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Chagas disease: clinical and therapeutic features

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Resumen

La enfermedad de Chagas fue considerada inicialmente una infección enzoótica típica de animales selváticos, entre los que *Trypanosoma cruzi* fue identificado en más de 100 especies.
A medida que el hombre invadía las regiones más salvajes a través de la deforestación descontrolada para la construcción de casas y crecimiento de su agricultura y ganadería, los chinches triatomíneos establecieron su ciclo doméstico adaptándose a zonas más urbanizadas a través de la implicación del hombre y sus animales domésticos en su ciclo vital.
Después de una fase aguda, la mayoría de veces asintomática, y un período de latencia de 10 a 15 años conocido como la fase indeterminada, la enfermedad puede progresar a su forma cardíaca, presentando miocarditis, fallo cardíaco, arritmias y muerte súbita, o a la forma digestiva, asociada a megaesófago y megacolon. En este artículo se revisan los aspectos clínicos, patogénicos y terapéuticos de la enfermedad de Chagas.

Palabras clave: Enfermedad de Chagas. Patogénesis. Tratamiento

Summary

Chagas disease was considered, originally, an enzootic infection typical of sylvatic animals, among which, *Trypanosoma cruzi* infection was registered in more than 100 species. As man occupied wild regions with uncontrolled deforestation for building their houses, for agriculture and cattle breeding, triatomine bugs finally were adapted to human dwellings or next to them, using domestic animals and man as source of food, establishing, thus, the domestic cycle. After an acute phase, most of the times asymptomatic, and a latency period of 10 to 15 years, known as indeterminate chronic form, the disease may develop into a cardiac form, presenting chronic myocarditis, heart failure, arrhythmias and sudden death, or for a digestive form, presenting megaesophagus and megacolon. In this article we review clinical, pathogenical and therapeutic aspects of Chagas disease.

Key words: Chagas disease. Pathogenesis. Treatment.

Introduction

Chagas disease or American Trypanosomiasis, discovered by Carlos Chagas in 1909, in the village of Lassance, Minas Gerais State, is a zoonosis that affects between 12 and 16 million people in Latin America, where more than 100 million people are exposed to the risk of this infection[1] Its agent, *Trypanosoma cruzi,* is a flagellated protozoan (Mastigophora), from Trypanosomatidae family and its evolutionary cycle includes, necessarily, passage through vertebrate hosts (various classes of mammals, including man) and invertebrates ones (triatomine bugs), genera *Panstrongylus, Rhodnius or Triatoma*. In vertebrate hosts, *T. cruzi* flows along the blood under the form of trypomastigote (free flagellum) and reproduces within the tissues under the form of amastigote (intern flagellum); while in invertebrate ones, it evolves from blood trypomastigote into round forms and epimastigote (insect reproduction form), which are eliminated through triatomine bug faeces and urine, as metacyclic trypomastigotes (infecting forms). Infection transmission occurs mainly through vector and blood transfusion; occasionally, it occurs due to oral or congenital contagion and, accidentally, through manipulation of contaminated material (syringes, needles, laboratory animals) or organ transplant.

Infection has two very distinct phases: the initial acute one, asymptomatic or oligosymptomatic, in the majority of cases, or symptomatic, presenting fever, adenomegaly, hepatosplenomegaly, unilateral conjunctivitis (Romaña's sign), myocarditis and meningoencephalitis, being fatal in 10% of serious cases; this phase is characterized by the presence of *T. cruzi* on direct blood exam. Near two months after the beginning of acute phase, *T. cruzi* disappears from blood for the direct exam and will only be detected by xenodiagnosis, hemoculture or by the polymerase chain reaction (PCR), as the patient enters the chronic phase. After a latency period of 10 to 15 years, known as indeterminate form, the disease may develop into a cardiac form, presenting chronic myocarditis, heart insufficiency and sudden death due to cardiac arrhythmia; into a digestive form, presenting isolated or associated megaesophagus and megacolon; or into a mixed form, presenting both cardiopathies and the "megas". Nearly 50% of the cases, considering an endemic area, remain on indeterminate form, presenting no cardiac or digestive manifestations, normal electrocardiograms and normal x-ray of heart, esophagus and colon, but positive serology and PCR for chagasic infection and, even, with positive xenodiagnosis and hemoculture, with *T. cruzi* isolation in 30% to 50% of cases.

Origin and distribution of Chagas disease

Chagas disease was considered, originally, an enzootic infection typical of sylvatic animals and *T. cruzi* infection has already been registered in more

than 100 reservoirs species, as marsupials, chiroptera, rodents, edentates, carnivores and primates. On the other hand, several sylvatic triatomine bugs species, *Panstrongylus, Rhodnius and Triatoma* genera, were identified as *T. cruzi* carriers, establishing with those animals the infection enzootic sylvatic cycle. Although triatomine bugs are known since 14TH century, only from 1773, with De Geer[2], they were scientifically identified. It was Carlos Chagas who, during Chagas disease discovering process, revealed the *T. cruzi* infection in triatomine bugs and humans[3].

The adaptation process of triatomine bugs to human dwellings has two complementary factors: the need for feeding and the genetic mutations that happened in the course of time. As a consequence of deforestation, there is a withdrawing of sylvatic animals, natural feeding source for triatomine bugs; therefore, due to their surviving instinct, they started to feed from domestic animals and human beings, becoming adapted to human dwellings, after genetic adaptations and simplifications. On the other hand, sylvatic triatomine bugs may be attracted by home lights or brought within the firewood or even on the palm tree leaves used to cover houses. In any way, it is necessary that triatomine bugs should adapt to domestic cycle. Many studies have analyzed the origin, pre-adaptation or domiciliation of triatomine bugs in Brazil[4,5].

It seems that *Trypanosoma cruzi* presence in this continent began a long time ago, though its origin and the origin of its vectors is not exactly known, as well as it is also uncertain the reason for its restricted distribution on American continent: from south of United States to south of Chile and Argentine (except for the cosmopolitan *T. rubrofasciata,* found not infected by *T. cruzi* in India, China, Malaysia, Indonesia and New Guinea, probably due to human dispersion)[2]. However, the human disease, at least in its endemic form, seems to be not that old[6]. Some accidental cases of human infection must have occurred when man still inhabited the caverns and so entered into the enzootic cycle. In Chile, it was found 4.000 year mummies that were infected with *T. cruzi*[7]. During the mining cycle, in Brazil, when there was practically no deforestation, there is no evidence that triatomine bugs had adapted to dwellings; this started to happen during the agriculture cycle, when deforestation initiated, and in the cattle cycle, when deforestation was intensified[8]. Dwelling adapted triatomine bugs can only be found at deforested or savannah areas. In regions with dense forests, as Amazonia, there is no adaptation, though there are many species of triatomine bugs over there[9].

In the American continent, *T. cruzi* dispersion is considerably wide, specially speaking of sylvatic enzootic infection, which spreads from 42º N latitude, in the United States, till 49º S parallel, in southern regions of Chile and Argentine, including Guyanas and Caribees[10].

As Carlos Chagas had anticipated in 1909, the geographic distribution of endemic Chagas disease occurs in areas where there are anthropophilic triatomine bugs, adapted to human dwellings, from Mexico to south Argentine (Figure 1).

There are at least 44 identified species of triatomine bugs in Brazil, most of them sylvatic and, therefore, no dwelling adapted. Five species are considered domestic and epidemiologically important: *Triatoma infestans,* distributed from Rio Grande do Sul to some regions of Pernambuco, Paraíba and Piauí; *Panstrongylus megistus,* considered an important vector with irregular adaptation and distribution, spread from Santa Catarina and Rio de Janeiro, where it is sylvatic, to Minas Gerais and Bahia, where it is domiciled or sylvatic, and in other Northeast regions; *Triatoma brasiliensis* and *pseudomaculata*, also ubiquitous, may live inside or outside the dwellings, mainly in Northeast; and *Triatoma sordida,* which has a wide distribution, from Rio Grande do Sul to the southeast of Pernambuco and south of Piauí and sometimes occupies niches from where *T. infestans* had been eliminated. *T. sordida* is considered a vector of secondary importance.

Figure 1. Distribution of Chagas disease in the America's

Figure 2. Distribution of Chagas disease in Brazil

The fig 2. shows the endemic or under control areas in Brazil, the enzootic ones or with isolates cases.

Epidemiological determinants of Chagas disease

The existence of human chagasic infection depends on the presence of an efficient vector, on the existence of *Trypanosoma cruzi* reservoirs and on the existence of people exposed to the risk of infection. Infection transmission may also occur from individual to individual, through contaminated blood transfusion, from mother to child, through transplacental via, birth channel or breast-feeding, through *T. cruzi* infected food, or by accident, through laboratory contaminated material, infected animals' manipulation, or through organ transplant.

After the conception of "niche" being established by Elton, meaning animal behavior within its community, and after Pavlovsky's "natural disease foci" doctrine[11], the knowledge about enzootic transmission and distribution dynamic was renewed, among these, the Chagas disease one.

Nowadays, the notion of "space occupation" by man, for physical, social, economical, cultural or political reasons, has been extremely important for the study of infectious and parasitic diseases, specially in the case of Chagas disease that it is intimately related to social and economical factors[8].

Chagasic infection determinants

In the present work, it will be presented some determinant agents of chagasic infection, here understood as the penetration and multiplication of *T. cruzi* in human body, and of the disease, that is, the effects it causes and its morbi/mortality.

For the chagasic infection occurrence in natural conditions, it is necessary, firstly, a contact between susceptible people and *T. cruzi* infected triatomine bugs. It is also necessary the occurrence of many other variants, such as: contact intensity and "vector quality", as for instance, its anthropophilic level, infection rates, time between bite and defecation, number and volume of defecations within the unity of time, number of parasites eliminated, percentage of infecting forms and its penetration capacity, pruritus intensity and patient's sensibility for pruritus, what makes him to scratch bringing the parasite to the bite place or to the mucous membranes. Some species, although dwelling adapted, live far from man, in house roofs or basements, feeding from rats or any other animal; therefore, they are considered as having low anthropophilic level, such as *T. rubrofasciata.* Triatomine bugs infection rates are extremely important for infection transmission dynamic. A percentage of 10% of *T. cruzi* infected dwelling triatomine bugs is very high, considering transmission dynamic. Taking into account that infection transmission happens through faeces and urine of triatomine bugs, it is very important to consider time of defecation; triatomine bugs that defecate immediately after the meal or during the bite, as *T. infestans* and *P. megistus,* and deposit faeces at the bite area, have great importance for the transmission process. On the other hand, triatomine bugs that defecate after the meal, but already out of the patient, like *T. vitticeps*, have little or no importance in transmission. There are various studies about number and volume of evacuations, considering different species of triatomine bugs[12,13]. Number and volume of evacuations and number of eliminated parasites are obviously very important. A very interesting work has been done in our laboratory about the percentage of positive defecations and the number of eliminated parasites, considering 8 triatomine bugs species infected by *T. cruzi,* as presented in Table 1[14]:

Table 1. Relatioship between percentage of positive defecations of triatomine bugs and number of eliminated parasites

Triatomine species	% of positive defecations	Average number of parasites eliminated through defecation
P. megistus	55,1	232
R. prolixus	52,9	128
T. vitticeps	47,1	76
R. neglectus	44,4	276
T. brasiliensis	34,9	87
T. infestans	34,7	106
T. sordida	29,4	98
T. pseudomaculata	29,4	51
Average	42	132 parasites

This table points out the percentage of positive dejections and the low number of eliminated parasites. Obviously, not all eliminated parasites through dejection penetrate in the individual who become infected. This low level of inoculation may explain the great number of asymptomatic or oligosymptomatic cases, at the acute or initial phase of disease. On the other hand, depending on vector species, the percentage of eliminated infecting metacyclic forms may vary from 10% to 90%, according to the vector[15]. Still, the possibility of parasite penetration vary according to the pruritus intensity - as the host scratches himself, he may lead the parasite to the bite area and to the mucous membranes - and, possibly, according to parasite strain and host's local reaction. Experimentally, it was shown that only in 24% of mice, *T. cruzi* were able to penetrate through the bite point[16]. Studies indicate that the chance of an individual being infected by *T. cruzi* through a bite of infected triatomine bug, is 1 for 100 bites; obviously, taking into consideration all mentioned factors: exposition intensity, number of bites, percentage of infected triatomine bugs and total number of infected triatomine bugs; all of them are determining and important factors for infection.

Since transmission through blood transfusion was confirmed[17], it has been widely studied in Brazil. In a study accomplished in Rio de Janeiro, it was demonstrated retrospectively that, considering 24 individuals who received blood from patients with the chronic form of Chagas disease, 6 (25%) presented positive serology for infection and, among these, 3 (12,5%) had never left Rio de Janeiro, a none endemic area for Chagas disease; thus, they certainly have acquired the infection through transfusion.

Other ways of transmission are not common in Brazil, such as oral route, transplacental via, laboratory accidents, infected animals' manipulation and organ transplant; however in other countries, as Chile, the congenital form of infection occurs in almost 10% of newborns from chagasic mothers.

Disease determinants

Among the determinants of Chagas disease, it must be considered the *T. cruzi* inoculum in the initial infection and in the reinfections; strain characteristics and respective infecting clones; from one side, the histotropism determinants and from the other, the host reaction at cellular and humoral level, his chemical receptors and mediators. All those determinants are involved on disease pathogeny, which is very complex and have not been entirely explained.

The inoculum of initial infection is an important factor for illness development. Already mentioned studies, point that this inoculum, in

natural conditions, should be small, considering that the number of parasites in the triatomine bugs dejections after meal may vary from 51 to 276 in the analyzed vectors, but can reach a maximum of 1500 parasites, in one specific dejection[14]. Although this inoculum is absolutely inferior to those used for experimental studies: sometimes varying from 10.000 to 100.000 parasites for one mouse. It should be also considered that only a small part of the parasites that are on the patient skin are lead to the sting local or to the mucous membranes. The little inoculum in each infection, probably explain the discreet manifestations of infection initial phase, mostly not evident or oligosymptomatic. We have observed 510 chronic cases of Chagas disease, in Rio de Janeiro, for more than 30 years, and we verified that less than 1% referred acute form manifestations[18]. A survey that accompanied 544 individuals exposed to natural infection for 16 months, at an endemic region of Bahia, detected that only 14 (2,57%) have been infected and that only 5 of these presented manifestations compatible with infection[19]. Differently, another study that observed for almost three decades a great number of chagasic infection cases that had initial phase known, registered that the majority of severe chronic cases have had a serious acute form[20], probably due to a bigger initial inoculum. Another important determinant of illness severity is reinfection, as verified before. On the other hand, observing a series of cohorts from patients of non-endemic areas, we practically did not register any case of evolution from indeterminate form to severe clinical forms (cardiopathies and megas); differently from our field observations, where near 2% of these forms develop into cardiopathy, within a year[21].

Many studies have been accomplished about *T. cruzi* different strains and their experimental behaviour, about their morphological, biological, antigenic, biochemist and molecular characteristics and about its virulence and pathogeny. Experimental results, however, generally did not show any relation to patients' clinical manifestations, especially to those with the disease chronic form. At first, Chagas tried to relate the large and thin forms of *T. cruzi* and its sexual dimorphism[3], what has not been confirmed till now. Then, different strains of *T. cruzi* were classified in thin, large and very large (stout) and were related to a phase of the parasite cycle[22]. Others authors demonstrated an antigenic diversity of *T. cruzi* strains from different origins[23,24]; while clear pathogeny differences were detected in diverse parasite strains, however with no relation with antigenic differences[25]. After analyzing all those variations and also the regional variability of Chagas disease, we propose the designation of *"cruzi complex"* for this pathogenic conjunct[26].

A detailed study about morphological, biological and histopathological characteristics of different strains of *T. cruzi* has grouped the parasite into 3 different "biodemes", Type I, II and III[27,28], and tried to correlate them to "zymodemes"[29], to disease clinical forms, to the experimental pathology and to disease pathogeny[27,28]. Results indicate that there is no correlation between experimental findings and clinical manifestations, at least during the chronic phase of disease, as widely shown[30,31].

Recently, two phylogenetic lines of *Trypanosoma cruzi* were defined through DNA marker[32]; so, a group of researchers, gathered at Rio de Janeiro in April, 1999, agreed that they should start to be designated as *T. cruzi* 1, when corresponding to Zymodeme 1 and *T. cruzi 2,* when corresponding to Zymodeme 2[33]. Strains that were not characterized or do not have an exact characterization will be called *T. cruzi* and the hybrid ones, Z3 type, will maintain this designation, until future studies. Studies developed at the Amazon area, during the 10 latest years, pointed out that all *T. cruzi* strains isolated from humans, reservoirs and sylvatic vectors are *T. cruzi* 1 or Z3 and present low virulence, low pathogenicity for trial animals and low morbidity for patients[34-36].

Chagas disease pathogenesis

Chagas disease pathogeny is not completely understood, at least regarding to the chronic phase of disease. In acute or initial phase of infection, it occurs a parasitemia and the parasites spread all over the host's body, multiplying inside the macrophages and in many others cells, mainly on spleen, liver, lymphonodus and interstitial conjunctive tissue with type I strains (*T. cruzi 1*), myocardium with type II strains (*T. cruzi 2*) and skeletal muscles with type III strains[37]. Once in the tissue, the parasite replicates under the form of amastigote, forming pseudocysts that disrupt and lead to a mononuclear inflammatory reaction, with necrosis; the parasite liberates antigens that adhere to the surface of neighbour cells, which become targets for immunocellular and humoral response to *T. cruzi.*[38] Some parasites are destroyed *in loco* and others, as trypomastigotes, return to circulation and adhere and penetrates to others cells, reinitiating the cycle[39].

During the acute phase, a transitory phenomenon, there is inflammatory reaction, necrosis, neural destruction and fibrosis; the process continues probably because of an autoimmune mechanism together with the participation of the parasite and its antigens. Latest, Chagas disease immunopathology has been widely reviewed[40,41].

In the chronic phase, Chagas disease pathogeny seems much more complex. Disproportion between myocardial fibrosis and parasite presence in lesions lead to the autoimmunity theory, which has prevailed since the 70's[42-44]. Köberle[45] tried to explain the disease pathology and its syndromes from neural destruction, in the acute phase, and the consequences in the chronic phase; however, neither autoimmunity, nor neural destruction can explain the whole etiopathogenic factors. Lately, the chronic chagasic myocardiopathy is trying to be explained, through histochemical studies and confocal laser microscopy, as the result of multiple factors: myocarditis, immunodepression, fibrosis and microvascular dilatation, presence of *T. cruzi* and its antigens and an improper response from the host[46,47]. Although very interesting and remarkable in many aspects, the study does not explain properly the disease indeterminate form, does not refer the digestive form mechanism and does not relate them to the parasites strains and clones, in the disease pathogenesis. One of the most promising studies to explain the Chagas disease pathology is that of the clonal-histotropic model, which is in development and which relates the genetic variability of *Trypanosoma cruzi* and its implications for illness pathogeny[48].

Chagas disease morbi-mortality

In the acute phase, Chagas disease morbidity is relatively low, most cases are asymptomatic or oligosymptomatic. Severe cases, in this phase, present high fever, hepatosplenomegaly, generalized adenopathy, abatement, tachycardia and another signs of acute myocarditis and meningoencephalitis. Among most serious cases, until 10% may evolve to obit; the great majority of them, presenting meningoencephalitis, which is often fatal in children under two years old, according to records of Carlos Chagas himself[49].

In the disease chronic phase, at least 50% of cases stay in the indeterminate form, obviously differing from one area to another. Our field study at different endemic areas in Brazil did not register any case of this form that had evolved to obit within a period of ten years; although 2% of these cases may evolve to the first degree of cardiopathy within a year at endemic areas - what does not happen at non-endemic ones[50,51].

Cardiac chronic form is more expressive with regard to clinical manifestations and prognostic, due especially to the ventricular arrhythmias

and auricle-ventricular block characterized by palpitations, fainting, lipotimic episode and syncope, with sudden death due to ventricular fibrillation, in 2/3 of cases. Near 1/3 evolves to dilated cardiomyopathy and death due to myocardial collapse. We can delineate three prognosis patterns for chagasic cardiomyopathy: there are some cases that develop restricted lesions, like isolated right bundle branch block, and so remain for the whole life, as the illness process had suffered a pause. Other cases present complex arrhythmia, multifocal extrasystoles, paroxistic tachycardia, auricle fibrillation and right bundle branch block with left anterior hemiblock and atrioventricular block of third degree, with severe prognosis. A third group of patients has an uncertain prognosis; those who present discreet increase of cardiac area and electrocardiographic complex arrhythmia and other cardiac manifestation[18,21].

Chronic digestive form is characterized through manifestations of colon and esophagus disperistalsis, due to neural destruction of esophagic and mesenteric plexus, what leads to megaesophagus and megacolon. In the case of megaesophagus, there is difficulty for swallow, and there is constipation in great part of megacolon cases; though near 40% of these cases does not present these kind of symptoms. Generally, the prognosis for disease development and life is good, except for those presenting complications, as megaesophagus cancer or megacolon torsion or occlusion, what may lead to death. Figure 3 shows the distribution of 510 patients from various Brazilian states, observed in Rio de Janeiro, according to clinical form and age[18].

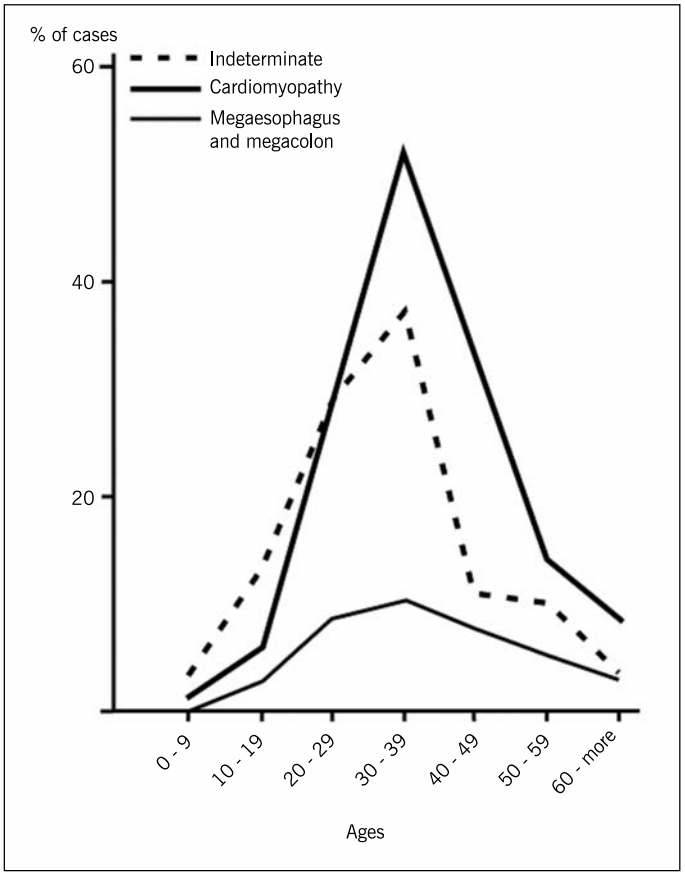

Figure 3. Distribution by clinical forms and ages of 510 cases of Chronic disease[19]

We have developed studies at different regions of Brazil that indicate Chagas disease evolutionary and severity patterns in a quite distinct way. In four areas of Minas Gerais State, northeast and west of the state, electrocardiographic gradient, that means, the difference for more in the alterations related to the control group, has varied from 18.4% to 22.4% and in two regions of Piauí State, the gradient was 18.2%. Cardiomyopathy evolution in different areas varied from 2,5% to 3% patient/year and lethality reached 2% a year, while in eight interior districts of Paraíba State, the ECG gradient was 12.8%, cardiomyopathy evolution reached 1.3% patient/year and lethality only 0,4% patient/year. In 12 districts of Rio Verde Region, at Mato Grosso do Sul State, ECG gradient was 13.8% and cardiomyopathy evolution and lethality (still in evaluation) seem to be low. In some regions of Rio Negro, Amazon State, ECG gradient is practically null and cardiopathy evolution and lethality, extremely low[35,36].

Etiological treatment

The ideal drug for Chagas disease treatment should fulfil the following requisites, according to World Health Organization:

- promotes parasitological cure of acute and chronic cases;
- is efficient in a single dosage or few ones;
- has a low price and is accessible to patients;
- do not produce collateral or teratogenic effects;
- do not require hospitalization for treatment;
- do not induce a parasitic resistance. Any drug tested, till the moment, has not fulfilled at least the first four requisites.

Almost one hundred drugs have been tested, but with few effective results, such as: quinoleine derivatives, various antimalarians, arsenicbenzol and others arsenics, fenantridines, salts of gold, bismuth, zinc, copper, sodium iodide, gentian violet, aminopterine, paraminosalicylic acid, hidracide of nicotinic acid, ACTH and cortisone, derivatives of estilomicine, amphotericin B, more than 30 antibiotics and some nitrofurans.

The first clear evidence of experimental cure of chagasic infection has been obtained through the use of nitrofurazone, in a long duration scheme with mice; in that opportunity, it was registered the cure of 95.4% (62/65) of the animals treated[48]. At the end of the 60's and beginning of the 70's, two drugs appeared, nifurtimox and benznidazole, considered the first effective drugs for human chagasic infection treatment in acute and initial phase; however they present very low cure rates in the chronic phase, need to be taken for long periods (30 to 60 days) and present important collateral effects[52,53]. However, these drugs are the only options for clinical use, at present.

The collateral effects of nifurtimox clinical use are: anorexia, weight lost, excitement or lethargy, and digestive episodes, such as nausea, vomiting, intestinal cramp, and diarrhoea. Other side effects from nervous system are polineuritis, insomnia, tremor, fainting and hallucination. Adverse effects of benznidazole may be classified into three groups:

- Hypersensibility symptoms, dermatitis with cutaneous eruption, generalized oedema, fever, muscular and joint aches;
- Bone marrow depression, thrombocytopenic purpura and agranulocytosis, the most severe manifestation;
- Polineuralpathies, paresthesias and polineuritis of peripheral nerves. Beside the collateral effects, the great disadvantage of both drugs is the necessity of long term use (60 days), and little effect in chronic cases and in disease evolution. The treatment is indicated in the acute or initial phase of infection for children under 12 years old and in cases of chronic phase, according to medical prescription.

Four drugs are being tested, in different forms and schemes, on chagasic infection, but with no guaranteed results: allopurinol, cetoconazole, fluconazole and itraconazole. Allopurinol 1,5-dihydro-4H-pyrazolo [3,4-d] pyrimidin-4-one is analogue to hypoxanthine and hinders or reduces uric acid through xanthine-oxidase inhibition and through blockage of purines biosynthesis, reason to be widely used in hyperuricaemia treatment. Although some initial in vitro studies have indicated its activity on trypanosomatides[54], studies considering patients on Chagas disease acute phase revealed an absolute inefficacy[55]. The action of this medication on the evolution of chronic undetermined forms cases and on the treatment of *T. cruzi* reactivation, after heart transplant and immunosupression, must be better analyzed. Antifungic cetoconazole (nitroimidazole) and the triazoles fluconazole e itraconazole have demonstrated, experimentally, healing effect in acute phase[56]; nevertheless, tests with cetoconazole in human infection chronic cases and in the disease reactivation in AIDS cases revealed its inefficacy[57,58] Other clinical studies developed with cetoconazole, fluconazole and itraconazole, in the disease chronic phase, also must be better evaluated. Recent studies with a fluconazole isomer, D 0870 compose, used in *T. cruzi* infected mice, considering acute and chronic phases, revealed a parasite suppressor effect 30 to 50 times higher than that obtained with cetoconazole and nifurtimox.

Chagas disease Control and Reemergence perspectives

In the latest 20 years an important work has been developed in order to control *Triatoma infestans,* Chagas disease's main vector, in Brazil and in South Cone, Argentine, Chile, Uruguay and Paraguay, where, from 1991, the "South Cone Initiative" represented a great impact regarding disease control. Uruguay and Argentine were officially certificated free from transmitting human Chagas disease in 1997 and 1999, respectively. In Brazil, there were 711 districts, in 11 states, infested by *T. infestans,* in 1983; in 1997, however, it was registered a significant reduction in these numbers, and less than 100 districts still reported the vector presence. Some states, as Goiás, Mato Grosso do Sul, Paraíba, Rio de Janeiro, São Paulo and, latest, Minas Gerais were certificated free from *T. infestans*[59].

Lately, as dengue cases increase in Brazil and, consequently, there is a great demand of material and human resources for its control, Chagas disease control, including *T. infestans* eradication program, has been neglected, particularly, if we consider the decentralization of Fundação Nacional de Saúde (FNS) for states and districts, which do not have technical skills nor political power to decide about disease control. It should be considered, then, the worrying possibility of a *Triatoma infestans* reemergence, as well as Chagas disease as a whole, from the residual focuses of the insect, in five Brazilian states. On the other hand, we should consider the wide distribution of *Panstrongylus megistus* and of *Triatoma brasiliensis;* as they are ubiquitous and may live inside or outside the residences, they cannot be eradicated. Other vectors, also considered dwelling adapted, as *Triatoma pseudomaculata*, in Northeast of Brazil, and *Triatoma sordida* should be considered too.

Emergence of Chagas disease in Brazilian Amazon and the risks of the disease become endemic in that area are the major concern of epidemiologists dedicated to the disease's study[9,35,36,60,61]. It is alarming that at least 16 species of sylvatic triatomine bugs, 10 of which infected with *T. cruzi,* and several infection reservoirs have already been described over there, as well as increasing number of acute infection cases have been reported on that vast area that occupies a third part of Brazilian territory[60,61]. For the next years, we should worry not only about primary vectors (*T. infestans, P. megistus* e *T. brasiliensis*), secondary vectors (*T. pseudomaculata e sordida*) and tertiary sylvatic vectors, but also about the risks of they becoming adapted to dwellings, about blood storage control and about *T. cruzi* direct transmission from marsupials to human beings, through urine and odoriferous secretion, as experimentally demonstrated[62]. This way of transmission and other alternative ones, especially via oral, should be constantly watched. Finally, from a physician point of view, we must realize that for the next 30 years we will still have a huge number of patients already infected to be treated, according to etiological point of view and/or clinical support, pacemaker implantation and hospitalization, procedures that represent very high social and economical costs.

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