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Screening, prevention and treatment of congenital Chagas disease

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Epidemiology and transmission	**Evidence-levels**
Chagas disease (CD) is a chronic parasitic infection caused by *Trypanosoma cruzi*. It can be acquired through the following routes by order of decreasing frequency: (a) vectorial transmission through the contact of mucous membranes or skin wounds with dejections of infected triatomine bugs (vectors); (b) ingestion of food contaminated with dejections of infected vectors; (c) congenital transmission from an infected mother; (d) infected blood-component transfusion and e) organ transplantation from an infected donor; and f) rarely laboratory accident. There are about 6 to 7 million people worldwide living with the disease and 70 million at risk. The highest disease prevalence is found in continental Latin America. However, due to increased population movements over the past decades the disease has spread to the USA, Canada, many European countries, Japan and Australia. Outside Latin America, congenital transmission is considered to be the main mode of transmission. Since 2018, World Health Organisation (WHO) has switched from control to elimination of congenital CD disease and it is one of the objectives of the 2021-2030 WHO road map of neglected tropical diseases, unanimously endorsed by the 73rd World Health Assembly, in November 2020.	
CD has an initial acute phase usually followed by a chronic phase in absence of early therapy initiation. During the acute phase, most patients are asymptomatic but can also present nonspecific symptoms such as malaise, fever, edema, and anorexia. Two-third of lifelong chronic infections remain asymptomatic. One third of patients at the chronic stage develop clinical manifestations, one to three decades later, particularly cardiomyopathy associated with conduction blocks, arrhythmias and congestive heart failure leading to an increased risk of cardio-embolic events. Digestive, neurological or mixed alterations are present in up to 10% of patients. Typical CD manifestations include dyspnea, sudden death, cerebro-vascular events, dysphagia and severe constipation. Immunosuppression greatly increases the risk of complications and fatal outcomes. Currently, the efficacy of available antitrypanosomal therapy varies depending on the duration of infection as well as the age of the patient and the existence of clinical manifestations and complications. Treatment is highly effective among neonates and young children and is usually well tolerated [1-3].	Ib
Implications for pregnant women and their infants in Switzerland	
In Switzerland, the overall prevalence of CD among pregnant women from Latin America origin is estimated to be around 4%. Importantly, pregnant women from Bolivia tend to have higher prevalence rates with average values around 15% [4]. The majority of these pregnant women infected with *T. cruzi* are in the chronic stage of the disease and have no or mild symptoms.	
According to the current evidence, in regions where the triatomine vector is not present, congenital transmission rates from chronically infected mothers range from 2.7% to 3.5% [4]. The transmission rate can be much higher in women in the acute phase, and those with a reactivation of the disease due to immunosuppression. The majority of infected newborns are asymptomatic at birth, but at risk of developing long-term complications in the absence of treatment. Up to 28% of the children may develop mild to severe	

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clinical manifestations.

Hepatosplenomegaly is one of the conditions most frequently reported, followed by low birth weight, prematurity, low Apgar score, anemia, thrombocytopenia and jaundice [5]. Severe complications—such as meningoencephalitis, pneumonitis, or anasarca—and even death can occur in infected infants but are rare.

The potential benefits of **screening** are:

A. Primary prevention of congenital transmission through treatment of childbearing age women prior to conception. The administration of treatment to women chronically infected with Chagas disease outside of pregnancy has been shown to prevent congenital transmission. [6-9]. However, the effect of the timing of treatment before conception remains uncertain. — IIb

B. Adapted pregnancy follow-up for CD-infected women and secondary prevention of congenital CD by early treatment of the infants. Pregnant women with CD shall be followed accordingly to reduce the risk of complications. Also, early detection of congenital infection among exposed newborns allows early treatment to prevent immediate and long-term complications with treatment efficacy rates > 90% when given in the first year of life [1, 10]. — Ib

C. Secondary and tertiary prevention of long-term complications among chronically infected women through postnatal treatment. Treatment of chronically infected patients without signs and symptoms of disease has been shown to reduce the risk of subsequent clinical manifestations and complications, especially when the treatment is given prior to 40 years of age. Among those patients, efficacy rates range from 40 to 70% [11-13]. Debate exists about the impact of treatment given to young too middle-aged patients at the chronic stage with early signs of organ damage [14, 15]. — IIa / IV / III

D. Identification of silent infections among the family group. Adopting a family screening strategy prompted after the identification of an infection in a pregnant woman leads to uncovering other infections among the household members who might be at risk of infection [16].

Whom to screen?

A screening strategy during - reimbursed by the insurance- and before pregnancy - not currently reimbursed if done for prevention - is cost-effective when considering an expected prevalence > 0.06% to 0.9% [17-19].

Women should be considered at risk of CD if they or their mothers are original from one of the following south- and central-american countries: Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, and Venezuela (Bolivarian Republic of). Screening should be proposed to all pregnant women from the above-mentioned countries. Screening should also be proposed to women coming from countries where the disease is endemic and have suggestive cardiac/digestive symptoms and/or have an immunosuppressive condition [20,21]. — IIb

In addition, screening should be offered to pregnant women with a history of blood transfusion in Latin America, and pregnant women that report cases of CD among family members. — III

Laboratory tests and clinical management

Non-pregnant childbearing age women at risk:

- Serological testing for *T. cruzi* antibodies (ELISA or Rapid Immunochromatographic test) is recommended for screening women at risk of CD with a second confirmatory test in case the first test result is positive [22]. PCR, or a third serological test with different antigen target can be used in case of discordant serological results in a specialized laboratory. The woman shall be informed that the test might not be covered by the insurance. — Ib/IIb
- In the case of a positive diagnosis, medical history and evaluation by an infectious diseases/internal medicine specialist is recommended to identify whether the patient may have any CD manifestations and may require further diagnosis procedures, as well as for patient's treatment.

• Available treatments include Benznidazole, 5 mg/kg daily (max. 300 mg/day), or Nifurtimox, 8–10 mg/kg daily, for 60 days [27, 28]. In general, Benznidazole has been more studied in clinical trials and is better tolerated and considered the first line treatment by most experts. The total daily dose of Benznidazole is usually given in two doses, preferably after meals. Nifurtimox is administered every 8 hours, also after meals.	III
Pregnant women at risk	IV
• Serological testing for *T. cruzi* antibodies (ELISA or Rapid Immunochromatographic test) is recommended, ideally in the first trimester, with a second confirmatory test in case the first test result is positive [22], and PCR, or a third serological test with different antigen target in case of discordant serological results.	III
• In case of a positive diagnosis, detailed medical history and ECG are needed. An evaluation by an infectious or tropical diseases' specialist to assess CD manifestations that require further diagnosis is recommended. Fetal growth should be monitored in case of a positive diagnosis in the mother [26].	III
• During pregnancy, antiparasitic treatment is contraindicated because the risks of using the available medicines on the fetus are unknown [23-24], and the risk of adverse reactions in adults is moderate-to-high.	IIb
• Maternal treatment with antitrypanosomal therapy should be started after the breast-feeding period. Effective contraception should be assured [26].	
Newborns	IIb
• Newborns should be considered at risk and evaluated by the pediatrics services for congenital CD if: (a) the mother has been diagnosed with CD; (b) the newborn has signs suggestive of CD and the at-risk mother's CD status is unknown [29, 30]. Signs in newborns include low birth weight, prematurity, hepatosplenomegaly, anemia, thrombocytopenia in milder cases and meningoencephalitis, pneumonitis, or anasarca in severe cases. Most newborns are asymptomatic though, which must not prevent immediate screening at birth.	
• The diagnosis in neonates should be performed at birth using PCR in a sample from the newborn peripheral blood or from the umbilical cord (if no maternal blood contamination) [29, 30]. For those facilities where services are available, microscopic detection of the parasite through microhematocrite technique may also be implemented. In the event of a positive result in cord blood, the test must be repeated in peripheral blood because of the possibility of contamination by maternal blood.	III
• If the PCR and/or microscopictest performed at birth are negative, testing should be repeated at 1 month and at 9-12 months of age. Chagas PCR is more sensitive at 1 month of age than at birth (given the peak of parasitaemia). However, a negative PCR result at one month does not rule out the disease. It is the serology test carried out from the age of 9 months which, if negative, definitively rules out the diagnosis.	Ib
• For this reason, serology between 9 and 12 months is necessary. If the patient/parents are reluctant to undergo several tests, or if these are complicated to organize, the 9-12 months serology should be preferred to the 1-month testing, which can then be considered optional.	
• Because the infected mother's IgG antibodies to *T. cruzi* can persist in her infant for up to 9–12 months [6], serologic testing is not useful for detecting congenital infection in infants before 8 months of age. In infants older than 12 months of age, serological testing is recommended to diagnose a congenital infection in infants born from infected mothers, especially if the previous screening tests (PCR and/or microscopic detection) were negative or if no screening test was performed before.	
• Cases of congenital *T. cruzi* infection should be treated as soon as the diagnosis has been confirmed.	
• Antitrypanosomal therapy in infants include Benznidazole or Nifurtimox and should be given following national and international recommendations [26]. There is more recent clinical trial data for the use of benznidazole, which was used in both pediatric trials in the 1990s.	

Summary and recommendations:

- CD is a life-long chronic infection in the absence of a successful treatment. The disease is associated in one third of the patients with potentially fatal complications. People from south- and central American countries are at risk for CD. Infected people can transmit the parasite through blood or infected organs.
- Women in childbearing age (not reimbursed) and pregnant women (reimbursed) at risk for CD should be screened for *T. cruzi* infection.
- Women with CD should be treated prior to their pregnancy to prevent congenital transmission.
- Medical treatment is contraindicated during pregnancy and breast-feeding. Treatment with Benznidazole or Nifurtimox should be done after birth and after completion of the breastfeeding period.
- Children born from infected mothers should be tested for *T. cruzi* at birth, 1 month of age and at 9 -12 months of age to evaluate potential congenital infection.
- Children infected with *T. cruzi* should start treatment with Benznidazole or Nifurtimox as soon as possible after confirmatory diagnosis.

Conflict of interest statements: BMT has participated as advisor for Effik, Sanofi and Exeltis. Other authors declare no conflict of interests.

The Swiss Pediatrics Infectious Disease Society endorses this document.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

Guideline RCOG Nr. 44, 2006

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