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Apresentação LAPAM-UniFacid

Doença de Chagas: Estado da Arte no Diagnóstico e Tratamento

Alejandro Marcel Hasslocher-Moreno

14 de Maio de 2021

CARLOS JUSTINIANO RIBEIRO CHAGAS

Prof. Dr. Carlos Chagas

Director do Instituto Oswaldo Cruz

† 8 de Novembro de 1934

ABRIL DE 1909

Anno XXIII — 22 de Abril de 1909 — Num. 16

Brazil-Medico

SUMMARIO

Pathologia Intertropical: — *Nova especie morbida do homem, produzida por um trypanozoma (trypanozoma Cruzi)*, pelo Dr. Carlos Chagas.
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Boletim Demographico: — *Mortalidade da cidade do Rio de Janeiro*, por R. C.

PATHOLOGIA INTERTROPICAL

Nova especie morbida do homem, produzida por um trypanozoma (trypanozoma Cruzi)

Nota prévia

(Trabalho do Instituto OSWALDO CRUZ)

PELO DR. CARLOS CHAGAS

(Assistente do Instituto)

Vimos, desde mezes, estudando o cyclo evolutivo de um hemo-flagellado, o *trypanozoma Cruzi*, que tem para hospedeiro intermediario um hematophago, o *conorrhinus sanguisuga* (?). Fizemos, de nossas pesquisas ainda não concluidas, uma publicação prévia (1), aguardando opportunidade, após esclarecimento de alguns pontos, para publicação definitiva. A infecção que serviu de inicio a nossos estudos fôra obtida experimentalmente pelo Dr. OSWALDO CRUZ, fazendo picar por alguns conorrhinos, levados de Minas, um sagui (*hapalle penicillata*). Por inoculações de sangue e ainda por picada de conorrhinos obtivemos a infecção em diversos animaes, taes como a cobaya, o cão, o coelho, sendo ella sempre mortal para alguns destes vertebrados. Ignoravamos, porém, qual fosse o hospedeiro habitual do trypanozoma e o esclarecimento deste ponto levou-nos a realizar novas pesquisas, na zona onde haviamos colhido o hematophago, pesquisas cujo resultado essencial, pela sua importancia, merecem immediata publicidade.

O *conorrhinus sanguisuga* (?) existe em grande abundancia no norte de Minas, nas zonas percorridas pelo prolongamento da E. de F. Central do Brazil. E' um hematophago, conhecido pelo nome vulgar de *barbeiro*, que habita os domicilios humanos, preferindo sempre o sangue do homem para suas refeições. Nas casas o *conorrhinus* habita as cavidades das paredes, encontrando guarida favoravel nas paredes não rebocadas, e só ataca o homem á noite, depois de apagadas as luzes. Constitue um terrivel flagello, em extremo incommodo ao homem, cujo repouso nocturno elle difficulta. Outros animaes domesticos, aquelles que pernoitam no interior dos domicilios, são tambem picados pelo *conorrhinus*. No gato verificamos a infecção natural pelo trypanozoma que aquelle hematophago transmitte.

Dada a preferencia do *conorrhinus* pelo sangue humano, suspeitamos, de accôrdo com a theoria da evolução phylogenetica dos hemo-flagellados, pudesse ser parasita do homem o trypanozoma encontrado no apparelho digestivo daquelle hematophago. Orientamos dest'arte nossas pesquisas e desde logo chamou nossa attenção um quadro morbido uniforme, apreciavel em quasi todas as crianças da zona onde abunda o invertebrado.

Daquelle quadro, presente ás vezes em adultos, porém mais frequente nas crianças, os elementos mais salientes são os seguintes: grande anemia, decadencia organica accentuada, edema sub palpebral e frequentemente edemas generalisados, engurgitamento ganglionar consideravel, havendo volumosos ganglios nas pleiades periphericas (axilla, regiões inguinal e crural, pescoço, etc.). Em algumas crianças, é notavel a atrophia do desenvolvimento. E' uma condição morbida permanente, com incidentes agudos, que se expressam em reacção febril e outros elementos morbidos. As noções clinicas que temos da molestia são ainda muito incompletas, estando apenas iniciadas, nesse sentido, nossas observações. Nem sabemos muito sobre o prognostico, parecendo, pelas informações colhidas, ser molestia ás vezes mortal, resistindo-lhe, porém, alguns doentes, que, segundo nos parece, ficarão immunisados.

Repetidos exames de sangue, em crianças na condição morbida chronica, fôram negativos. N'um doente febricitante, profundamente anemiado e com edemas, com pleiades ganglionares engurgitadas, encontramos trypanozomas, cuja morphologia é identica á do *trypanozoma Cruzi*. Na ausencia de qualquer outra etiologia para os symptomas morbidos observados e ainda de accôrdo com a experimentação anterior em animaes, julgamos tratar-se de uma trypanozomiase humana, molestia occasionada pelo *trypanozoma Cruzi*, cujo transmissor é o *conorrhinus sanguisuga* (?).

Em nossas pesquisas temos sido vantajosamente acompanhado pelo Dr. BELISARIO PENNA, a quem deixamos aqui os mais sinceros agradecimentos.

Lassance, E. de F. Central, 15 de Abril de 1909.

(1) *Neue Trypanosomen*. — Tr. Minasense e T. Cruzi, n. 30, in «Archiv. f. Schiff u Tropenhygiene, 1909, pag. 120.

TRABALHOS ORIGINAES

A epilepsia de Bonaparte

(Nota de psychologia morbida)

PELO PROF. A. DIAS DE BARROS

(Conclusão)

Apraz-me expôr, antes de manifestações outras dessa anestesia moral á qual me refiro, e para contraste com ella, antes que analogos factos no simples dominio das relações sociaes que passo a expôr, o opposto dessa crueldade, o verdadeiro reverso da medalha cujo anverso se acabou de vêr....

Occorre-me lembrar a serie de attenções de toda a especie, patenteadas para com a velhice e a des-

112 anos depois da descoberta, como está a Doença de Chagas no Brasil ?

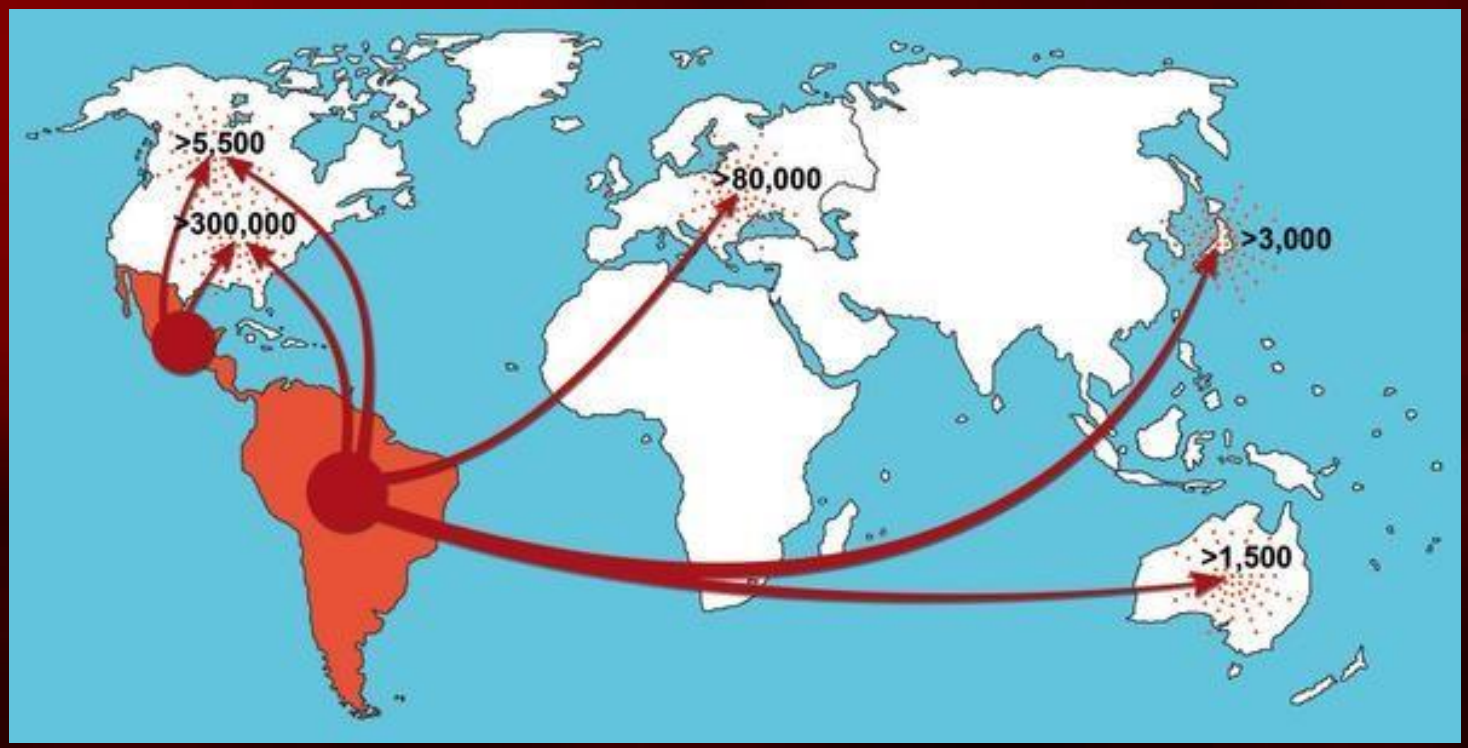
2nd Brazilian Consensus on Chagas Disease, 2015*

TABLE 2

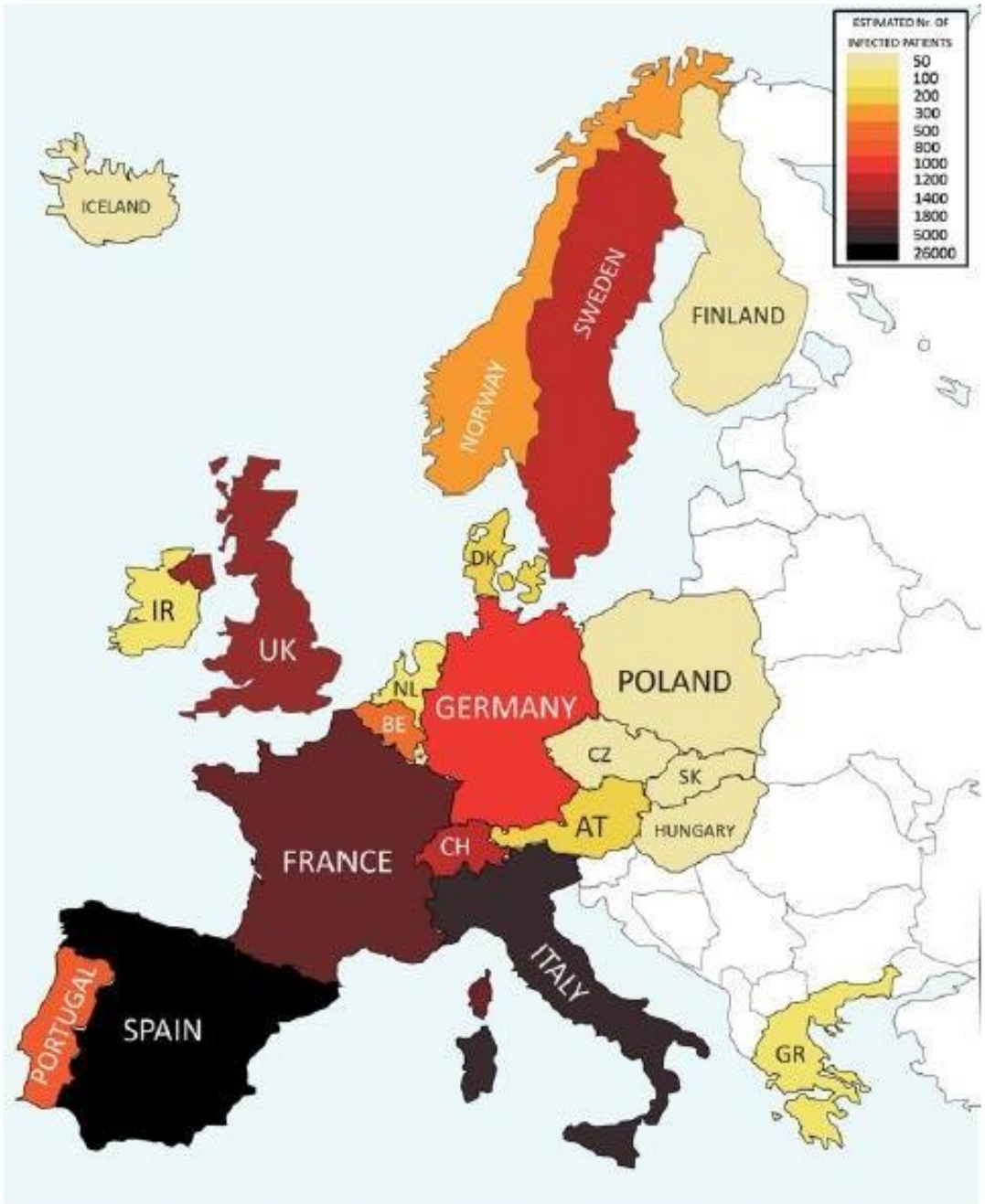
Projection of the prevalence estimates of *T. cruzi* infection and chronic-phase Chagas disease, cardiac and digestive forms, in Brazil, from 2000 to 2055.

Year	Estimate of the Brazilian population	Reference age range			Estimated number of infected people		Estimate of cases with the digestive form		Estimate of cases with the cardiac form	
		age range	Population	%	infection 1.02%[a]	infection 2.4%[b]	infection 1.02%[a]	infection 2.4%[b]	infection 1.02%[a]	infection 2.4%[b]
2000	173,448,346	≥5	156,133,836	90.0	1,592,565	3,747,212	159,257	374,721	477,770	1,124,164
2005	185,150,806	≥10	150,944,641	81.5	1,539,635	3,622,671	153,964	362,267	461,891	1,086,801
2010	195,497,797	≥15	145,563,676	74.5	1,484,749	3,493,528	148,475	349,353	445,425	1,048,058
2015	204,450,649	≥20	139,901,357	68.4	1,426,994	3,357,633	142,699	335,763	428,098	1,007,290
2020	212,077,375	≥25	133,880,929	63.1	1,365,585	3,213,142	136,559	321,314	409,676	963,943
2025	218,35014	≥30	127,334,466	58.3	1,298,812	3,056,027	129,881	305,603	389,644	916,808
2030	223,126,917	≥35	120,096,221	53.8	1,224,981	2,882,309	122,498	288,231	367,494	864,693
2035	226,438,916	≥40	112,013,898	49.5	1,142,542	2,688,334	114,254	268,833	342,763	806,500
2040	228,153,204	≥45	102,983,115	45.1	1,050,428	2,471,595	105,043	247,160	315,128	741,479
2045	228,116,279	≥50	92,984,144	40.8	948,438	2,231,619	94,844	223,162	284,531	669,486
2050	226,347,688	≥55	82,097,220	36.3	837,392	1,970,333	83,739	197,033	251,218	591,100
2055	222,975,532	≥60	70,485,475	31.6	718,952	1,691,651	71,895	169,165	215,686	507,495

Rotas migratórias desde a América Latina e estimativas do número de infectados por Doença de Chagas em regiões não endêmicas



Fonte: Coura JR & Albajar-Viñas *Nature* 465, S6—S7 (24 June 2010)



Estimated number of Chagas' disease (infected) patients in Europe. Colour-code denotes expected frequency.

Source: Guerri-Guttenberg et al. 2008. European Journal 29:2587-2591

MECANISMOS DE TRANSMISSÃO: TRADICIONAIS

- **Por vetores domiciliados (*Triatoma infestans*)**
- **Por hemotransfusão**
- Por via congênita / transplacentária
- Por via oral (alimentos contaminados com *T. cruzi*)

Revista da Sociedade Brasileira de Medicina Tropical 39(5):507-509, set-out, 200

Eliminação da transmissão da doença de Chagas pelo *Triatoma infestans* no Brasil: um fato histórico

O Ministério da Saúde do Brasil recebeu no dia 9 de junho de 2006, a Certificação Internacional de Eliminação da Transmissão da Doença de Chagas pelo *Triatoma infestans*, conferida pela Organização Pan-Americana da Saúde[6]. Torna-se importante enfatizar, no entanto, que tal certificação não representa o controle efetivo da doença no Brasil. A certificação representa somente a eliminação (interrupção momentânea) da transmissão da doença especificamente pelo triatomíneo da espécie *T. infestans*. Diferentemente da erradicação – que representa a interrupção definitiva da transmissão mesmo na ausência de qualquer ação de controle – a eliminação pressupõe a manutenção de alguma ação de controle e vigilância para que a interrupção se mantenha[15].

MECANISMOS DE TRANSMISSÃO: ATUAIS (NO BRASIL)

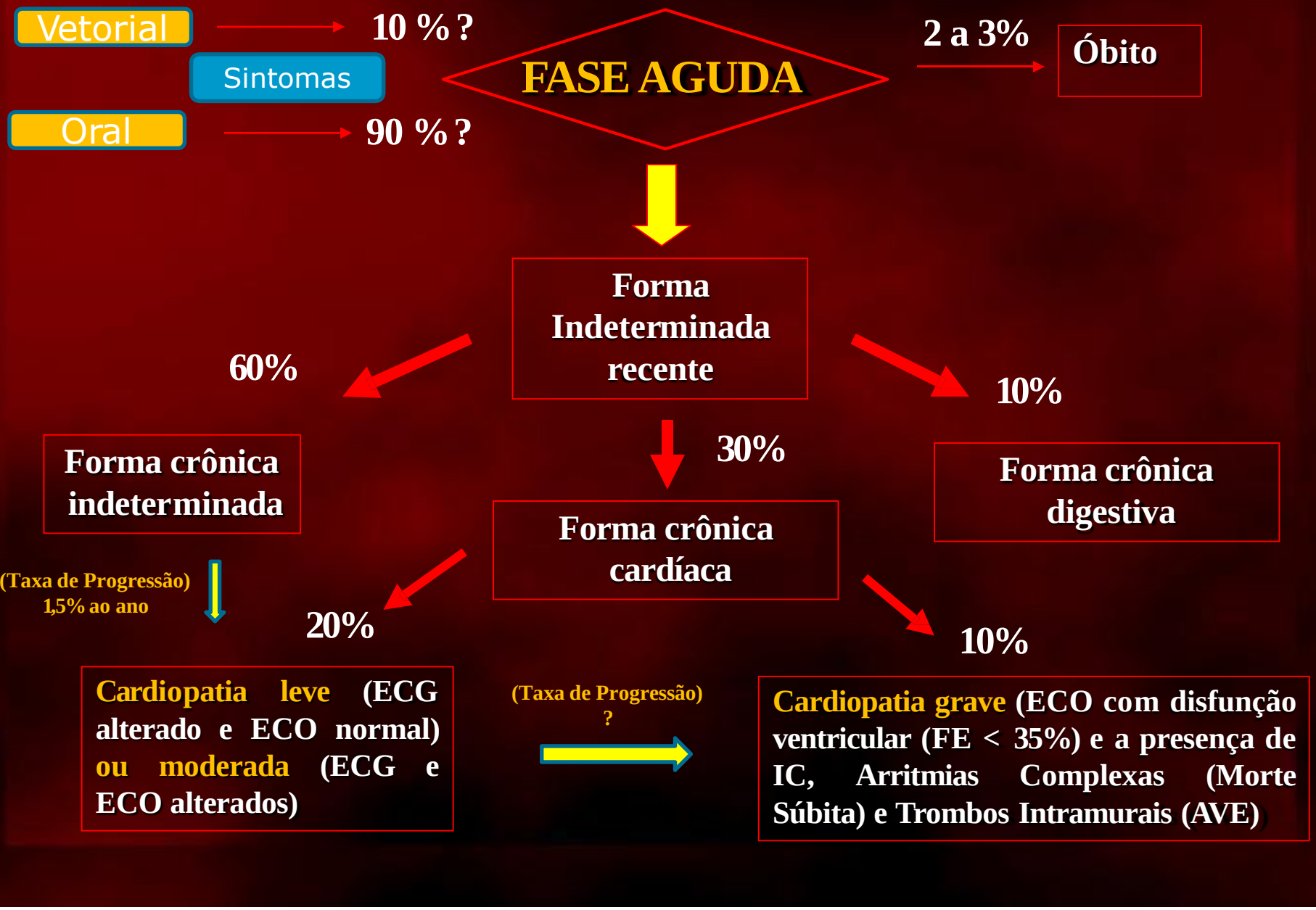
- ~~Por vetores domiciliados (*Triatoma infestans*)~~

- ~~Por hemotransfusão~~

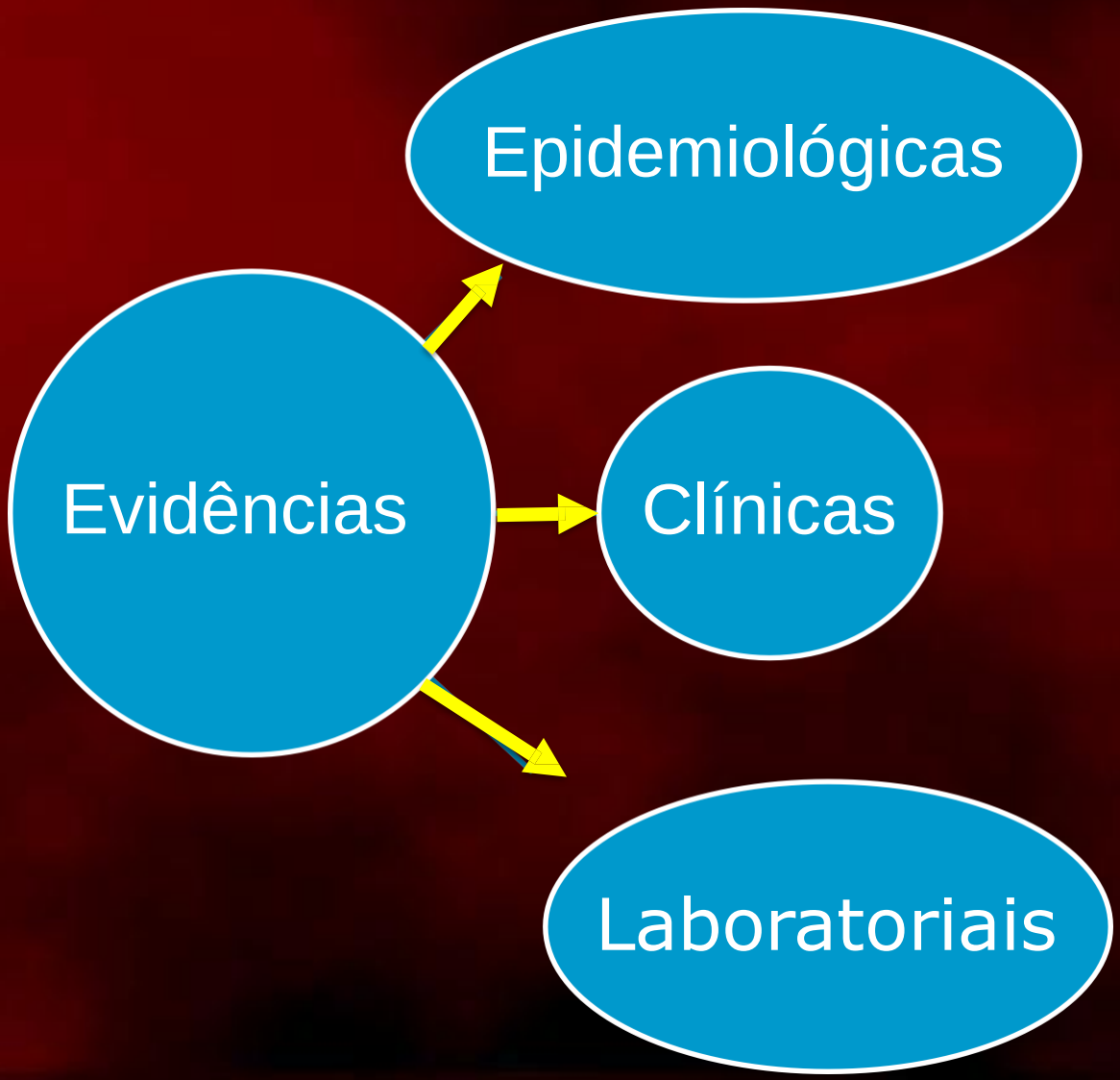
- **Por via congênita / transplacentária**

- **Por via oral (alimentos contaminados com *T. cruzi*)**

História Natural da Doença de Chagas



Suspeição de Doença de Chagas



Suspeição de Doença de Chagas Aguda
Evidência Epidemiológica

- ✓ História de febre persistente >7 dias
- ✓ História de viagem recente para áreas com transmissão ativa da Doença de Chagas
- ✓ História de contato direto com triatomíneo
- ✓ História de ingestão de alimento suspeito de estar contaminado por *T. cruzi*

Suspeição de Doença de Chagas Aguda
Evidência Clínica

- ✓ Edema de face ou de membros.
- ✓ Exantema.
- ✓ Adenomegalia.
- ✓ Hepatomegalia.
- ✓ Esplenomegalia.
- ✓ Miocardite Aguda.
- ✓ Manifestações hemorrágicas.
- ✓ Icterícia
- ✓ Chagoma de inoculação.

Suspeição de Doença de Chagas Crônica Evidência Epidemiológica

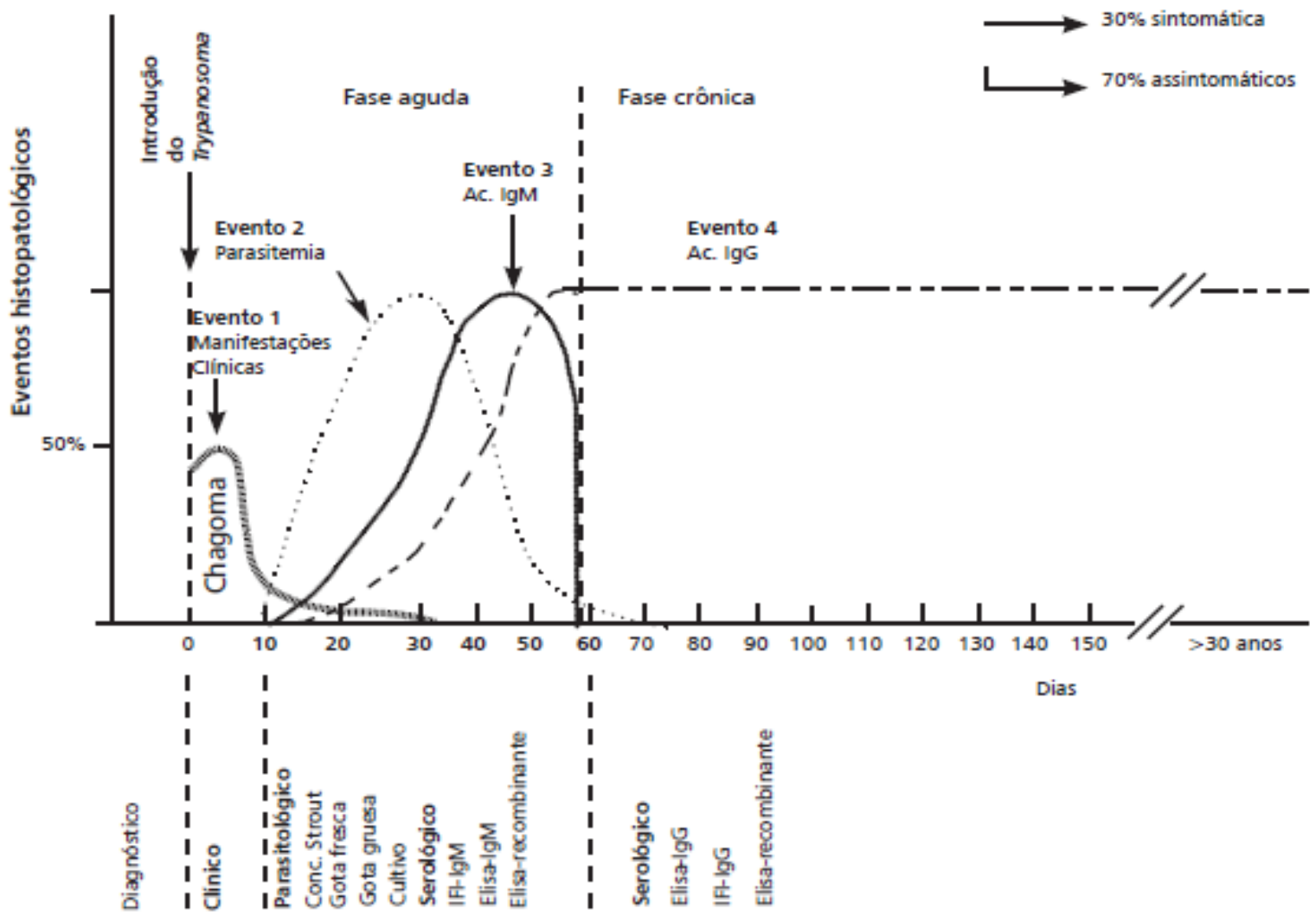
- ✓ Ter nascido e ou morado em área rural de área endêmica
- ✓ História de ter conhecido o "barbeiro" e ou ter sido picado pelo "barbeiro"
- ✓ História de Hemotransfusão antes de 1992
- ✓ Mãe portadora de Doença de Chagas

Suspeição de Doença de Chagas Crônica
Evidência Clínica

- ✓ Insuficiência Cardíaca
- ✓ Arritmia Cardíaca
- ✓ Acidente Vascular Cerebral
- ✓ ECG: BRD3º + HBAE / EV / APRP / BAV
- ✓ Ecocardiograma: disfunção segmentar ventricular (acinesia, discinesia e aneurisma)
- ✓ Megaesôfago
- ✓ Megacólon

Suspeição de Doença de Chagas
Evidência Laboratorial

Figura 2 – Eventos fisiopatológicos da doença de Chagas



Fonte: OPAS (2007).

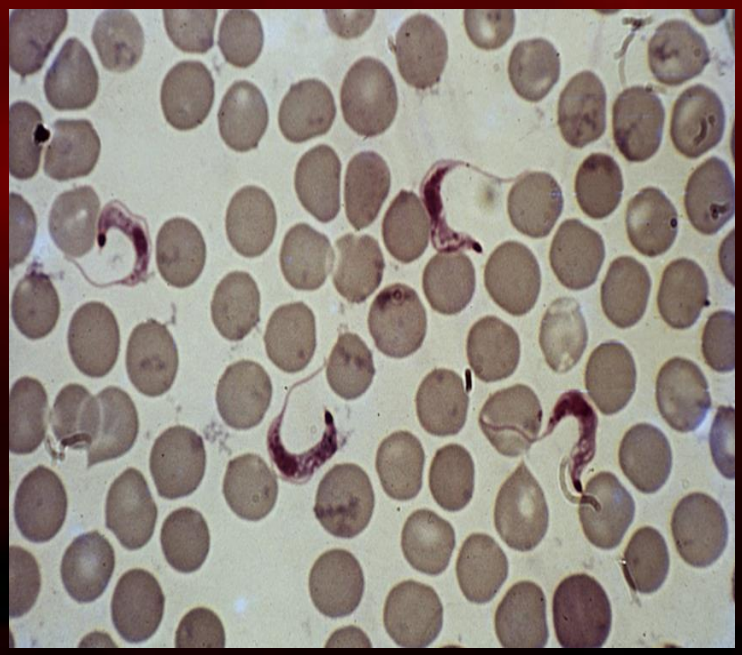
Confirmação de Doença de Chagas Aguda
Evidência Laboratorial

- ✓ Exames parasitológicos à fresco (diretos) positivos para *T. cruzi* no sangue, líquor e outros fluídos
- ✓ Exame sorológico com IgM positiva
- ✓ Exame sorológico com soroconversão de IgG

DOENÇA DE CHAGAS AGUDA

Exames Parasitológicos

- Exame a fresco
- Gota espessa
- Microhematócrito (Strout)



Confirmação de Doença de Chagas Crônica - Evidência Laboratorial

- ✓ Sorologia (IgG) positiva pra *T. cruzi*

95-100% de Sensibilidade e 90-95% de Especificidade

- ✓ Xenodiagnóstico ou Hemocultura positivas para *T. cruzi*

(30-40%) de Sensibilidade e (100%) de Especificidade

- ✓ PCR positivo para *T. cruzi*

(40-60%) de Sensibilidade e (100%) de Especificidade

SOROLOGIA NA DOENÇA DE CHAGAS
História

Fixação de Complemento (Machado-Guerreiro)

1913- anos de 1970

Astrogildo Machado

DR. ASTROGILDO MACHADO

Anno XXVII 15 de Junho de 1913 N. 23

Brazil-Medico

SUMMARIO

Trabalhos do Instituto Oswaldo Cruz: — *Revisão do cyclo evolutivo do Trypanozoma Cruzi*, pelo Dr. Carlos Chagas. *Da reacção de Bordet e Gengou na molestia de Carlos Chagas como elemento diagnostico*, pelos Drs. Cezar Guerreiro e Astrogildo Machado.

Será o homem, como muitos animaes domesticos, passivel de ser parasitado por aquelle protozoario?

Essa hypothese não nos parece impossivel, dada a frequencia do parasito em diversas especies animaes. Ou teria havido, em nossas pesquizas, sem que possamos comprehendel-a, troca de laminas no momento das fixações e colorações do material humano?

Da reacção de Bordet e Gengou na molestia de Carlos Chagas como elemento diagnostico

PELOS DRS.

CEZAR GUERREIRO e ASTROGILDO MACHADO

(*Nota preliminar*)

SOROLOGIA
"Tradicional"

- Hemoaglutinação Indireta (1962)

- Imunofluorescência Indireta (1966)

- ELISA (1975)

ELISA
(marcas aprovadas pela Anvisa)

Kits Diagnósticos	S%	E%
Adaltis	100	60
Bio-manguinhos convencional	100	93
Bio-manguinhos recombinante	97	98
Biomérieux	100	95
Bioschile	99	98
Biozima Chagas	100	97
Ebram	99	97
Hemagen	100	97
Pathozyme – Chagas	99	97
REM Gold	99	97
Wama diagnóstica	99	98
Wiener	100	95

E=Especificidade; S=Sensibilidade

Imunocromatografia (Teste Rápido)

PLOS Neglected Tropical Diseases | https://doi.org/10.1371/journal.pntd.0007271 May 31, 2019

Table 1. Characteristics of studies.

References	RDT (index test)	Reference tests	Period of study	Country of implementation	Type and Number of participants	RDT Sensitivity/ Specificity
Angheben 2017 [14]	Chagas Quick Test	ELISA para Chagas III, (BioChile, Chile) and Bio-Elisa Chagas, (Biokit, Spain)	2009–2015	Italy	Migrants from Latin America, all age, 640	83%/99%
Bern 2009_a [18]	InBios—Trypanosome detect	In-house IFAT, Chagatek ELISA (BioMerieux, Lab. Lemos, Argentina), and Chagatest ELISA Recombinante (Wiener lab., Argentina)	2006–2007	Bolivia	Bolivian pregnant women, 519	91%/100%
Bern 2009_b [18]	Stat-Pak		2006–2007	Bolivia	Bolivian pregnant women, 530	90%/100%
Brutus 2008 [17]	InBios—Trypanosome detect	IHA (Polychaco, Argentina) and Chagatest ELISA Recombinante (Wiener lab., Argentina)	2002–2004	Bolivia	Bolivian pregnant women, 460	93%/99%
Chappuis 2010 [12]	Stat-Pak	ELISA cruzi (bioMérieux Diagnostica, Brazil) and Bio-Elisa Chagas, (Biokit, Spain) + results of quality control of a reference lab in Brazil (performing other 4 serology tests)	2009	Switzerland	Migrants from Latin America, Adults, 999	96%/100%
Eguez 2017_a [19]	Stat-Pak	IHA (Polychaco, Argentina), Chagatest ELISA Recombinante (Wiener lab., Argentina), Chagatest ELISA Lisado (Wiener lab., Argentina)	2014	Bolivia	Bolivians from >1 years old up to 60 years old), 342	99%/100%
Eguez 2017_b [19]	InBios—CDP					90%/100%
Lopez-Chejade 2010 [15]	Simple Chagas WB	ELISA in house and BioELISA Chagas	Not declared	Spain	Migrants from Latin America, Adults, 148	100%/97%
Mendicino 2014 [13]	WL Check Chagas test	Chagastest ELISA, IHA, IFAT for discrepancies	Not declared	Argentina	Patients attending Primary Health Care Centers, 238	96%/100%
Navarro 2011 [20]	Simple Chagas WB	IFAT and ELISA (not specified)	2008–2009	Spain	Migrants from Latin America, all age, 276	88%/94%
Roddy 2008 [11]	Stat-Pak	Chagastest ELISA, Indirect hemagglutination test (HAI) (Polychaco, Argentina)	2007	Bolivia	Bolivians from >6 months to 17,9 years old, 1913	93%/99%
Shah 2014 [16]	InBios—CDP	Indirect hemagglutination test (HAI) (Polychaco, Argentina), IFAT, Chagatest ELISA Recombinante (Wiener lab., Argentina) or Chagatest ELISA Lisado (Wiener lab., Argentina)	2011–2012	Bolivia	Bolivians from >2 to 17 years old, 200	100%/99%

Acurácia dos testes sorológicos de acordo com a regição geográfica

Comparative Performance of Latest-Generation and FDA-Cleared Serology Tests for the Diagnosis of Chagas Disease – março 2021

Emily A. Kelly, Christina A. Bulman, Emma L. Gunderson, Amanda M. Irish, Rebecca L. Townsend, Judy A. Sakanari, Susan L. Stramer, Caryn Bern, Jeffrey D. Whitman

	Region of Birth					
	South America (n = 65)		**Central America** (n = 77)		**Mexico** (n = 86)	
	N Pos	Sensitivity (95% CI)[a]	N Pos	Sensitivity (95% CI)[a]	N Pos	Sensitivity (95% CI)[a]
Wiener Lisado ELISA	65	100% (94.5, 100.0)	74	96.1% (89.0, 99.1)	80	93.0% (85.4, 97.3)
Wiener v.4.0 ELISA	65	100% (94.5, 100.0)	77	100% (95.3, 100.0)	85	98.8% (93.7, 100.0)
Wiener v.3.0 ELISA	64	98.5% (91.7, 100.0)	74	96.1% (89.0, 99.2)	79[b]	91.9% (83.9, 96.6)
Hemagen ELISA	60	92.3% (83.0, 97.5)	68[c]	88.3% (79.0, 94.5)	71[d]	82.6% (72.9, 89.9)
Ortho ELISA	63	96.9% (89.3, 99.6)	75	97.4% (90.9, 99.7)	74	86.0% (76.9, 92.6)
InBios CDP LFA	64	98.5% (91.7, 100.0)	77	100% (95.3, 100.0)	84	97.7% (91.9, 99.7)
Abbott PRISM ChLIA	64	98.5% (91.7, 100.0)	74	96.1% (89.0, 99.2)	78	90.7% (82.5, 95.9)

Acurácia dos testes sorológicos de acordo com a regição geográfica

CellPress

Trends in Parasitology

Review

Serological Approaches for *Trypanosoma cruzi* Strain Typing

Virginia Balouz,[1] Leonel Bracco,[2] Alejandro D. Ricci,[2] Guadalupe Romer,[1] Fernán Agüero,[2,*] and Carlos A. Buscaglia,[1,*]

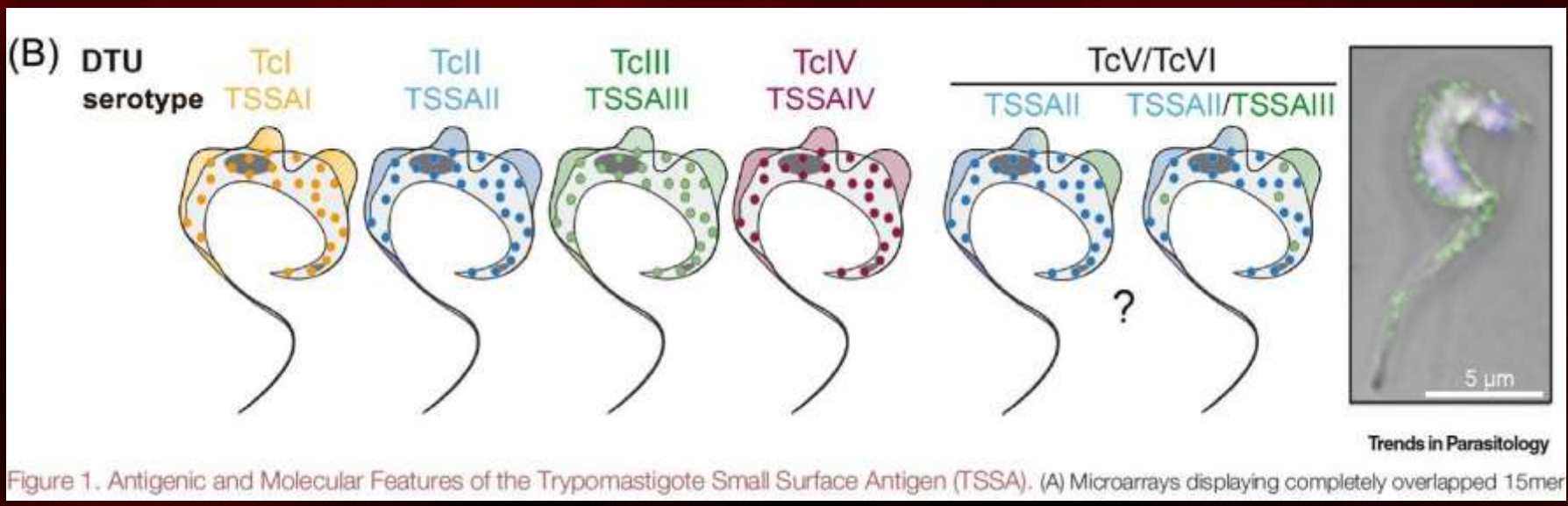


Figure 1. Antigenic and Molecular Features of the Trypomastigote Small Surface Antigen (TSSA). (A) Microarrays displaying completely overlapped 15mer

DTUs - Trypanosoma cruzi

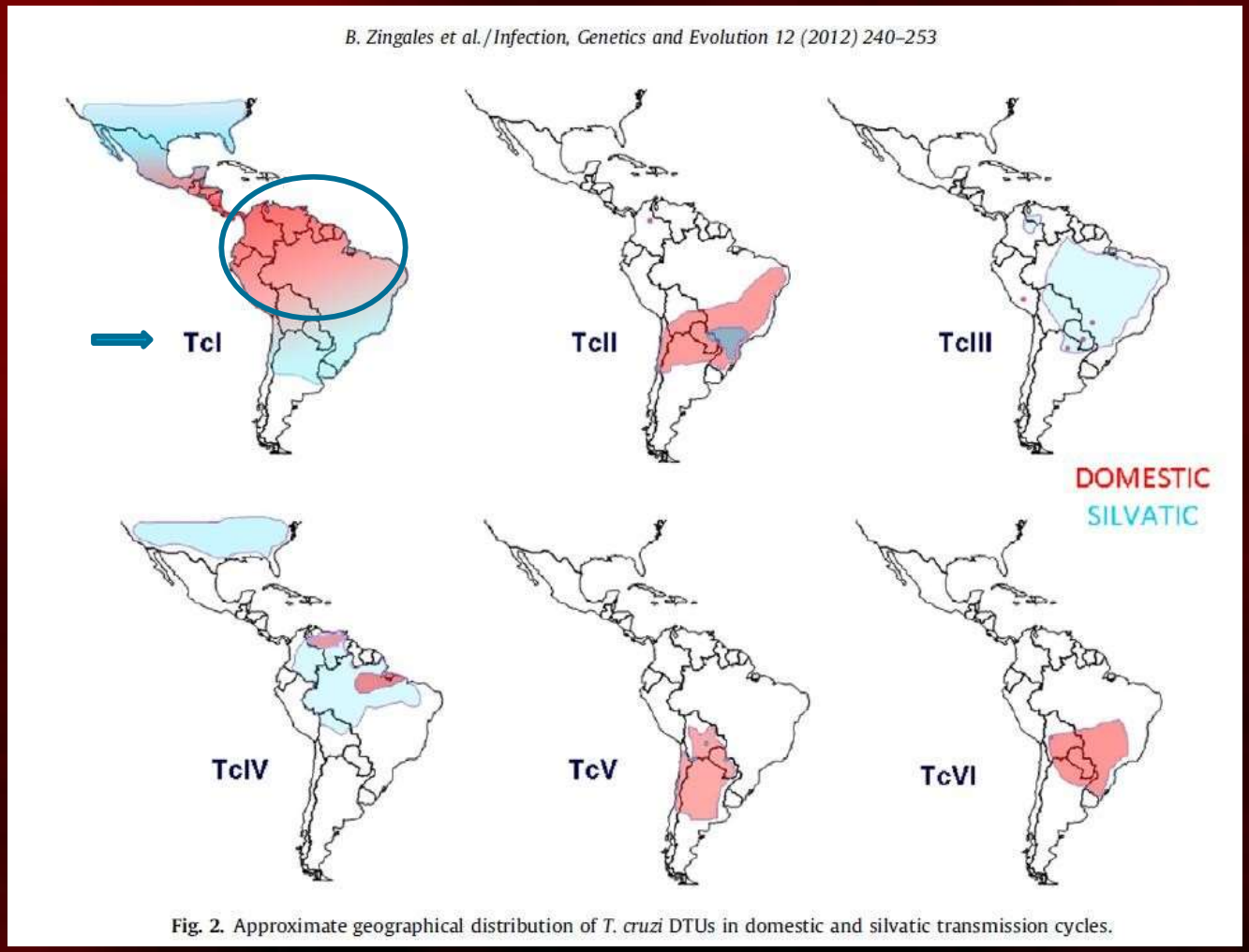
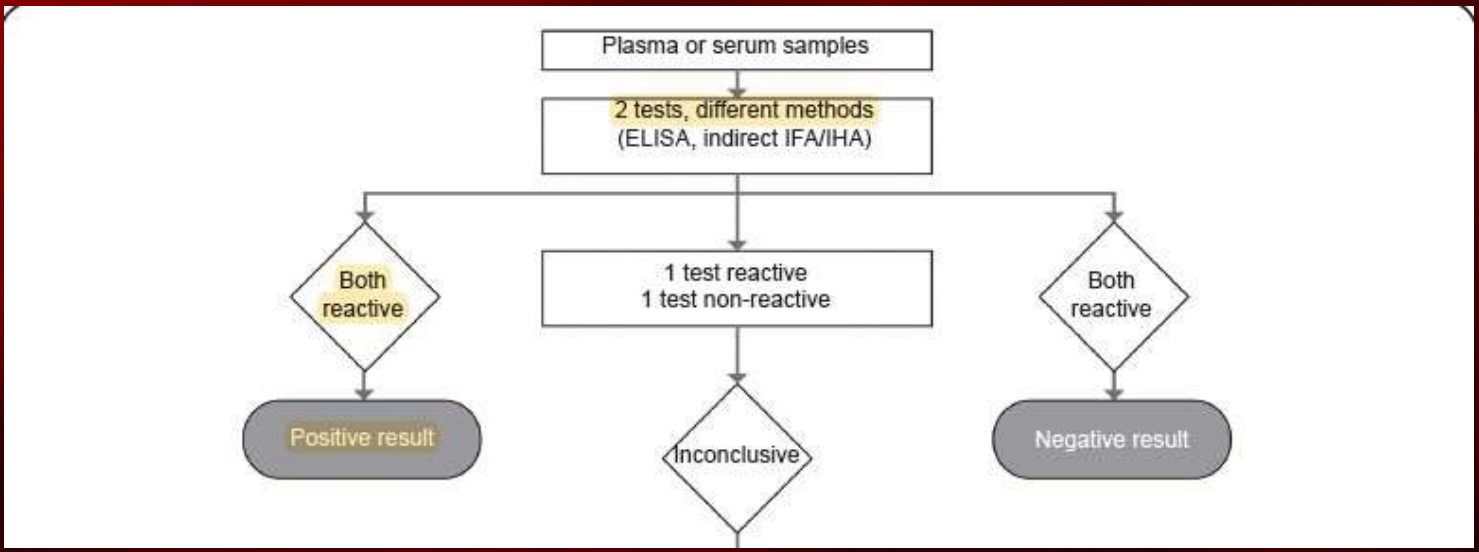


Fig. 2. Approximate geographical distribution of *T. cruzi* DTUs in domestic and silvatic transmission cycles.

2nd Brazilian Consensus on Chagas Disease, 2015*



Quando o PCR é utilizado para diagnóstico ?

- Doença de Chagas Congênita do Recém Nato

- Diagnóstico de Reativação Clínica e Subclínica Pós Transplante

Doença de Chagas Congênita do Recém Nato

- Mãe soropositiva para doença de Chagas
- Recém nato (RN) tem uma grande probabilidade de apresentar sorologia positiva (+)
- RN com sorologia positiva ≠ Doença de Chagas
- Aos nove meses de idade, se a sorologia persistir (+) = Doença de Chagas

Doença de Chagas Congênita
PCR e Sorologia
nas primeiras semanas

- 1) Sorologia positiva e PCR negativo = Não-Chagas
- 2) Sorologia positiva e PCR positivo = DChagas
- 3) Sorologia negativa e PCR negativo = Não-Chagas
- 4) Sorologia negativa e PCR positivo = DChagas

Reativação Pós Transplante de Coração

- O conceito preponderante é que, por ser portador de infecção por T. cruzi, o **paciente chagásico deva receber a menor intensidade de imunodepressão possível,** desde que sem rejeição

- Balanço delicado entre **Reativação X Rejeição**

E a PCR na Reativação ?
O valor do PCR reside no diagnóstico precoce de reativação

Table 3 Diagnostic tests according to ChD manifestation

Diagnostic test	Samples tested	Specific comments	Recommended tests		
			Acute ChD	Chronic ChD	Reactivation ChD
Direct microscopic examination of trypanosomatids	Blood fluids – CSF, cavitary fluids	Quick and easy to perform. Non-concentration methods (Giemsa stain or thick smear) present lower sensitivity compared to concentration methods (SM, microhematocrit, and QBC)	Yes	No	Yes
Xenodiagnosis	Blood	Low sensitivity if low parasitemia, highly specific; labor-intensive and time-consuming (up to 2 weeks or longer). Results can be semiquantitative indicating the percentage of nymphs per assay, useful for monitoring risk of ChD reactivation	No	Yes	No Predictive of ChD reactivation
Blood culture	Blood	Low sensitivity if low parasitemia,	No	Yes	No
Polymerase chain reaction	Blood, CSF	High sensitivity and specificity. Not commercially available, performed by only few research/ reference centers, need standardization protocols. Results can be quantitative (IU/ml), useful for monitoring risk of ChD reactivation and monitor therapy response	Yes	Yes, in special situations to confirm inconclusive serological results	Yes Predictive of ChD reactivation Monitor therapy response
Serological testing	Blood	Conventional tests – ELISA, IFA, IHA have less than 100% sensitivity and specificity; diagnosis based on two different tests performed in parallel	Possibly useful to confirm the diagnosis in difficulty diagnosis cases	Yes	No

The Journal of Heart and Lung Transplantation
December 2004

Using Polymerase Chain Reaction in Early Diagnosis of Re-activated *Trypanosoma cruzi* Infection After Heart Transplantation

Cecilia Maldonado,[a] Susana Albano,[a] Lorena Vettorazzi,[a] Oscar Salomone, MD,[b] Juan C. Zlocowski, MD,[c] Claudio Abiega,[c] Marcos Amuchastegui, MD,[b] Roque Córdoba, MD,[b] and Teresita Alvarellos, MD[a]

Table 1. Results From 4 Patients Serologically Positive for Chagas Disease

Patient #	Clinical re-activation	Parasitemia	Histology	PCR	Clinical response	Negative PCR results
1	Hematogenous chagoma	Strout (−)	Without amastigotes	PB (+) EMC Bx (+) Skin lesion (+)	Good	1 month
2	Myocarditis	Strout (−)	Without amastigotes	PB (+) EMC Bx (+)	Good	2 months
3	Hematogenous chagoma Myocarditis	Strout (+)	Without amastigotes	PB (+) EMC Bx (+) Gastric Bx (+) Skin Bx (+)	Good	1 month
4	Hematogenous chagoma	ND	ND	PB (+) Skin Bx (+)	Good	1 month

Bx, biopsy; EMC, endomyocardial; ND, not determined; PB, peripheral blood; PCR, polymerase chain reaction.

DIAGNÓSTICO DA DOENÇA DE CHAGAS (Resumo)

- Métodos Diagnósticos:
  - parasitológico
  - sorológico
  - molecular

- Diagnóstico X Fase Clínica:
  - Aguda = parasitológico
  - Crônica = sorológico
  - Congênita Recente = molecular

TRATAMENTO ETIOLÓGICO COM DROGA TRYPANOCIDA

Table 8 Specific available drugs to Chagas disease treatment

	Benznidazole	*Nifurtimox*
Formulation	Benznidazole (BZD; *N*-benzyl-2-nitroimidazole acetamide	Nitroheterocyclic compounds nifurtimox (NFX; 3-methyl-4-[59-nitrofurfurylideneamine] tetrahydro-4H-1,4-tiazine-1,1-dioxide)
Presentation	Tablet 100 mg	Tablet 120 mg
Adult dosing	5–7.5 mg/kg/day; recommended maximum dose 300 mg/day Up to 15 mg/kg/day in cases of meningoencephalitis	15 mg/kg/day for children and acute disease 8–10 mg/kg/day
Times per day	Two to three doses	Three to four doses
Administration	Oral	Oral
Adjust for renal function	No need	No need
Adjust for hepatic function	No need	No need
Duration of treatment	Usually 60 days For adults >60 kg, duration of treatment may be prolonged beyond the 60 days	60–90 days
Most important adverse reactions	Rash, polyneuropathy, bone marrow suppression, anorexia, nausea, vomiting	Anorexia, abdominal pain, nausea, vomiting, and weight loss
Laboratory monitoring	Baseline: complete blood cell count, hepatic enzymes, bilirubin, serum creatinine, blood urea nitrogen. While on therapy: complete blood cell count every 2–3 weeks	Baseline: complete blood cell count, hepatic enzymes, bilirubin, serum creatinine, blood urea nitrogen. While on therapy: repeat lab tests every 4–6 weeks
Drug interactions	Risk of disulfiram-like effects with concomitant use of alcohol and should be avoided Concomitant use with aspirin may increase the risk of bleeding The effect of coumarin-derived anticoagulants, such as warfarin, can be potentiated due to inhibition of its enzymatic metabolism	Alcohol increase risk of adverse effects and should be avoid Concomitant use with tacrolimus can increase tacrolimus levels
Contraindications	During pregnancy and for patients with kidney and liver failure If hypersensitivity history to the drug	

Drogas Trypanocidas

BENZONIDAZOL

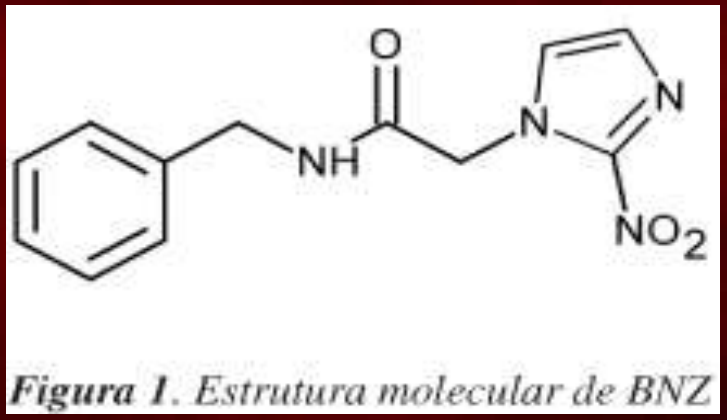
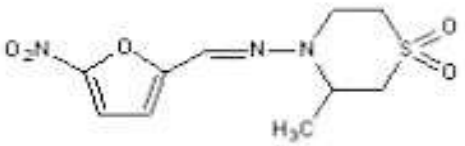
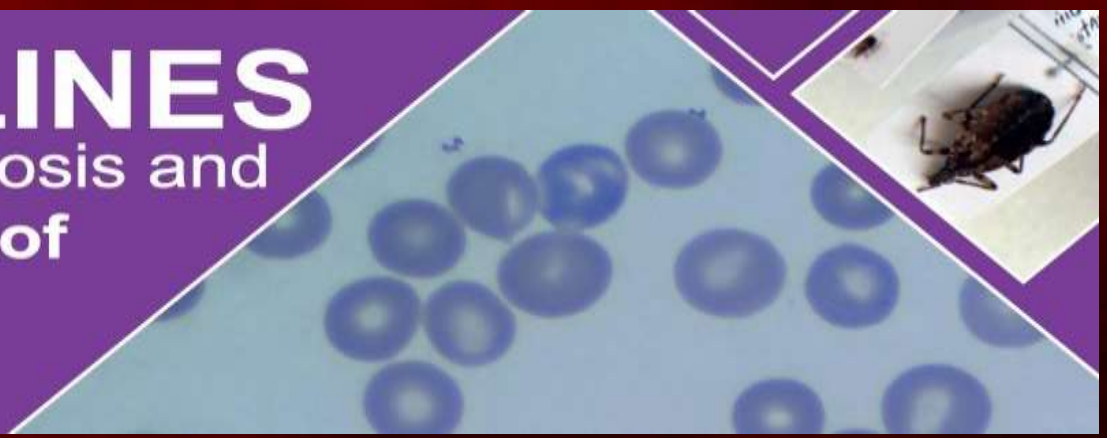


Figura 1. Estrutura molecular de BNZ

NIFURTIMOX



GUIDELINES
for the Diagnosis and Treatment of Chagas Disease



INFECÇÃO AGUDA

Treatment in acute infection

Results Number of participants (studies)	Relative effect (CI 95%)	Expected absolute effects (CI 95%)			Certainty	Effect
				Difference		
Negativization of serology Follow-up: 20 months Number of participants: 151 (1 observational study)[11]	RR 25.5 (2.7-37.0)[a]	Bajo 2.7%b	**69.1%** (7.3-100.0)	**66.4% más** (4.6 more to 97.6 more)	⊕⊕⊕◯ MODERATE[c,e]	Trypanocidal treatment probably increases the likelihood of negativizing serology.
Negativization of parasitemia evaluated with: any method Follow-up: 1 year Number of participants: (16 observational studies)[1-16]	16 studies were considered (n = 1,087) Benznidazole: 89,66% (n = 466) Nifurtimox: 74.74% (n = 621)				-	

Clinical Follow-Up of Responses to Treatment with Benznidazol in Amazon: A Cohort Study of Acute Chagas Disease

Ana Yecê das Neves Pinto[1]*, Vera da Costa Valente[2], José Rodrigues Coura[3], Sebastião Aldo da Silva Valente[2], Angela Cristina Veríssimo Junqueira[3], Laura Cristina Santos[3], Alberto Gomes Ferreira Jr.[4], Roberto Cavalleiro de Macedo[5]

PLOS ONE | www.plosone.org 1 May 2013 | Volume 8 | Issue 5 | e64450

66% de Cura

Table 2. Anti- *T. cruzi* IgG antibody titers measured in treated patients follow-up.

Number of years after treatment	Anti-*T. cruzi* IgG antibody titers					Total positive (%)	Total negative (%)	Total
	1/40	1/80	1/160	1/320	1/1280			
≤1 year*	13	8	2	0	0	23 (76.7)	7 (23.3)	30
2 years	32	22	4	1	0	59 (81.9)	13 (18.1)	72
3 to 4 years*	15	7	4	0	0	26 (76.4)	8 (23.5)	34
5 to 6 years	9	10	1	0	0	20 (66.7)	10 (33.3)	30
≥7 years	2	1	1	0	0	4 (30.8)	9 (69.2)	13
Total	71	48	12	1	0	132 (73.7)	47 (26.3)	179

DTUs - Trypanosoma cruzi

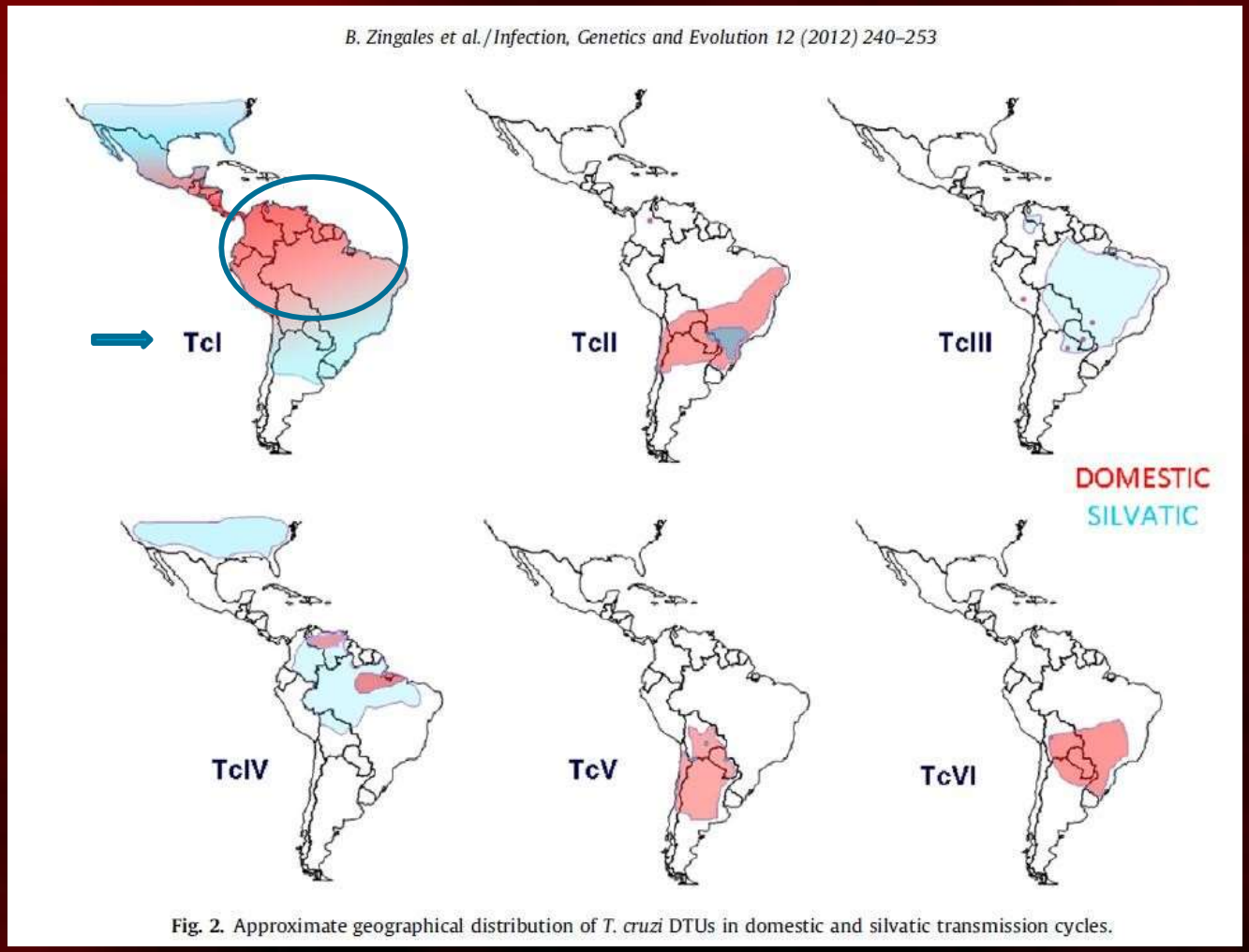


Fig. 2. Approximate geographical distribution of *T. cruzi* DTUs in domestic and silvatic transmission cycles.

CRIANÇAS E ADOLESCENTES

Treatment in children

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Negativization of serology (2-3 years)	447 (2 RCT)[1,2,d]	⊕⊕⊕◯ MODERATE[c,e]	**RR 2.41** (1.16-5.02)	Population study 229 per 1,000[d]	**323 more per 1,000** (37 more to 922 more)
Progression or development of myocardiopathy	129 (1 RCT)[1,a]	⊕⊕◯◯ LOW[b,c]	Not estimable	Population study 0 per 1,000	**0 less per 1,000** (0 less to 0 less)
Early negativization of parasitemia (1-2 months)	106 (1 RCT)[2,d]	⊕⊕⊕◯ MODERATE[c]	**RR 1.69** (1.33-2.16)	Population study 176 per 1,000[d]	**122 more per 1,000** (58 more to 205 more)
Withdrawal from treatment due to adverse effects	235 (2 RCT)[1,2,f]	⊕⊕⊕◯ MODERATE[g]	**RR 0.55** (0.22-1.41)	Population study 95 per 1,000[f]	**43 fewer per 1,000** (74 fewer to 39 more)

Conclusions

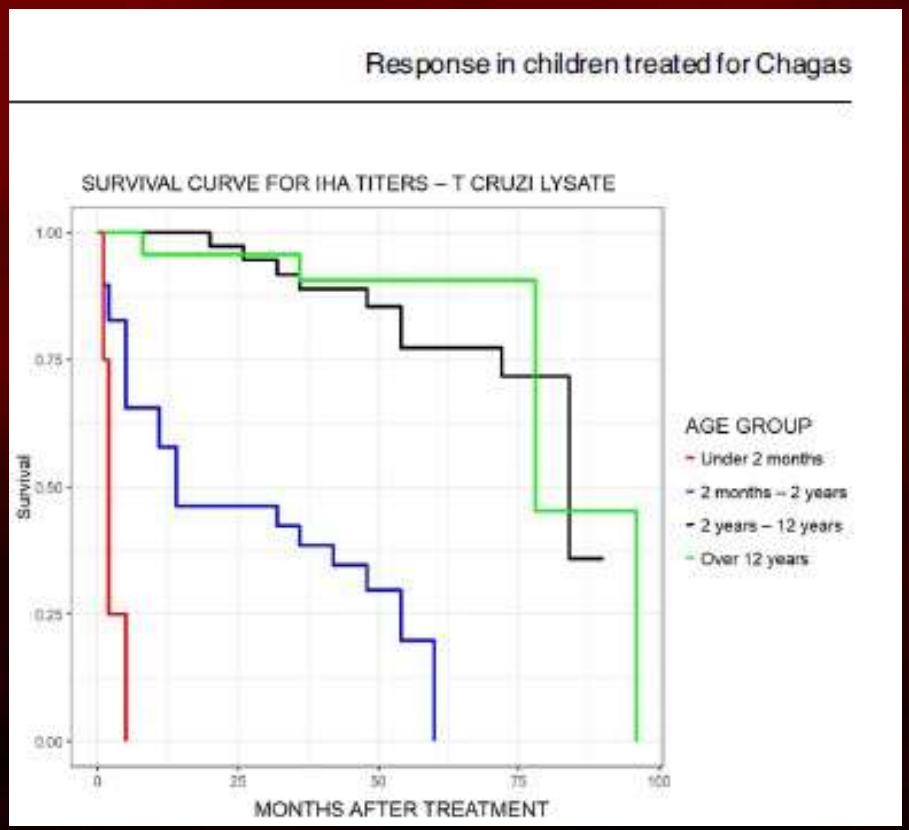
Should trypanocidal drugs be administered to children with chronic Chagas disease or is it better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention or of the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●

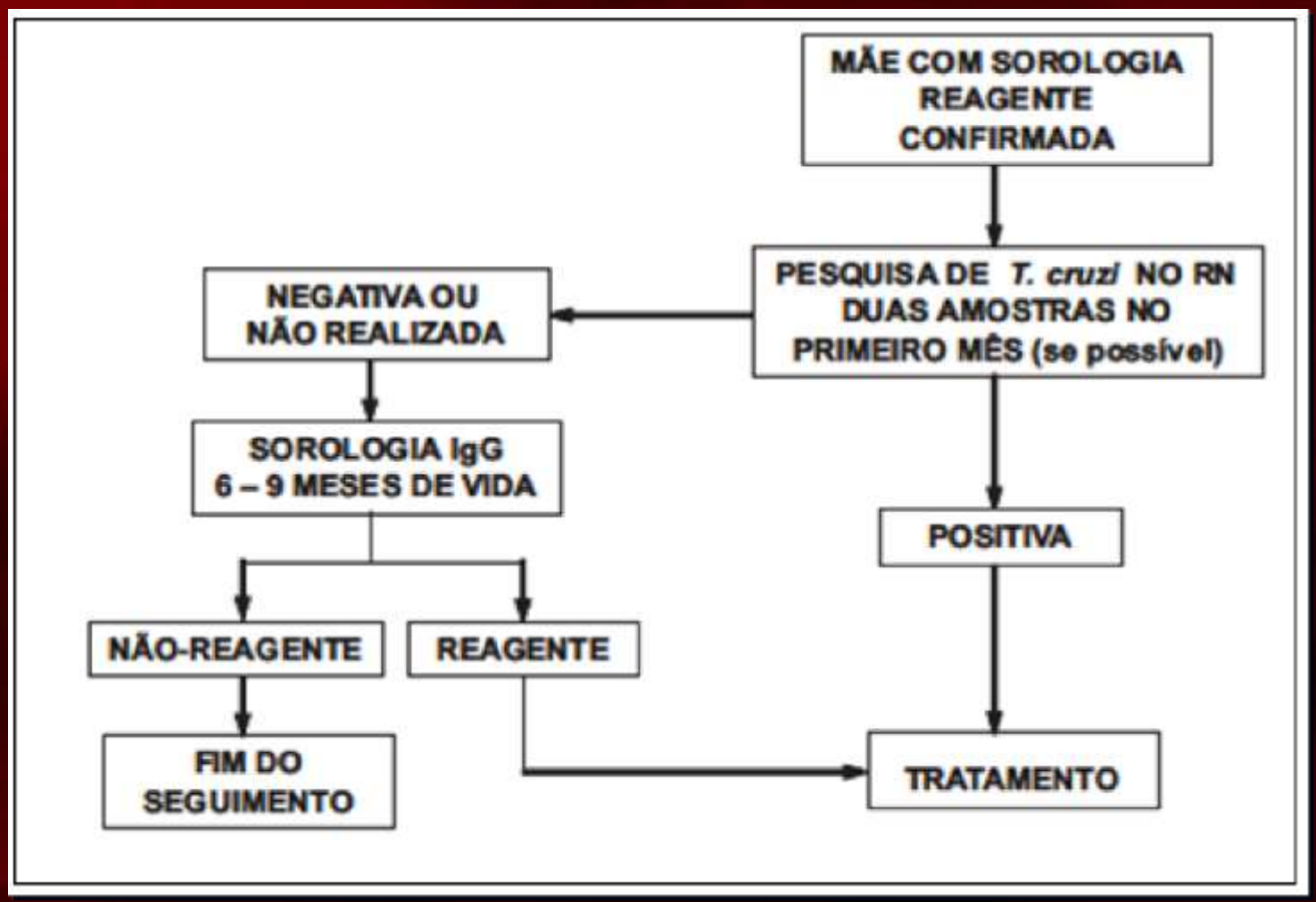
Longitudinal follow up of serological response in children treated for Chagas disease

Guillermo Moscatelli[1,2]*, Samanta Moroni[1,2], Facundo García Bournissen[1,2], Nicolás González[1], Griselda Ballering[1], Alejandro Schijman[3], Ricardo Corral[1], Margarita Bisio[1], Héctor Freilij[1], Jaime Altcheh[1,2]

PLOS Neglected Tropical Diseases | https://doi.org/10.1371/journal.pntd.0007668 August 29, 2019



Fluxograma de Tratamento em Recém Natos com Suspeita de Doença de Chagas Congênita



MULHERES EM IDADE FÉRTIL

Treatment in girls and women of childbearing age

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Vertical transmission	735 (4 observational studies)[1-4]	⊕⊕⊕◯ MODERATE[d]	OR.07 (0.02-0.30)	Low	
				20 per 1,000[a]	**19 fewer per 1,000** (20 fewer to 14 fewer)
				High	
				50 per 1,000[b]	**46 fewer per 1,000** (49 fewer to 34 fewer)
				Population study	
				147 per 1,000	**135 fewer per 1,000** (143 fewer to 98 fewer)
Adverse fetal effects	0 (observational studies)[1-4]	-	-	None of the analyzed studies reports adverse fetal effects in women who received antiparasitic treatment.	
Withdrawal from treatment due to adverse effects: adults	3,697 (4 RCT)[5-7,9]	⊕⊕⊕⊕ HIGH	**RR 5.71** (2.46-13.29)	Population study	
				33 per 1,000[c]	**157 more per 1,000** (49 more to 409 more)
Withdrawal from treatment due to adverse effects: children	235 (2 RCT)[8,10,f]	⊕⊕⊕◯ MODERATE[e]	**RR 0.55** (0.22-1.41)	Population study	
				95 per 1,000[c]	**43 fewer per 1,000** (74 fewer to 39 more)

Conclusions

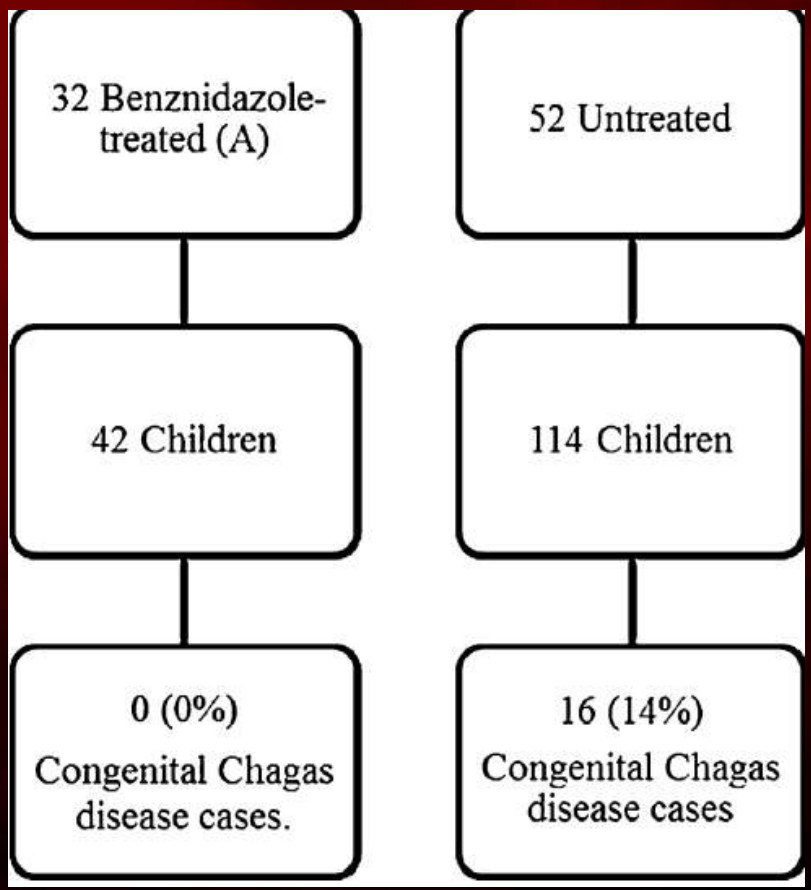
Should trypanocidal drugs be administered to women of childbearing age with chronic Chagas disease or is better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention or of the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●

Acta Tropica 174 (2017) 149–152

Prevention of congenital Chagas disease by Benznidazole treatment in reproductive-age women. An observational study

María G. Álvarez, Carlos Vigliano, Bruno Lococo, Graciela Bertocchi, Rodolfo Viotti*



FORMA CRÔNICA INDETERMINADA

Treatment in adults with no specific organ damage

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Mortality	2,328 (5 observational studies)[1-5,a]	⊕◯◯◯ VERY LOW[b,c]	**OR 0.57** (0.21-1.51)	Population study 39 per 1,000[a]	**16 fewer per 1,000** (31 fewer to 19 more)
Development of myocardiopathy	1,173 (5 observational studies)[1,3,5-7,a]	⊕⊕◯◯ LOW[b]	**OR 0.38** (0.18-0.78)	Population study 138 per 1,000[a]	**81 fewer per 1,000** (110 fewer to 27 fewer)
Early negativization of parasitemia (1-2 months)	260 (1 RCT)[8,d]	⊕⊕◯◯ LOW[e,f]	**RR 1.44** (1.21-1.72)	Population study 657 per 1,000[d]	**289 more per 1,000** (138 more to 473 more)
Negativization pf parasitemia (end of treatment) evaluated with: PCR	1,175 (1 RCT)[11]	⊕⊕⊕◯ MODERATE[h]	**RR 1.98** (1.75-2.24)	Population study 335 per 1,000	**328 more per 1,000** (251 more to 415 more)
Negativization of serology (2-3 years) Adults	1,787 (4 observational studies)[1,3-5,d]	⊕⊕◯◯ LOW[b]	**OR 3.32** (1.40-7.88)	Population study 199 per 1,000[d]	**253 more per 1,000** (59 more to 463 more)
Negativization of serology (2-3 years) Pediatric patients	447 (2 RCT)[12,13]	⊕⊕◯◯ LOW[i,j,k]	**RR 2.41** (1.16-5.02)	Population study 229 per 1,000[d]	**229 per 1,000**[d]
Withdrawal from treatment due to adverse effects	3,697 (4 RCT)[8-11]	⊕⊕⊕⊕ HIGH	**RR 5.71** (2.46-13.29)	Population study 33 per 1,000[g]	**157 more per 1,000** (49 more to 409 more)
Serious adverse effects	2,911 (2 RCT)[10,11]	The incidence of (any) serious adverse effects with benznidazole was from 8.3% to 10%. The most frequent effects were: skin rashes (4.1%), gastrointestinal symptoms (4.1%), neuropathies (1.8%), and leukopenia (1.0%).			

Conclusions

Should trypanocidal drugs be administered to patients with chronic Chagas disease and no specific organ damage or is it better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

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Research Paper

Benznidazole decreases the risk of chronic Chagas disease progression and cardiovascular events: A long-term follow up study

Alejandro M. Hasslocher-Moreno[a,*], Roberto M. Saraiva[a], Luiz H.C. Sangenis[a], Sergio S. Xavier[a], Andrea S. de Sousa[a,b], Andrea R. Costa[a], Marcelo T. de Holanda[a], Henrique H. Veloso[a], Fernanda S.N.S. Mendes[a], Filipe A.C. Costa[c], Marcio N. Boia[c,d], Pedro E.A.A. Brasil[a], Fernanda M. Carneiro[a], Gilberto M.Sperandio da Silva[a], Mauro F.F. Mediano[a]

[a] Evandro Chagas National Institute of Infectious Disease, Oswaldo Cruz Foundation, Rio de Janeiro, RJ, Brazil

Table 2
Survival estimates for progression from indeterminate to cardiac form of Chagas disease and death according to BZN treatment ($n = 228$).

	Number of events	Cumulative incidence	Incidence rate (95%CI) (per 1000 person-years)	Unadjusted		Adjusted*	
				HR (95%CI)	*p-value*	HR (95%CI)	*p-value*
BZN treatment			Progression from indeterminate to cardiac form of Chagas disease				
No	24	21.1%	1.10 (0.74 to 1.64)	1.00 (Reference)	0.04	1.00 (Reference)	0.04
Yes	9	7.9%	0.49 (0.25 to 0.95)	0.46 (0.21 to 0.98)		0.44 (0.20 to 0.99)	
BZN treatment			Composite of cardiovascular events (heart failure, stroke, or device implantation)				
No	10	8.8%	0.42 (0.23 to 0.79)	1.00 (Reference)	0.06	1.00 (Reference)	0.02
Yes	2	1.8%	0.10 (0.03 to 0.42)	0.23 (0.05 to 1.07)		0.15 (0.03 to 0.77)	
BZN treatment		Death					
No	10	8.8%	0.41 (0.22 to 0.77)	1.00 (Reference)	0.85	1.00 (Reference)	0.95
Yes	7	6.1%	0.35 (0.17 to 0.74)	0.91 (0.35 to 2.39)		1.04 (0.37 to 2.89)	

FORMA CRÔNICA CARDÍACA

Treatment in adults with specific organ damage

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (CI 95%)	Expected absolute effects* (CI 95%)	
				Risk with placebo	Risk difference compared to trypanocidal
Mortality	2,854 (1 RCT)[1,a]	⊕⊕⊕◯ MODERATE[b]	OR 0.94 (0.78-1.14)	Population study	
				181 per 1,000[a]	**9 fewer per 1,000** (34 less to 20 more)
				Low	
				20 per 1,000[c]	**1 less per 1,000** (4 fewer to 3 more)
Progression of myocardiopathy	2,854 (1 RCT)[1,a]	⊕⊕⊕◯ MODERATE[b]	OR 0.88 (0.67-1.15)	Population study	
				86 per 1,000[a]	**10 fewer per 1,000** (27 fewer to 12 more)
Negativization of parasitemia (end of the treatment) Evaluated with: PCR	1,175 (1 RCT)[2]	⊕⊕⊕⊕ HIGH	RR 1.98 (1.75-2.24)	Population study	
				335 per 1,000	**328 more per 1,000** (251 fewer to 415 more)
Withdrawal from treatment due to adverse effects	3,697 (4 RCT)[1-4]	⊕⊕⊕⊕ HIGH	RR 5.71 (2.46-13.29)	Population study	
				33 per 1,000[d]	**157 more per 1,000** (49 more to 409 more)

Conclusions

Should trypanocidal drugs be administered to patients with chronic Chagas disease and specific organ damage or is it better not to prescribe treatment?

Type of decision	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention or of the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○

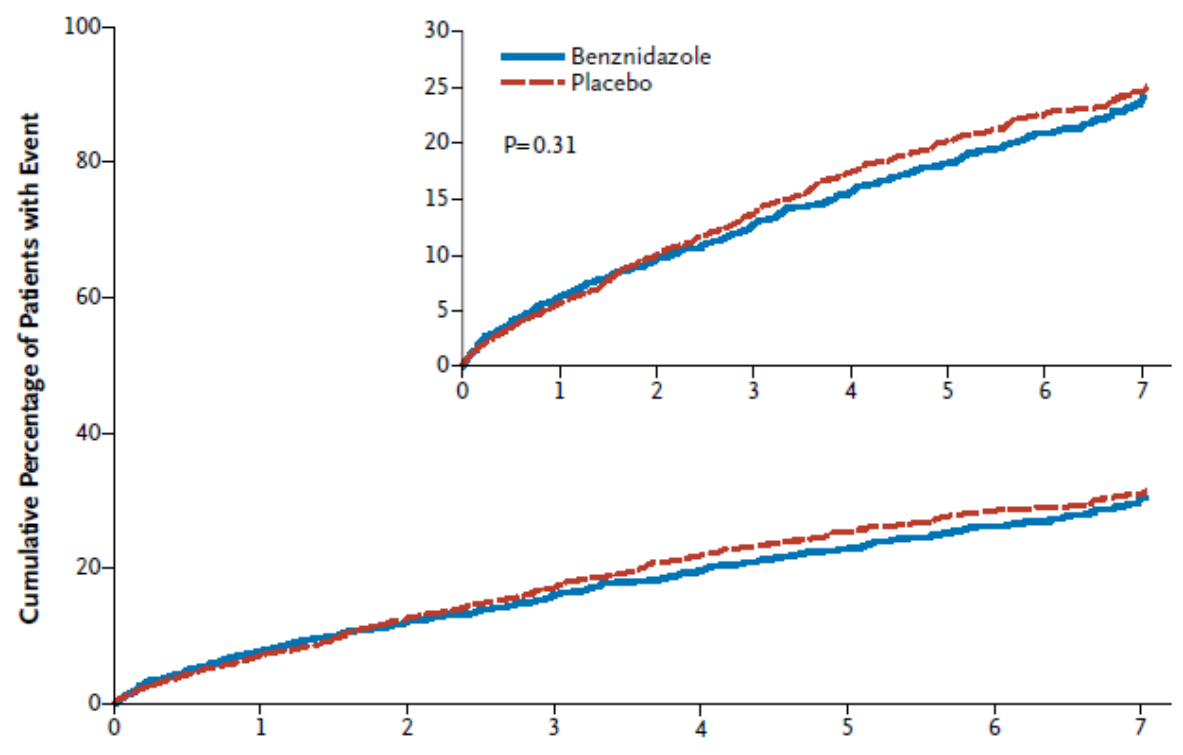
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy

C.A. Morillo, J.A. Marin-Neto, A. Avezum, S. Sosa-Estani, A. Rassi, Jr., F. Rosas, E. Villena, R. Quiroz, R. Bonilla, C. Britto, F. Guhl, E. Velazquez, L. Bonilla, B. Meeks, P. Rao-Melacini, J. Pogue, A. Mattos, J. Lazdins, A. Rassi, S.J. Connolly, and S. Yusuf, for the BENEFIT Investigators*

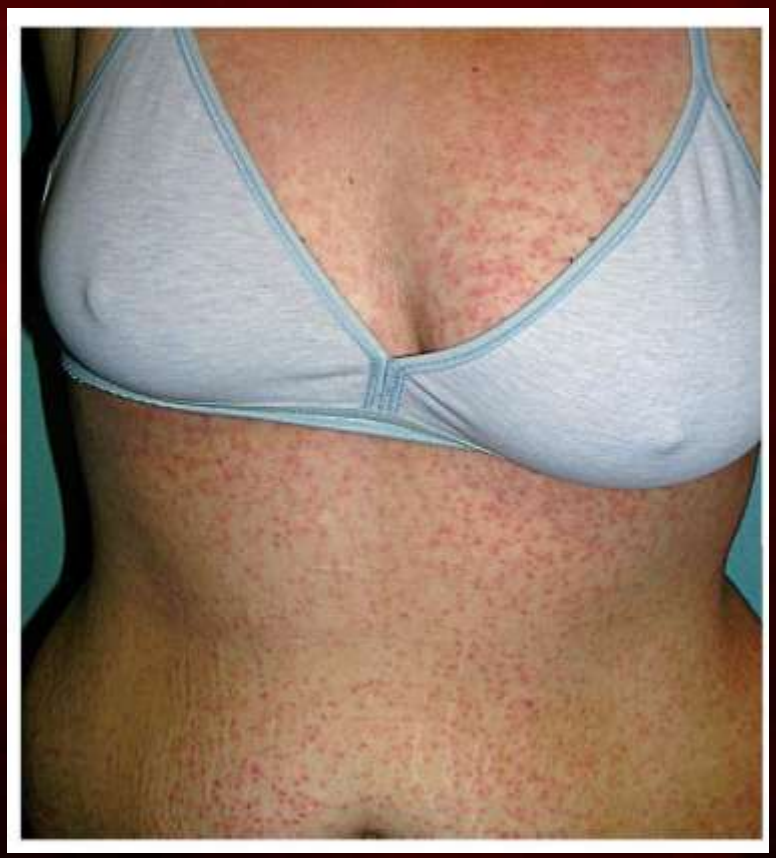
This article was published on September 1, 2015, at NEJM.org.



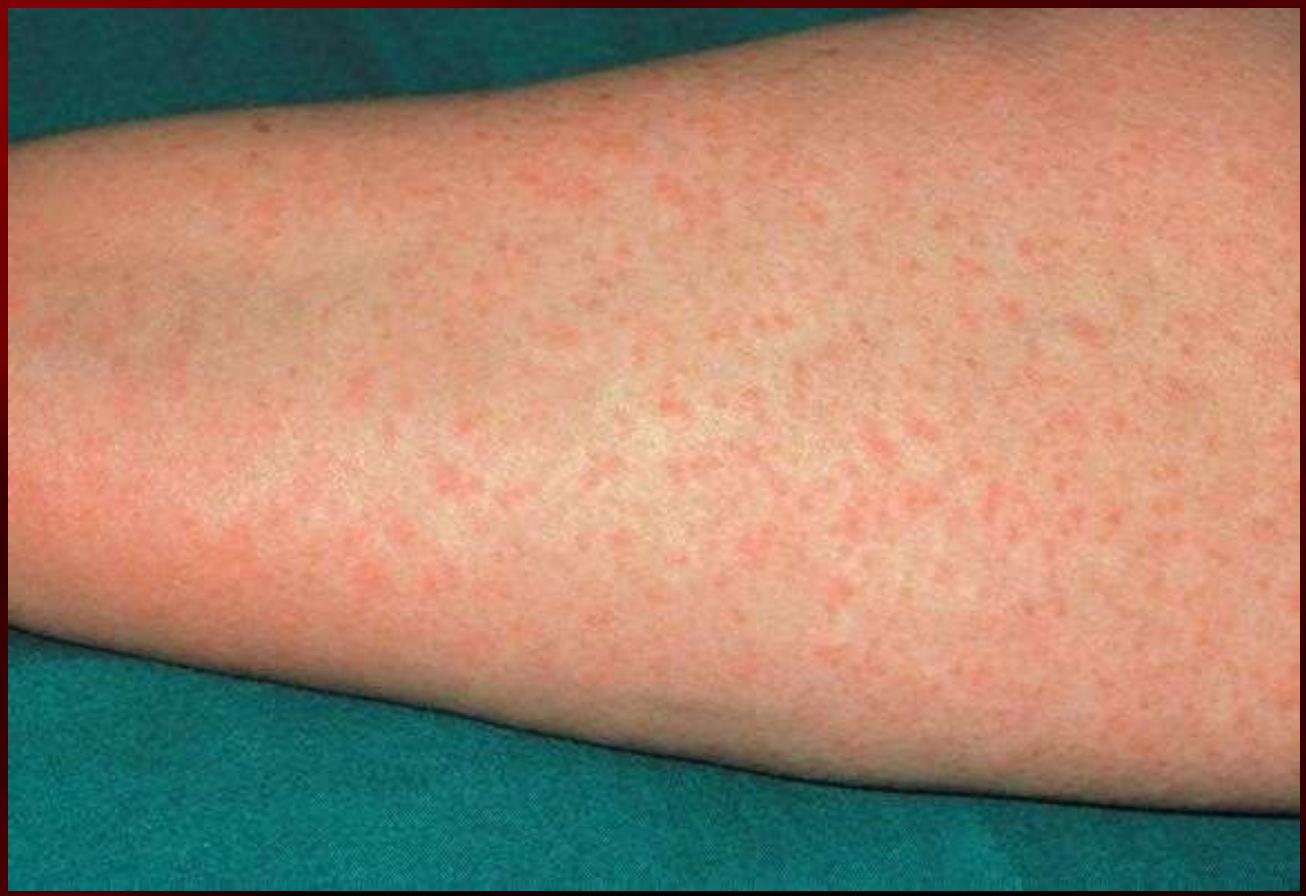
Manejo dos Efeitos Adversos do Benzonidazol

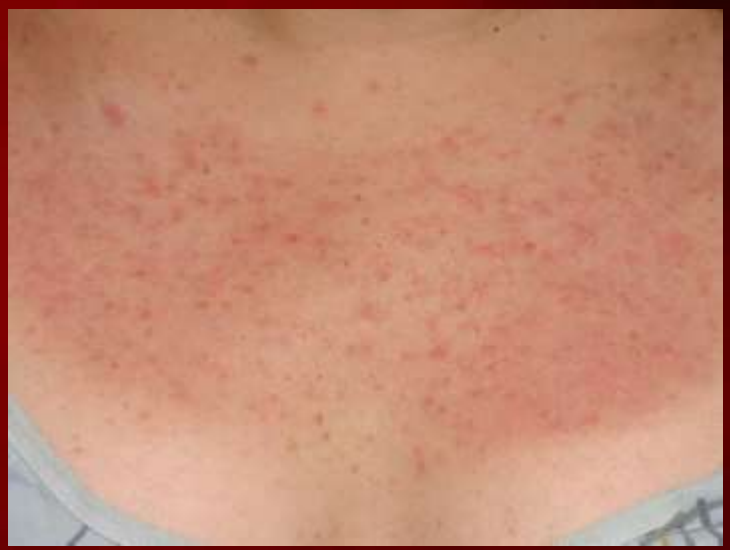
Hipersensibilidade dermatológica

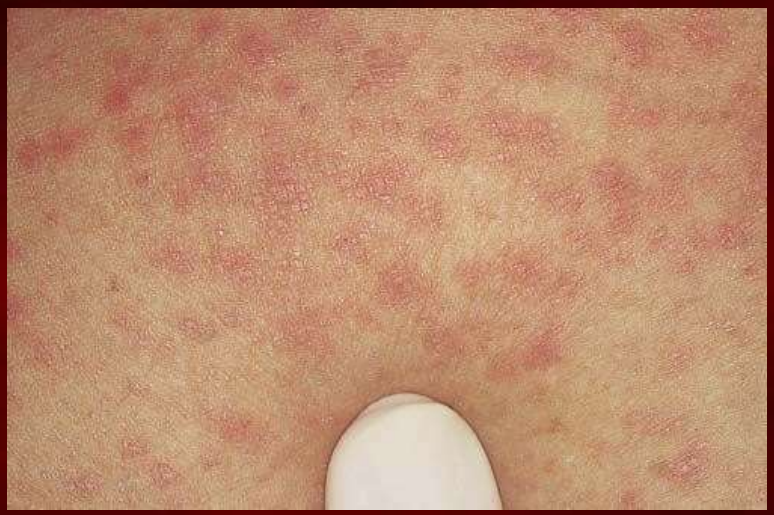
- Muito comum
- De 30 a 40% dos casos
- Caráter benigno na maioria dos casos
- Mais comum no sexo feminino
- Normalmente surge por volta do 10º dia de tratamento
- Características: exantema maculopapular, eritema polimorfo não bolhoso, prurido e descamação



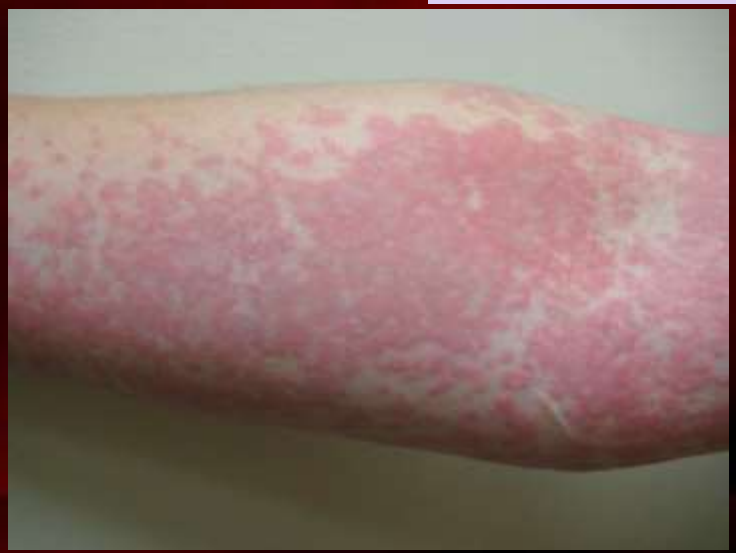
Exantema maculopapular

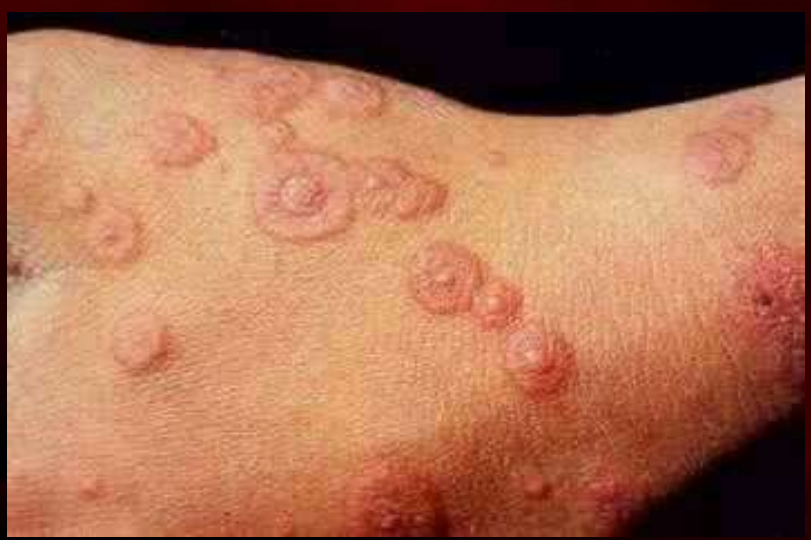




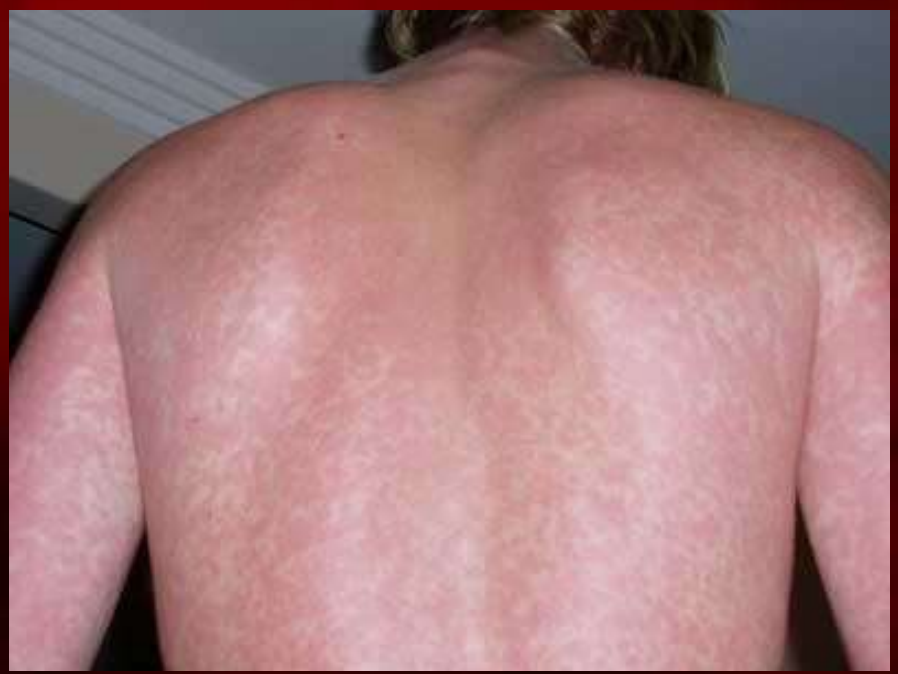


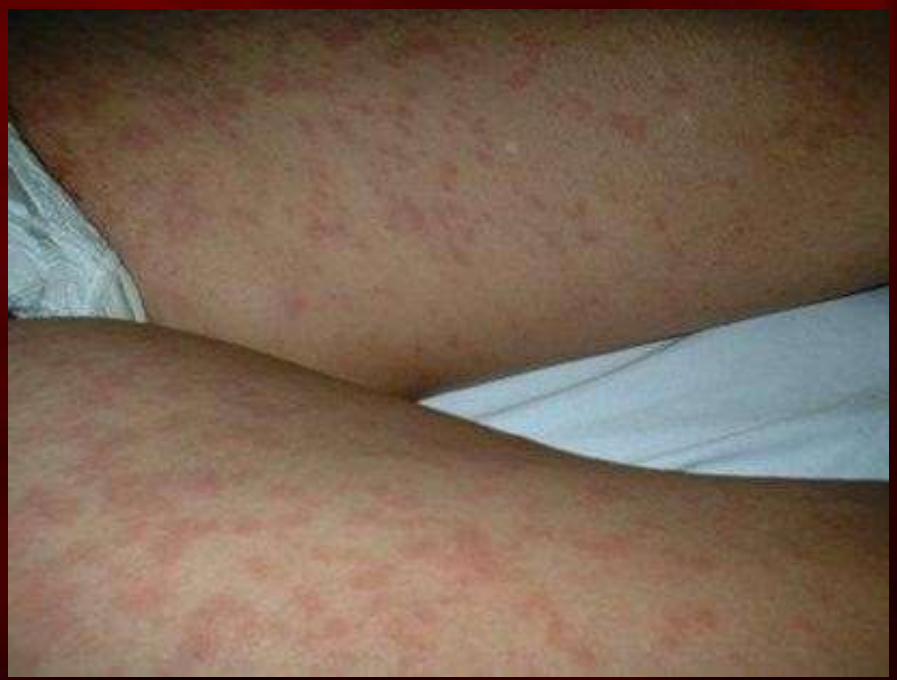
Eritema polimorfo



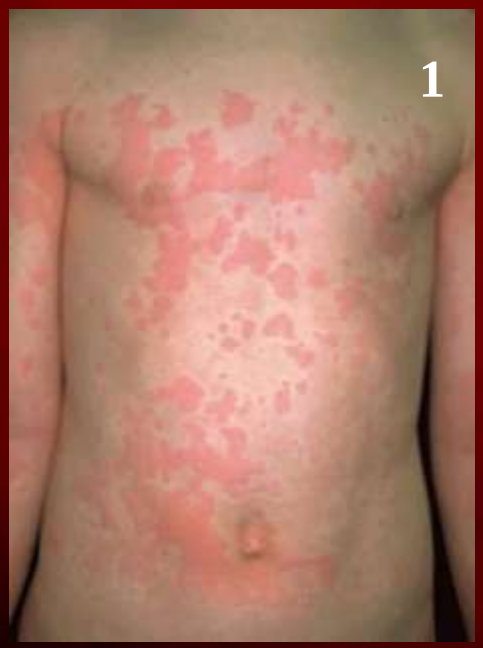


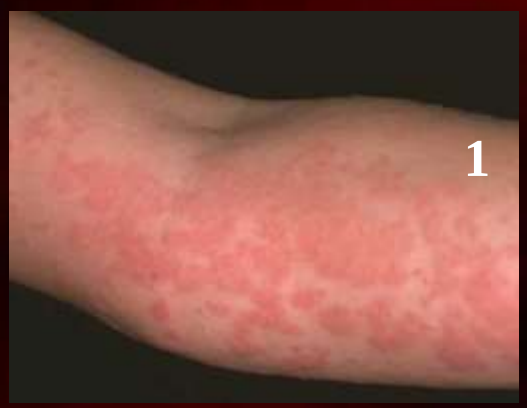
Sinal de gravidade: lesões generalizadas

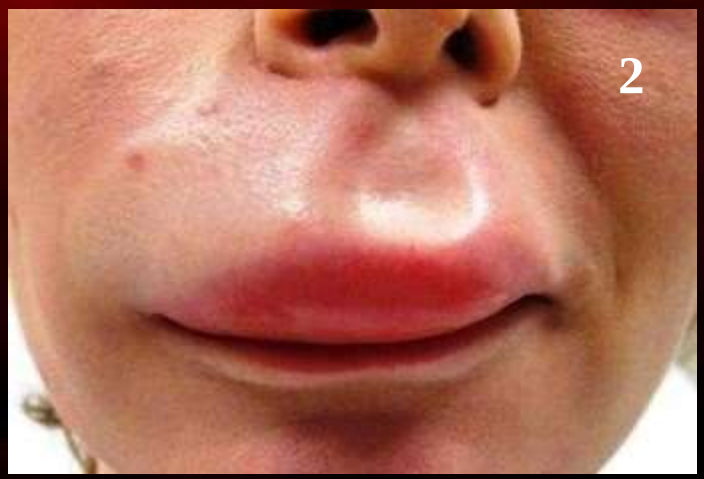




Sinais de gravidade: 1.urticárias, 2.edema de Quincke e 3.Stevens-Jhonson





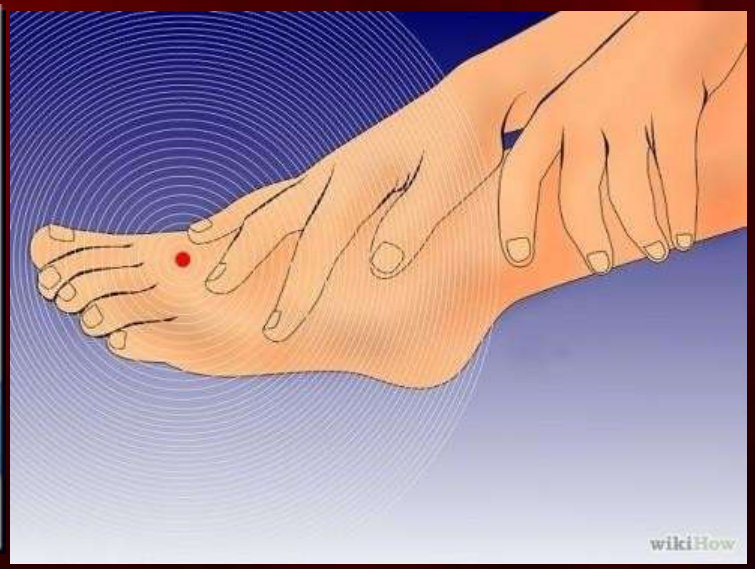


Manejo das reações dermatológicas

- ✓ **formas leves – manter o tratamento, anti-histamínicos, loções hidratantes (creme de uréia a 10%)**
- ✓ **formas moderadas – manter o tratamento, associar corticóides (prednisona) em dose baixa (5 mg/dia)**
- ✓ **formas graves – suspender o tratamento, administrar corticóide (prednisona) 20 a 40 mg/dia, internação**

❖**Nas reações graves indica-se trocar o benznidazol por alguma droga alternativa – nifurtimox ou antifúngicos**

Neurite periférica: tardio; dose e tempo dependente



Manejo: suspensão do tratamento e medicamentos (gabapentina ou amitriptilina)

Depressão da medula óssea: tempo dependente (~30 dias)

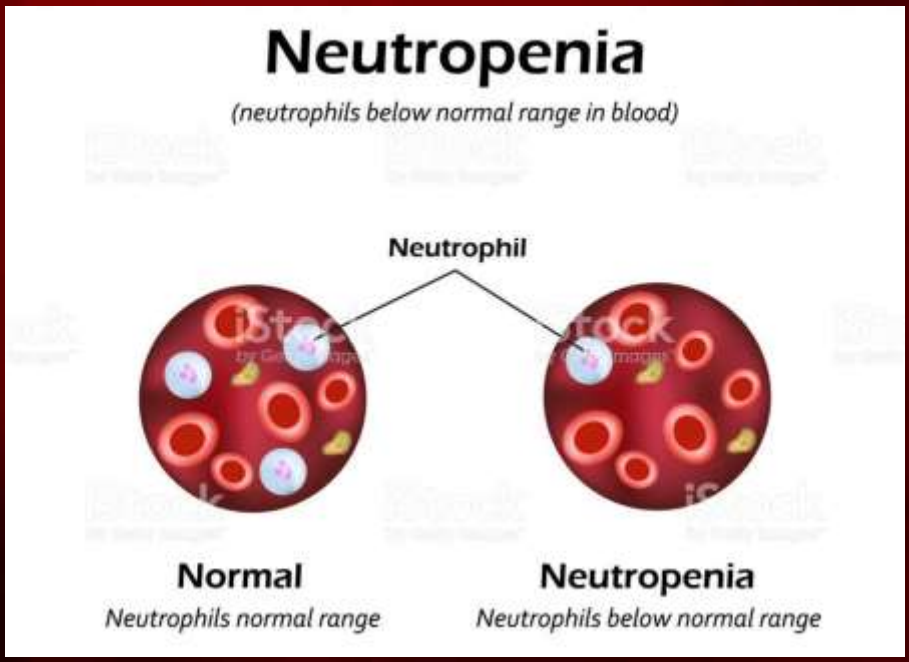


TABELA 51.1 Classificação das neutropenias

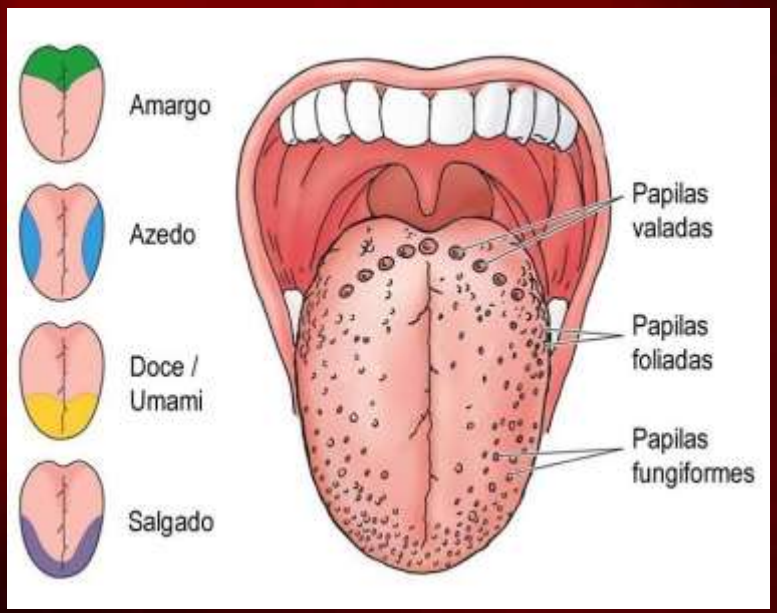
Neutrófilos/μL	Classificação
1.500 a 1.000	Leve
1.000 a 500	Moderada
< 500	Grave

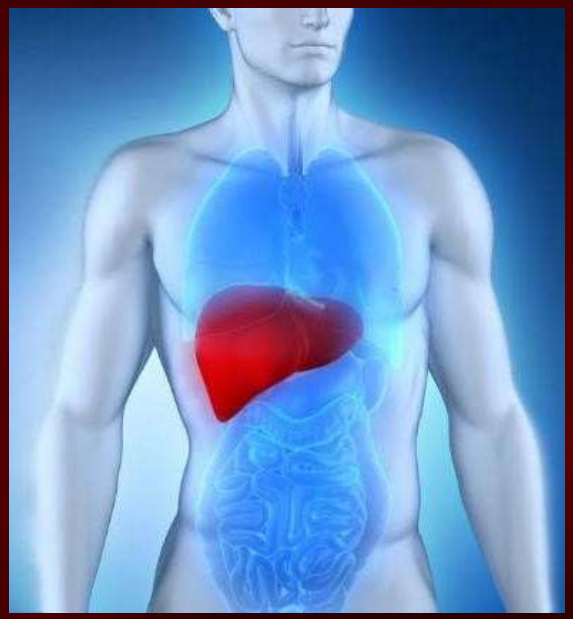
Manejo: leve - Leucograma semanal / Monitoramento
: moderada e grave – suspender o tratamento

cefaleia, dor abdominal, náuseas e dispepsia

Manejo: manter o tratamento e sintomáticos (dipirona, bromoprida e omeprazol)

Efeitos raros: ageusia, hepatite e nefrite





Manejo: nas apresentações moderadas e graves, suspender o tratamento

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Journal of Antimicrobial Chemotherapy

Safety of benznidazole use in the treatment of chronic Chagas' disease

Alejandro M. Hasslocher-Moreno, Pedro E. A. A. do Brasil, Andrea S. de Sousa, Sergio S. Xavier, Mayara C. Chambela and Gilberto M. Sperandio da Silva*

Table 2. ADR rates according to system organ class during treatment and relationship with treatment interruption in patients using benznidazole ($n=190$)

Code	WHO–ART class	Interruption of treatment: yes	Interruption of treatment: no	*n*	%
100	skin and appendage disorders	33	17	50	26.3
600	gastrointestinal system disorders	10	8	18	9.5
410	central and peripheral nervous system disorders	7	3	10	5.3
1810	body as a whole—general disorders	2	4	6	3.2
433	special senses other, disorders	3	0	3	1.6
1220	white cell and reticuloendothelial system	2	0	2	1.1
431	vision disorders	0	1	1	0.5
200	musculoskeletal system disorders	0	1	1	0.5
420	autonomic nervous system disorders	1	0	1	0.5
1830	resistance mechanism disorders	1	0	1	0.5
Does not apply	ADRs doubtful/improbable	0	97	97	51.1
Total		59	131	190	100

Table 1. Demographic characteristics, treatment, causality and severity associated with the onset of ADR in patients using benznidazole ($N=190$)

Variable	Category	ADRs: yes, *n* (%)	ADRs: no, *n* (%)	*P* value	Total, *n* (%)	Percentage of 190 patients
Sex	male	44 (39.3)	68 (60.7)	0.001	112 (100.0)	58.9
	female	49 (62.8)	29 (37.2)		78 (100.0)	41.1
Age	>20 and ≤40 years	79 (53.4)	69 (46.6)	0.022	148 (100.0)	77.9
	other ages	14 (33.3)	28 (67.7)		42 (100.0)	22.1
Daily dose of benznidazole	50–200 mg	62 (49.2)	64 (50.8)	0.680	126 (100.0)	66.3
	250–500 mg	9 (40.9)	13 (59.1)		22 (100.0)	11.6
	unknown[a]	22 (52.4)	20 (47.6)		42 (100.0)	22.1
Duration of treatment	≤30 days	32 (86.5)	5 (13.5)	<0.001	37 (100.0)	19.5
	>30 and <60 days	21 (42.0)	29 (58.0)		50 (100.0)	26.3
	≥60 days	40 (38.8)	63 (61.2)		103 (100.0)	54.2
Interruption of treatment	yes	59 (100.0)	0 (0.0)	<0.001	59 (100.0)	31.1
	no	34 (26.0)	97 (74.0)		131 (100.0)	68.9
Causality	definite	3 (100.0)	—		3 (100.0)	1.6
	probable	75 (100.0)	—		75 (100.0)	39.5
	possible	15 (100.0)	—		15 (100.0)	7.9
	doubtful ADRs	—	97 (100.0)		97 (100.0)	51.1
Severity	mild	72 (100.0)	—		72 (100.0)	37.9
	moderate	20 (100.0)	—		20 (100.0)	10.5
	severe	1 (100.0)	—		1 (100.0)	0.5
Total		93 (48.9)	97 (51.1)		190 (100.0)	100

November 2014 Volume 58 Number 11 Antimicrobial Agents and Chemotherapy p. 6371–6377

A Clinical Adverse Drug Reaction Prediction Model for Patients with Chagas Disease Treated with Benznidazole

Gilberto Marcelo Sperandio da Silva, Mauro Felippe Felix Mediano, Pedro Emmanuel Alvarenga Americano do Brasil, Mayara da Costa Chambela, Joyce Almeida da Silva, Andrea Silvestre de Sousa, Sergio Salles Xavier, Andrea Rodrigues da Costa, Roberto Magalhães Saraiva, Alejandro Marcel Hasslocher-Moreno

Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

TABLE 1 Patient characteristics (n = 195) and incidence of overall ADRs by variable category

Variable	Mean (SD)	Category	Frequency (% [n])	ADR incidence (% [n])	P value
Age (yr)	32.2 (9.8)	13-19	3.1 (6)	33.3 (2)	0.136
		20-40	79.5 (155)	52.2 (81)	
		>40	17.4 (34)	35.3 (12)	
Sex		Male	57.9 (113)	39.8 (45)	0.004
		Female	42.1 (82)	61 (50)	
Race		Black	7.7 (15)	13.3 (2)	0.016
		White	58.5 (114)	50.9 (58)	
		Mulatto	33.8 (66)	53.0 (35)	
Schooling		Failed to graduate from elementary school/illiterate	40.5 (79)	36.7 (29)	0.006
		Graduated from elementary school	59.5 (116)	56.9 (66)	
Use of other drug prior to BZN treatment		Yes	12.3 (24)	54.2 (13)	0.568
		No	87.7 (171)	47.8 (82)	
BZN dose (mg/day)	223.1 (55.5)	100 to 200	64.6 (127)	49.6 (63)	0.681
		250 to 500	14.9 (29)	41.4 (12)	
		ND[a]	20.5 (40)	50 (20)	
Duration of treatment (days)	58.5 (36.3)	≤30	20.0 (39)	87.2 (34)	<0.001
		>30 and <60	25.6 (50)	42 (21)	
		≥60	54.4 (106)	37.7 (40)	

INDICAÇÃO DE TRATAMENTO (RESUMO)

MANDATÓRIO

- ✓ FASE AGUDA
- ✓ CONGÊNITO
- ✓ REATIVAÇÃO EM IMUNOSSUPRIMIDOS
- ✓ ACIDENTE OCUPACIONAL (Profilaxia Primária)

RECOMENDADO

- ✓ CRIANÇAS E ADOLESCENTES
- ✓ MULHERES EM IDADE FÉRTIL
- ✓ PRÉ TRANSPLANTE (Profilaxia Primária)

INDIVIDUALIZADO

- ✓ INFECÇÃO RECENTE (ATÉ 12 ANOS)
- ✓ FORMA INDETERMINADA ATÉ 50 ANOS

OBRIGADO