

Letter

Clinical Practice Guidelines for Chagas Disease: Recent Developments and Future Needs

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Dear Editor:

A review by Olivera and colleagues compared five South American clinical practice guidelines for Chagas disease, assessing quality using the Appraisal of Guidelines Research and Evaluation (AGREE II) method¹. The analysis determined the overall quality of the guidelines issued by ministries of health or professional associations prior to 2016, which ranged from low to moderate. The authors noted that these guidelines did not have a strong connection to the best available evidence.

Since the period covered by the analysis, new evidence has come to light. The results of the BENEFIT trial were published in the last quarter of 2015, suggesting that treatment with benznidazole in older adults with moderate to severe cardiomyopathy was no more effective than placebo². However, the trial's results underscore the importance of providing etiological treatment before the onset of cardiomyopathy. Along with other recently concluded studies, this study contributed new evidence supporting the antiparasitic efficacy of the drug³⁻⁵. Other evidence suggests that treatment with benznidazole prevents future congenital transmission⁶⁻⁹.

Additionally, reiterating a point made by Novaes and Silvestre¹⁰, important clinical practice guidelines have emerged since 2015. Argentina's guidelines were updated in 2015; in 2016, Médecins sans Frontières/Doctors without Borders produced a manual on treatment of Chagas disease based on its experience in rural Bolivia; and the Second Brazilian Consensus on Chagas Disease was published¹¹⁻¹³. These guidelines make stronger recommendations in favor of treatment in the chronic indeterminate phase. The 2015 Argentinian guidelines and the Brazilian

Consensus contain clear evidence-based recommendations, which Olivera et al. noted was a weakness of the earlier guidelines that they reviewed. The Brazilian Consensus provides recommendations for etiological treatment linked to strength of evidence; treatment of adults in the chronic indeterminate phase is considered a Class IIa recommendation (Evidence Level B). Another important development is the recent publication of clinical guidelines by the Pan American Health Organization¹⁴.

In August 2017, the Chagas Clinical Research Platform conducted a workshop¹⁵ at the Annual Meeting of the Brazilian Society of Tropical Medicine, which compared guidelines/recommendations for treatment of Chagas disease in Brazil, Argentina, and Colombia^{11,12,16}. * The three countries' guidelines showed general agreement on considering etiological treatment for adults in the chronic indeterminate phase; initiating diagnosis and etiological treatment through the primary care level; monitoring during drug therapy, using complete blood count and tests of renal and hepatic function; and implanting defibrillators for cases of conduction system damage. There was also concordance on the need to set a maximum limit for the daily dose of benznidazole (400 mg/day in Argentina, and 300 mg/day in Brazil and Colombia). However, the guidelines continued to differ in terms of diagnostic procedures, frequency of monitoring during treatment, handling of treatment suspension due to adverse reactions, criteria for retreatment, and provision of pre- and post-treatment consultations.

Olivera et al.'s assertion that inconsistency in guidelines can create a potential barrier to treatment is still valid. Nevertheless, there is now a stronger tendency to use evidence-based guidelines that favor offering treatment to adults with

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Received 11 September 2018

Accepted 18 December 2018

*Marisa Fernandez (Argentina), Alejandro Luquetti and Veruska Maia da Costa (Brazil), and Rafael Herazo (Colombia) prepared and/or presented the information in the workshop. See:

https://www.ndi.org/wp-content/uploads/2018/06/Consensusstable_COL_BRA_ARG_ENG.pdf

indeterminate chronic infection. Further, the need for greater clarity regarding diagnosis, assessment of treatment efficacy (or failure), dosage and monitoring of benznidazole and nifurtimox, and use of ace inhibitors and beta blockers for chronic Chagas cardiomyopathy remains. Future advancement in these areas hinges on ongoing clinical research, and will be especially enhanced by improved understanding of biomarkers. Use of the GRADE methodology to update various countries' guidelines in the future would be one way to reinforce consistency.

While new evidence has strengthened recent clinical practice guidelines, substantial work is required to ensure that evidence-based recommendations are utilized consistently and appropriately in the various countries where Chagas disease is a public health concern¹⁰. Indeed, there will be some heterogeneity in guidelines due to the unique, context-specific challenges in each country, which stem not only from regional variation in the characteristics of *T. cruzi*-induced pathology, but also from differences in the organization of public health systems and the needs of patient populations. At present, with few people with Chagas disease receiving any form of diagnosis or treatment, clinicians' lack of awareness of up-to-date treatment recommendations poses a major point-of-entry barrier for patients. Effective guidelines are but one component, which, in conjunction with greater investment in public health programs, improved safety and efficacy of drug therapy, better diagnostics and markers of treatment efficacy, expanded provider and public education initiatives, and affirmation of healthcare as a universal human right, can begin to turn back the global tide of neglect of Chagas disease.

Acknowledgments: The Drugs for Neglected Diseases *initiative* (DNDi) is grateful to its donors, public and private, who have provided funding for all DNDi activities since its inception in 2003. DNDi received financial support from the following donors: Department for International Development (DFID), UK; Reconstruction Credit Institution-Federal Ministry of Education and Research (KfW-BMBF), Germany; Directorate-General for International Cooperation (DGIS), The Netherlands; Swiss Agency for Development and Cooperation (SDC), Switzerland; and Médecins Sans Frontières (Doctors without Borders). The donors had no role in the design, decision to publish, or preparation of the manuscript.

Conflict of Interest: The authors declare that there is no conflict of interest.

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