Gascón Brustenga J.

Abstract

A cross-sectional descriptive study was carried out to detect the seroprevalence of chagasic infection in children and women of child-bearing age in a primary care health centre in Barcelona (Spain). Serological screening was performed with an immunochromatography (IC) test (Stat Pak Chagas de Chembio) and all positive and doubtful results were confirmed by two ELISA tests using recombinant and whole *Trypanosoma cruzi* antigens. Prevalence of 4.3% was detected in the child-bearing age group women. General practitioners and paediatricians are concerned by Chagas disease, now an emergent health disease in non-endemic countries.

Table 1. Characteristics of included observational studies of congenital *Toxoplasma* and infection

First author, publication year	Country	Study setting	Sample size (N+3 of MH)	Method of diagnosis of congenital infection	Timing of diagnosis	Congenital infection rate	Study weight
Alegria, 2011 ¹⁰	Spain	Hospital	27	Microhaematocrit, PCR, symptomatology	Birth	28.6*	0.05
Angheloni, 2011 ¹¹	Italy	Multi-hospital	68	Microhaematocrit, PCR, serology	Birth, 1 month, 3 months	0	0.13
Apf, 2010 ^{12,13}	Chile	Health centres	280	Parasitology, serology (IF, ELISA), PCR	Birth	3.5	2.89
Araujo, 2009 ¹⁴	Brazil	Multi-hospital	61	Serology	1 month	0	0.00
Arcavi, 1993 ¹⁵	Argentina	Hospital	2738	Microhaematocrit, serology (IF, IHA)	Neonatal period	5.9	1.09
Avila-Arcevegui, 2012 ¹⁷	Spain	Hospital	1719	Serology, PCR	Birth to 1 week (PCNS), 1 month (PCR), 8-9 months (S)	5.3*	0.60
Barona-Mila, 2012 ¹⁸	Spain	Multi-hospital	8726	Microhaematocrit, serology (IF, ELISA), PCR x 2 samples	Birth (MH/PCNS), 2-3 months (PCR), 7-9 months (PCNS), 12 months (S)	3.7	3.80
Basa, 2011 ^{19,20}	Spain	NA	69	PCR	NA	0	0.29
Bern, 2002 ²¹	Bolivia	Hospital	102154	Parasitology, serology (IF, ELISA), PCR	Birth, 7 days, 21 days, 30 days, 90 days, 180 days, 270 days	6.5	2.47
Biso, 2011 ²²	Argentina	Hospital	3546	Microhaematocrit, serology (ELISA, Western blot)	Birth to 3 days (MH), 8 months (S)	4.7	1.75
Bianco, 2000 ²³	Argentina	Hospital	28115	Microhaematocrit, serology (IHA, ELISA, IF)	Birth to 30 days (MH), 8 months, 6 months (MH/S)	7.1	9.10
Blasco, 2011 ^{24,25}	Spain	Hospital	195	Microhaematocrit, PCR, serology	Birth (MH/PCR), 1 month (MH/PCR), 9 months (PCNS)	0	0.09
Brutus, 2007 ²⁶	Bolivia	Population - communities	873	Serology	0-24 months	11.0*	1.02
Brutus, 2008 ²⁴	Bolivia	Hospital	4151	Parasitology	Birth	5.2	2.76
Cruz Conde, 2010 ²⁷	Spain	Hospital	272	PCR or microhaematocrit, serology (ELISA/IF)	Birth (PCRMH), >7 months (S)	2.7	2.99
Cucunubá, 2010 ²⁴	Colombia	Multi-hospital	694 599	Haemoculture, serology (ELISA, IF) PCR	Birth to 1 year Birth to 1 year	0 12.8	0.94
de Bosis, 2004 ²⁸	Argentina	Multi-hospital	28267	Parasitology, serology (IF, IHA, ELISA)	1-12 months (S), 6-12 months (S)	10.9	2.52
de Bosis, 2010 ²⁷	Argentina	Multi-hospital	2674377*	Parasitology, serology x 2 (ELISA, IHA, IF)	1-12 months (S), 6-12 months (S)	6.1	5.97
Dier, 2008 ²⁹	Argentina	Hospital	2104 9104	Microhaematocrit PCR	Birth Birth	1.9* 8.7*	2.21
Florez-Chavez, 2011 ^{30,31}	Spain	Multi-hospital	4752*	Serology	NA	2.6	3.68
Gambou-Leon, 2011 ³²	Mexico	Multi-hospital	64	Serology (ELISA x 2, S-IH-Pk)	10 months	0	0.06
Hoff, 1978 ³³	Brazil	Hospital	117	Parasitology, culture, serology (IF)	Birth to 102 days	5.8	0.49
Jackson, 2009 ³⁴	Switzerland	Hospital	28	Parasitology, PCR, serology	Birth (MPCR), 9 months (S)	25.0	0.06

Table 1. (Continued)

First author, publication year	Country	Study setting	Sample size (N/No. of MI)	Method of diagnosis of congenital infection	Timing of diagnosis	Congenital infection rate	Study weight
Lusa, 2009 ⁷¹	Spain	Hospital	1,97 ^a	Microhaematocrit, PCR, serology	Birth (MI-PCR), 6 months, 12 months (S)	2.7	1.75
Ludro, 2007 ⁶⁹	Argentina	Multi-hospital	8,704 12,704	Parasitology, serology (IFA, ELISA) PCR	Birth Birth	7.7 11.5	1.48
Mallinaci, 2010 ⁷³	Argentina	Not stated	3,68	Microhaematocrit, serology (IFA, ELISA)	Birth (MI), >9 months (S)	4.4	1.90
Meiro, 2009 ⁷⁴	Spain	Hospital	693	PCR	0-1, 3-9 months	0	2.85
Mora, 2005 ⁶⁸	Argentina	Health centres	8,272 18,287 15,235	Microhaematocrit Haemoculture PCR	Birth to 15 days Birth to 15 days Birth to 15 days	2.9 6.3 6.4	3.51
Moya, 1989 ⁷⁵	Argentina	Hospital	29,721	Strout method, smears, agglutination, haemoculture, serology (IF, IHA)	Birth (P), 1st year of life (PS)	4.02 ^b	4.79
Munoz, 2009 ⁷⁶	Spain	Multi-hospital	3,41	Parasitology, PCR, IFA, serology	Birth (MP-PCR), 1 month (PCR), >6 months (S)	7.3	0.88
Munoz-Viches, 2012 ⁷⁷	Spain	Hospital	64	Microhaematocrit, PCR, serology (ELISA, IF)	Birth to 30 days (MI-PCR), 4 months (PCR), 8 months (S)	0	0.06
Murcia, 2012 ⁷⁸	Spain	Hospital	9,62	PCR, serology (IF, ELISA, S, S)	0-2 months, 6, 9, 12 months (culture/PCR), 12 months (S)	13.8	0.76
Olivera Mar, 2006 ⁷⁹	Mexico	Multi-hospital	6,6	Haemoculture, PCR	Birth	0	0.13
Otero, 2012 ⁸⁰	Spain	Hospital	1,20	PCR	21 days	5.0	0.66
Panico-Talayero, 2008 ⁸¹	Spain	Multi-hospital	6,29	Microhaematocrit, PCR, immune precipitation	0-1 month (MI-PCR), 7 months (immune precipitation)	0	2.01
Polo Mga, 2012 ⁸²	Spain	Hospital	1,74	PCR	Birth	11.1 ^a	0.15
Ramos, 2012 ⁸³	Spain	Hospital	6,8	Serology (ELISA, IF), PCR	Birth, 1 year	0	0.18
Romero, 2011 ⁸⁴	Bolivia	Door to door and antenatal care	12,249	Microhaematocrit	Birth	4.0	3.99
Ruz, 1992 ^{85a}	Argentina	Hospital	3,219	Strout method	Birth	1.4	4.71
Rusomando, 1998 ^{85b}	Paraguay	Multi-hospital	6,58	Parasitology, PCR, haemoculture, serology (ELISA, IF)	Weeks: birth to 8 months	10	0.88
Rusomando, 2005 ⁸⁶	Paraguay	2 departments (6 sites)	20,736 60,815 89,734	Parasitology PCR Serology (ELISA, IF)	Birth to 6 months (1995-97), >6 months (1998-) Birth to 6 months (1995-97), >6 months (1998-) Birth to 6 months (1995-97), >6 months (1998-)	1.44 7.4 7.0	4.87
Sala Challo, 2012 ⁸⁸	Bolivia	Multi-hospital	125,0725	Parasitology	Birth	3.4	5.44
Sala, 2007 ^{87a}	Bolivia	Hospital	58,7144	Parasitology	Birth, 1 month	5.1	4.93
Sala, 2011 ^{87b}	Spain	Hospital	6,9	Serology (IF, ELISA) x 2, PCR	NA	0	0.03
Scapellato, 2009 ⁸²	Argentina	Hospital	13,64	Parasitology x 3, serology x 2 (IFA, ELISA, latex agglutination)	<6 months (P), >6 months (S)	13.8	1.03

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Parasitological diagnosis of Chagas disease

DIRECT METHODS:

- Haemoscopy:
 - Thin and thick blood smears
 - Microhaematocrit

INDIRECT METHODS:

- Xenodiagnosis
- Blood culture
- PCR

METHODS	Sensitivity (%)	
	Acute phase	Chronic phase
DIRECT		
Thin film	<60	<10
Thick film	<70	<10
Fresh microscopy	80-90	<10
INDIRECT		
Xenodiagnosis	100	20-50
Blood culture	100	20-50

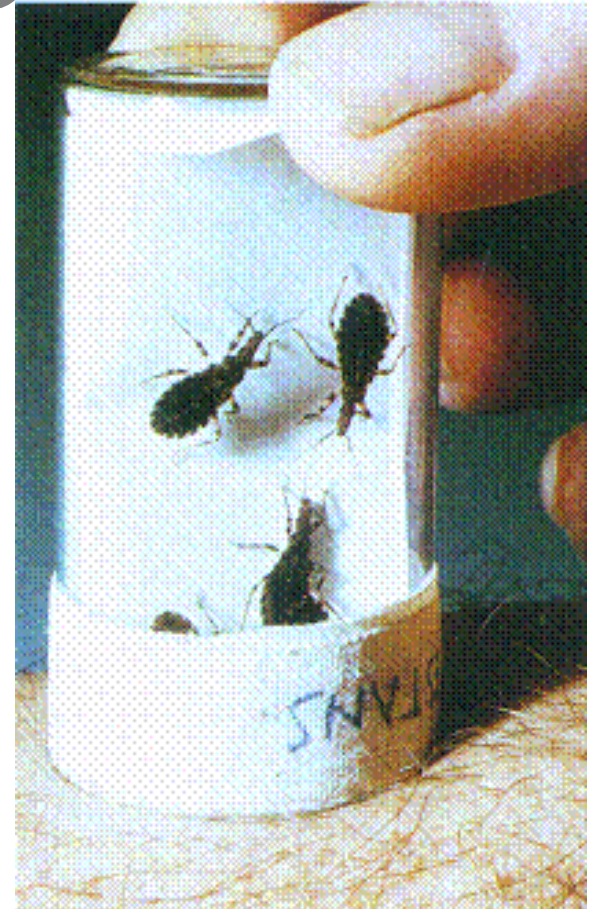
Parasitological diagnosis of Chagas disease

HAEMOSCOPY



Parasitological diagnosis of Chagas disease

XENODIAGNOSIS



Immunodiagnosis of Chagas disease

Acute phase: IgM

Chronic phase: IgG

Conventional serology tests:

- ELISA
 - IIF
 - IHA
- High sensitivity tests that employ a complex mixture of parasite antigens. At least two different tests must be used to confirm the diagnosis

Non-conventional serology tests:

- Recombinant antigen-based ELISA = these non-standardized methods display a high sensitivity and specificity and are rather simple to perform

Disease stage and diagnostic features

METHOD	ACUTE PHASE	INDETERMINATE PHASE	CHRONIC PHASE
HAEMOSCOPY	POS	NEG	NEG
SEROLOGY	POS	POS	POS
ECG	NEG	NEG/POS	POS
HEART/ OESOPHAGUS/ COLON DISEASE	NEG	NEG	POS

Diagnosis of congenital Chagas disease

All pregnant women from endemic areas should be screened for Chagas disease by using a high sensitivity **serologic test**, to be confirmed with a second test.

Newborns from seropositive women cannot be tested with serology since they receive IgG antibodies from their mother and IgM detection is not reliable.

Serology can be used in infants **6-9 months after birth**.

Congenital Chagas disease should be confirmed with **parasitological methods** such as microhaematocrit and PCR.

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Antiparasitic treatment

Uncomplicated cases:

- < 40 kg: **Benznidazole** 7.5 mg/kg in 2-3 daily doses for 60 days
- > 40 kg: **Benznidazole** 5 mg/kg in 2-3 daily doses for 60 days

Alternative regimen:

Nifurtimox 8-10 mg/kg in 3 daily doses for 90 days.

Congenital cases:

Full-term neonates: **Benznidazole** 5 mg/kg for the first 3 days and then increase to 10 mg/kg daily if neither leukopenia nor thrombocytopenia has developed.

Symptomatic treatment

In chronically ill patients cardiac and digestive symptoms and complications should also be managed.

- Beta-blockers
- ACE-inhibitors
- Angiotensin receptor blockers
- Diuretics
- Antiarrhythmic drugs
- ICD/pacemaker
- Anticoagulant therapy
- Cardiac surgery (including transplant)
- Proton-pump inhibitors
- Botulinus toxin injections in the LES
- Diet
- Prokinetic drugs
- Surgical treatment of megacolon and/or megaesophagus
- ...

Recommendations for treatment

Tabla1

Recomendaciones para el tratamiento antiparasitario de la enfermedad de Chagas según la edad del paciente, la fase y la forma clínica de la enfermedad

Siempre se debe ofrecer tratamiento

Infección aguda por *Trypanosoma cruzi*

Infección congénita inicial por *T. cruzi*

Los niños ≤ 12 años con infección crónica por *T. cruzi*

Los niños de 13-18 años con infección crónica por *T. cruzi*

Reactivación de *T. cruzi* en pacientes VIH/sida u otra inmunosupresión

Por lo general se debe ofrecer tratamiento

Mujeres en edad fértil

Adultos de 19-50 años con forma indeterminada o con cardiopatía leve a moderada (Kuschnir grados 0, I o II)

Tratamiento inminente con inmunosupresores

Tratamiento opcional

Los adultos de edad > 50 años y sin cardiomiopatía avanzada (Kuschnir grados 0, I o II)

Los pacientes con enfermedad de Chagas gastrointestinal, pero sin avanzada miocardiopatía

En general no se debe ofrecer tratamiento

Miocardiopatía chagásica avanzada con insuficiencia cardíaca congestiva (Kuschnir grado III)

Megaesófago con un deterioro significativo de la deglución

Nunca se les debe ofrecer tratamiento

Durante el embarazo

Insuficiencia renal grave o hepática

VIH: virus de la inmunodeficiencia humana.

Adaptada de Bern et al⁶⁷.

Assessment of cure

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Concluding remarks

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