Chagas Disease: Treatment in pediatrics patients

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Chagas’ is a disease that can be found in the American continent, in an area between 42° North and 45° South latitudes, where it infects about 16-18 million people. Some 100 million people, a quarter of the entire Latin American population, are at risk of acquiring the etiologic agent: *Trypanosoma cruzi* (1). A World Bank report shows that Chagas’ disease is the fourth cause for economic loss due to its morbidity, only after severe respiratory diseases, diarrhea and AIDS/HIV (2).

Struggle against this endemic entity points to the control of vectorial transmission and treatment of infected individuals. The sustained fight against the vector of this parasitosis and a better control of blood banks, particularly through the Southern Cone Initiative, brought about a halt to or lessening of new acute cases in several countries (3).

Despite the above, there are currently millions of infected children and adults and new cases of vectorial and congenital Chagas appear continuously. As regards the treatment of Chagas’ disease, while there is no ideal drug, as is the case with most diseases, the action of specific drugs has been shown to be very effective in acute vectorial and congenital infections. Research carried out in recent years has shown good results in children and teenagers during the undetermined phase too, as well as some improvement in adult patients, so much that in a meeting with experts organized by the WHO in 1998, the treatment was recommended for every infected patient (4).

This is an important fact to underline as it is still frequent to find publications with concepts such as “Chagas’ disease is a chronic and incurable parasitic infection…” (5).

Drugs are particularly effective in the pediatric age for their greater parasiticidal effect and lesser side effects than in adults, and its effect is easier to prove.

The implementation of parasiticidal treatment grew because of the parasite presence in the chronic disease pathogenesis was recognized (6) and new curing criteria were developed.

The source and transmission of this parasite is through the feces of triatominae inoculated when the bug bites, blood and hemoderivates transfusions, placenta and transplanted organs.

Notwithstanding the above, three phases are recognized in the evolution of this infection. Such phases exhibit different clinical and laboratory features:

a) **Acute**: the patient has high parasitemia, which can be detected through direct methods; in some cases, the patient can be negative for conventional serology; a small percentage has clinical manifestations.

b) **Undetermined**: the individual and the protozoan establish a balance, parasitemia is low and diagnosis is confirmed by means of two reactive serologic tests. The patient is asymptomatic.

c) **Chronic**: around 20% of patients in the undetermined stage develop lesions in the heart, digestive tract and peripheral nervous system 10-30 years after the parasite has entered the patient's body.

**LABORATORY DIAGNOSIS**

As in any other infectious disease, diagnosis is established by

- recognition of whole or fragments of parasite in blood or tissue;
- detection of specific antibodies.
a) Parasitologic Test

- **Direct**: Microhematocrit (MH) (7), Strout, Fresh drop, Thick drop.

These techniques are necessary for diagnosis and control of treatment in children with acute vectorial and congenital infection in their first months of life. We recommend MH in pediatrics as it only requires drawing 0.5 cc of blood, it may be carried out in non highly specialized laboratories and it is performed in 25 min. In this phase diagnosis sensitivity is near 100%.

- **Indirect**: Xenodiagnosis (Xd), Blood culture (BC).

These methods bear greater sensitivity than direct ones but they are only performed by some specialized laboratories. In the undetermined and chronic stages, sensitivity varies from 10% to 90%. These tests are not necessary to treat patients and are used in research centers.

b) Serologic Tests

The most widely used techniques are known as **Conventional Serology** (CS): Indirect hemagglutination, Indirect immunofluorescence, ELISA, Direct agglutination. These tests are useful for diagnosis during the undetermined and chronic phases and to asses therapeutic response.

c) New techniques

Difficulties to carry out diagnosis in some patients and to define cure brought about the development of new tests:

- Polymerase chain reaction (PCR), Lytic antibodies, ELISA using some parasite-defined antigens (GP 57/51, Shed antigen, P29) and synthetic peptides (8).

These tests still require further experimentation before they prove useful. They will have to be easy-to-perform and low-cost before they can be used at large scale.

**Topé**

PARASITICIDAL THERAPY

The use of parasiticidal drugs in human beings pursues two goals:

- To eradicate the parasite
- To avoid or improve organic lesions

Approximately 100 drugs have been tested since 1930s, but a small number has been used in humans. Stoppani (9) makes the following classification of parasiticidal drugs:

a. Drugs with clinically recognized use: Nifurtimox (Nf) and Benznidazol (Bz).

b. Drugs that are effective in experimental *in vivo* models, with no general clinical application: Ketaconazole, Itraconazole, Allopurinol, Anfotericine B.

c. Drugs that are useful for transfusion bags: gentian violet.

d. Drugs that are useful in experimental models with foreseeable clinical usefulness: *T cruzi* cysteine-protease-inhibiting peptides.

Benznidazol (2-Nitroimidazol) and Nifurtimox (5-Nitrofurano), the drugs of use in human beings, were first administered in 1970s. Both have an action on the *T cruzi* genome, and inhibit the synthesis of DNA, RNA and proteins.

We mention Nf because it has been used in a large number of studies, but unfortunately it is no longer manufactured.
Dose and schedule differ according to authors. Side effects of Bz and Nf are: lack of appetite, sleep difficulties, restlessness, leukopenia, thrombocytopenia, skin allergy. The percentage of children with these manifestations varies according to the publications, but interruption of drug administration for the above causes is exceptional. If a very intense allergic reaction takes place, an antihistaminic may be added. These side effect cease when drug therapy is discontinued.

**CURE CRITERIA**

Cure criteria evaluation implies considering clinical and parasitologic aspects.

**A) Clinical criteria**

There are situations where infected children have clinical manifestations with different severity.

- Intrauterine infected newborns: approximately 40% have clinical manifestations at birth (10).
- Patients with immunodeficiency: we have seen children from mothers infected with *T. cruzi* and HIV (11) who acquired both agents, and children with congenital immunodeficiencies.
- Acute infections in immunocompetent children.

**Treatment response in these patients is usually successful: improvement or remission of clinical manifestations can be observed in the short term.**

However, **children infected with *T. cruzi* are mostly asymptomatic**. In these cases, the therapeutic aim is to eliminate the parasites to avoid possible future organic lesions. We observed no cardiologic alterations in a group of children who were parasitologically cured and followed up for 15 years.

**B) Parasitologic Cure**

Parasite elimination is assessed by serologic and parasitologic tests.

**a) Serologic tests**

Paradoxically, **true parasitologic cure is determined by persistent negative CS after the treatment is over** (12, 13). Negative serology means that the host has neither parasites nor antigens stimulating the immune system and producing antibodies. In acute vectorial and congenital infections we have observed that CS became negative during treatment or after few months it was over (14, 15).

**During the undetermined phase, negative CS may take months or even years to appear, depending on the age of beginning the treatment.**

In our experience, the last technique to become negative is ELISA.

Another element that may be observed is **reduced antibody titration** in samples taken after the end of treatment. This parameter points to drug effectiveness, but not to remission (16).

A small group of patients may **become its serology spontaneously negative** (17).

**b) Parasitologic tests**

- In acute vectorial and congenital infection, parasitemia detected at diagnosis through direct methods usually becomes negative at day 15 of treatment (14).
- In the undetermined phase, patients positive for Xd or BC before drug therapy also tend to become negative for those tests during or at the end of treatment (13).

These facts shows that the employed drug is useful for the patient, however, parasitologic tests in some individuals have became positive after some years.
In order to state that there has been remission, negative parasitology must accompany negative serology.

c) The use of lytic antibodies (CoML) (18) is an attempt to incorporate a new cure criterion in patients persistently positive for CS at the end of treatment. CoMLs recognize trypomastigote epitopes and are positive while circulating parasites are present.

CoML test is a diagnostic tool to assess parasitological cure after specific therapeutics, based on data in treated mice and patients (negative for CoML and parasitological tests for many years) (19). CoML is consistently positive in non-treated patients and animals with ongoing infections detected by means of repeated BC. Treated pediatric patients showing positive for CS, and negative for CoML and BC may be now considered to be cured; several hypotheses have been developed to account for CS persistence (16).

The study of CoML is very complex, but fortunately several parasite molecules that recognize lytic antibodies have been recently discovered. The use of ELISA with gp 160 molecules (21), T-DAF (22), Shed antigen(23) and 24 kDa (24) offer similar information as obtained by CoML, with the advantage of easy execution.

Notwithstanding these concepts, Cancado stated "A diagnostic test based on only one epitope, or a small set of epitopes, in an infection caused by such a complex parasite as T cruzi needs further evaluation" (25).

d) Another promising tool is PCR, which has been used to detect T cruzi in the blood of chronic and acute chagasic patients. Recently, a strong correlation has been reported between positive PCR and CoML results among chagasic patients, suggesting that PCR could be effective in evaluating parasitologic cure in patients who received specific treatment (26).

With regard to cure criteria we must point out that there are two possibilities depending on how specialized the Institution is:

a) Assistance common services:

At these centers, CS and some direct parasitologic technique (MH, Strout) are enough to establish the diagnosis and to follow up treated patients. In these cases, cure criteria are:

- **Acute infection** (vectorial, transfusional, transplacental): negative CS and negative direct parasitologic tests
- **Undetermined phase infection**: negative CS.

b) Research centers:

At these centers, other serologic and/or parasitologic methods are investigated to improve cure criteria, especially in patients who still have reactive CS after being treated.

TREATMENT CRITERIA

Every child with positive serologic and/or parasitologic tests must be treated.

Patients with recent infections show very good and easily evidenced response to drugs (14).

Curing of children in the undetermined phase is also very good but some require many years of follow-up before total cure can be demonstrated (13).

CONGENITAL CHAGAS’ DISEASE

In order to define whether a child has congenital Chagas' disease, the infant must: not have received any transfusions, not have remained in an endemic area and his mother must be serologically reactive.

Diagnosis is carried out:

- In the first months of life by the presence of the parasite in blood. We recommend the Microhematocrit
technique as it has 94% sensitivity. If the child has MH negative, must perform CS at 7 months old.
- After seven months old, the patient must have two reactive serologic tests (10).

**Treatment response is excellent, in our experience, success rate in children treated in their first year of life is close to 100%** (27). Therefore, early detection in these children is essential, **it is necessary to screen all newborns born from reactive mothers.**

In low birth weight infants, we start with Bz 2-3 mg/kg/d; then, if no alterations in the liver function test and hemogram are observed after 7 days, we administer 5-7 mg/kg/d. Children over 3,500 g. are given directly 5-7 mg/kg/d with hemogram and liver function test at day 10. Drug therapy may last 30-60 days.

If the infant has detectable parasitemia, the MH test must be performed 15 days after starting treatment. When therapeutics is effective, patient becomes negative for MH.

Causes for persistent parasitemia are: wrong dose, difficulties in taking medication or resistant protozoan strain.

When treatment is finished, a serologic test must be carried out every 3 to 6 months in the first year and yearly thereafter. **Total cure is when 2 consecutive samples remain CS negative;** after this, no further serology is required.

Clinical and cardiologic controls (EKG, and eventually echocardiography) are required at diagnosis and yearly thereafter.

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**ACUTE CHAGAS’ DISEASE**

Chagas' disease is termed acute in the first 60-90 days after the protozoan has entered the body, whatever the infection source may be.

- **Vectorial.** Fortunately, in countries where the struggle against the vector has been implemented, the number of theses patients has been reduced (28). Only children with symptoms at the beginning of the
infection are detected. Generally, they account for about 10% of total. The most frequent manifestations are temperature, hepatosplenomegaly, inoculation chagoma, and edema.

- **Transfusional.** We have observed this type of acute Chagas' disease in children with leukemia, congenital immunodeficiency, and fetal erythroblastosis.

**Diagnosis must be carried out through the search of the parasite in blood by direct methods; some patients show to be negative for CS (15).**

The treatment is Bz 5-8 mg/kg/d for 30-60 days. If child has immunodeficiency, this period is longer.

Cure criterion, clinical, parasitologic and serologic controls are similar to those for congenital Chagas' disease.

**CHAGAS IN THE UNDETERMINED PHASE**

Children are asymptomatic, they show two reactive serologic tests; parasitemia is very low and it cannot be detected through direct parasitologic methods.

The treatment is Bz 5 to 7.5 mg/kg/d for 30 to 60 days. An hematologic control is performed 10 days after the beginning of therapy.

At the end of treatment, serology must be done every 4 to 6 months during the first year and annually thereafter. **Becoming negative for CS, the cure criterion, takes longer if the child has been infected for a longer time.** There are patients who become negative for CS only 4 years after the treatment was over. Clinical and cardiovascular examinations must be performed annually.

**DIFFERENT EXPERIENCES**

There are several reasons why assessment and comparison of results in different studies on treatment are difficult: patients inclusion criteria, drugs and doses used, follow-up periods. On the other hand, most studies have been carried out in adults.

**UNDETERMINED PHASE**

- Ferreira studied 100 patients, mostly children and teenagers. All of them had 3 reactive serologic tests and were positive for Xd. The author treated them with Nf 10-15 mg/kg/d or Bz 5-8 mg/kg/d (29). Two years later, 8% proved to be negative for CS; these patients were followed up for 6-18 years and none had EKG, colon or esophagus alterations.

- Bustos studied 67 children and adolescents, 52 receiving Nf for 120 days and 15 placebo. Three months later, none of the treated patients had negative CS, but a fall in antibody titration could be observed (30).

- Del Barco studied 80 children (18 months - 14 years). They all had positive CS and Xd was positive in 63% of 38 assessed children. They were treated with Bz and Nf and Xd became negative in all (13). In 35 children (median age 9 years) with long follow-up, CS became negative in 63%.

The importance of follow-up time to define cure is highlighted in these studies. The highest percentage of cured patients could be observed in the study where follow-up was longer.

*Argentina: 106 children (age range: 6 to 12 years) were studied with 3 CS methods and 1 ELISA, employing a flagellar recombinant antigen of trypomastigote, F29. Fifty-five children received 7.5 mg/k/d Bz for 2 months and the remainder placebo (17). After 2 years in the treated group it could be observed: - CS titration fell significantly, - CS became negative in 11.3% and - F29 became negative in 62.1%*

*Brazil: 129 children (age range: 7 to 12 years) were studied with 3 CS techniques and Chemiluminescent-ELISA (CL-ELISA) using a purified trypomastigote glycoconjugate (AT antigen) that evaluates lytic antibodies. 64 were treated with Bz 7.5 mg/kg/d for 60 days and the remainder received placebo (16). After 3 year in the treated group it could be observed: - the initial geometric measure of CS titration was*
reduced fivefold versus the placebo group. CL-ELISA was negative in 58%.

These two WHO funded studies used a cure criterion outside CS. Cured patients were defined as those who become negative for antibodies to specific trypomastigote antigens (F/29, CL-ELISA). Thus, 58% and 62% of patients were deemed cured despite positive CS.

ACUTE VECTORIAL CHAGAS' DISEASE

- Barclay treated 86 children with Bz 5-7.5 mg/kg/d Bz for 2 months. After 18 months, 87% was cured as evidenced by parasitemia and negative CS or significantly lower titration (31).
- One of the largest studies was carried out among 601 patients, 550 of whom were treated with 15 mg/kg/d Nf and 51 were on placebo. At the end of a 24-month follow up period, Cerisola arrived at several conclusions:
  > only 65% showed reactive CS at the time of diagnosis
  > 81% was cured (negative CS)
  > cured patients showed different CS curves during follow-up (28).

- There are other experiences showing lower cure percentages in the treatment of this phase of Chagas' disease (32).
- As regards our Laboratory, 80.3% of patients were shown to be cured.

CONGENITAL CHAGAS' DISEASE

- Zaidenberg treated 12 infected newborns. MH was positive in 11/12. Bz (30 days) began during the first week. One non respondent showed excellent response for Nf. All 12 newborns were cured, parasitemia was negative at 15 days of treatment and CS between 4 and 8 months, except for one infant who was treated on two occasions (14).
- Forty three children treated early (before 16 months old) with Nf became permanently negative both for parasitologic and serologic tests (27).
- Streiger treated 9 children with congenital infection. He used Bz for 1 month or Nf for 2 months. The 7 children who could be studied at the end of treatment became negative for CS and parasitemia (33).

These and other studies with similar results prove the effectiveness of early therapy.

The following data summarize the experience in our laboratory:
- Children were treated with Nf. In April 2000 we started using Bz.
- Parasitemia was assessed with MH and CS method was ELISA. Indirect hemagglutination test and eventually Direct agglutination.
- We treated 223 children with the following characteristics:
  Way of infection: Congenital 62%, Unknown 22%, Vectorial 13%, Transfusional 3%.
  Age: Average 41 months, median 15 months (range 3 days – 204 months)
  We treated 5 newborns who had acquired T cruzi and HIV
  - Cure criteria: negative CS
    * Patients below one month: 100% were cured.
    * Patients up to 3 years old who were followed-up for 3 years: 97% were cured.
    * Patients above 3 years old with 6-year follow-up: 81,3% were cured.

CONCLUSIONS

- Treatment is highly effective in children and teenagers.
- The diagnosis and control of treatment may be done with CS and a direct parasitologic method (MH).
- Cure criterion is negative CS.
- Becoming negative for CS may take months or years.
- The other parasitologic or serologic methods are being studied and are not for large-scale use.
BIBLIOGRAPHY