Access to diagnosis and treatment of Chagas disease/infection in endemic and non-endemic countries in the XXI century

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In this article, Médicos Sin Fronteras (MSF) Spain faces the challenge of selecting, piecing together, and conveying in the clearest possible way, the main lessons learnt over the course of the last seven years in the world of medical care for Chagas disease. More than two thousand children under the age of 14 have been treated; the majority of whom come from rural Latin American areas with difficult access. It is based on these lessons learnt, through mistakes and successes, that MSF advocates that medical care for patients with Chagas disease be a reality, in a manner which is inclusive (not exclusive), integrated (with medical, psychological, social, and educational components), and in which the patient is actively followed. This must be a multi-disease approach with permanent quality controls in place based on primary health care (PHC). Rapid diagnostic tests and new medications should be available, as well as therapeutic plans and patient management (including side effects) with standardised flows for medical care for patients within PHC in relation to secondary and tertiary level, inclusive of epidemiological surveillance systems.

Key words: Chagas disease - Chagas infection - medical care - diagnosis - treatment

Médicos Sin Fronteras (MSF) is a non-profit, non-governmental humanitarian organization, which was created in Paris in 1971 by a group of doctors and journalists (http://www.msf.org). As stated in their Magna Carta, MSF provides assistance to populations in danger, to the victims of natural or man-made disasters, and victims of conflict situations irrespective of race, religion, creed or political affiliation. Every year more than 20,000 MSF professionals from all over the world provide medical attention to persons in need in more than 70 countries, pledging themselves with respect to the deontological rights of their profession and to remain completely independent from any political, economic or religious power. All of this is possible thanks to more than three million donors around the world.

In 1999 MSF was awarded the Nobel Peace Prize. MSF dedicated the award for the creation of the Drugs for Neglected Disease initiative (DNDi), collectively with a further six insitutions from different countries: the "Fundação Oswaldo Cruz", Brazil; the Indian Council of Medical Research; Ministry of Health, Malaysia; the Kenya Medical Research Institute; "Institut Pasteur", France; and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR) (http://www.dndi.org). Officially founded in 2003, DNDi is a non-profit initiative whose mission is to investigate and develop medications for neglected diseases which affect millions of people worldwide.

In 1999 MSF Spain also faced the challenge of working, for the first time, with patients with Chagas disease in a difficult context; the months after hurricane Mitch hit Honduras, between the 26th and 30th of October of the previous year. Until today, three MSF sections: France, Spain, and Belgium have worked directly in six diagnosis and treatment projects in five Latin American countries: Honduras, Nicaragua, Guatemala, Bolivia, and Brazil. They have directly developed, as well, information, education, and communication (IEC) components and/or consultancy in three further Latin American countries (Argentina, Ecuador, and Colombia) and two cities belonging to the European Union (Cayenne, French Guiana, France, and Barcelona, Catalonia, Spain). In addition, MSF collectively with the Pan American Health Organization (PAHO) produced the "Virtual medical training course in the diagnosis, management and treatment of Chagas disease" on the internet (http://www.paho.org/Spanish/AD/DPC/CD/dch-curso-virtual-msf.htm; http://www.msf.es/curso%5Fchagas/) and co-organized three physical course editions in Honduras, Bolivia, and Colombia.

In this report, MSF Spain wanted to select, summarise, and transmit the main lessons learnt, through mistakes and successes, in the multiple Chagas projects in which MSF has collaborated with many other national and international institutions (Albajar et al. 2007). Over the course of the last seven years more than two thousand children under the age of 14 have been diagnosed and treated, the majority of which have come from rural Latin-American areas with difficult access. An objective of this section is to make a brief analysis of the *status quo* of medical care for Chagas disease in Latin America and beyond that, the strengths and weaknesses, challenges, and future perspectives including proposals of action for the long and medium term.

METHODOLOGY FRAMEWORK

For this research, three framework references were analyzed in order to provide the basis of a systematic analysis; (1) lessons learnt from previous diagnostic and treatment projects; (2) the natural evolution of Chagas disease in areas with high morbimortality; (3) PAHO/WHO consensus documents.

The first part of the methodology framework selected was to compile the lessons learnt from projects where MSF have worked which included Chagas disease diagnosis and treatment. MSF's projects for paediatric diagnosis and treatment were: Yoro – Yoro – Honduras, Esquipulas and Totogalpa – Matagalpa – Nicaragua, Olopa – Chiquimula – Guatemala, Entre Ríos – O'Connor – Tarija – Bolivia and Sucre – Chiquimula – Bolivia. The latter included diagnosis and treatment for patients up to 18 years of age. The authors also included experience drawn from a project which aims to diagnosis acute Chagas disease in the population of eight states in the Amazonian region of Brazil which involved training laboratory staff to look for parasites whilst reading malaria slides.

It is significant that the different Chagas disease diagnosis and treatment projects were developed in six different Latin-American municipalities; four in the Amazon basin or Northern Hemisphere, in the called *Trypanosoma cruzi* I and zymogene 3 territory, and two in the *T. cruzi* II one (Anonymous 1999). All pilot projects, developed with permanent contact with national Chagas disease programs, became key demonstrative experiences.

For the systematic analysis of each project, two sets of data were considered. The first included pre-existing (or non-existing) elements around which the project was formed: buildings, supplies, equipment, human resources, and internal processes including flow-charts and protocols. The second set included elements from the project's context: national legislation; social, economic, and cultural determinants of health; relevant aspects of policies at local council, regional or national level, as well as information regarding medical services for Chagas disease (also at the aforementioned levels).

The second section of the methodology was chosen in respect to the natural evolution of Chagas disease; using as a reference an area in Brazil with one of the highest morbimortality, with patients presenting cardiac, digestive, and neurological complications during the chronic phase of the disease (Dias 1995). Based on the results of a prospective cohort of patients, the sum of the percentage of patients presenting the indeterminate form (60%), mild cardiac form (15%), and mild digestive form, represented 75% (minimum) of recorded cases (Xavier 1999).

The third section was constituted by consensus documents from WHO/PAHO: "Etiologic Treatment of Chagas disease" (PAHO 1998), "Chagas disease control" (WHO 2002), "PAHO Consultation on Congenital Chagas Disease, its Epidemiology and Management" (PAHO 2004), and the joint PAHO-MSF document "PAHO/MSF Regional Consultation on the Organization and Structure of Medical Care to infected/ill patients by *Trypanosoma cruzi* (Chagas disease)", Montevideo 2005. The latter document, among other important statements, stresses the need to "integrate patient management as a regular and sustainable component, to the already existing activities of prevention, control, and disease surveillance for diseases in health systems (public, private, and those of social security). It also recommends that those affected by Chagas disease be seen by a general practitioner as close to their place of residence as possible" (PAHO 2005).

ASSESSMENT OF MEDICAL CARE IN CHAGAS DISEASE

The contents of the analysis are presented below and summarised in seven sections: Primary Health Care, Surveillance Systems, Access to Diagnosis and Treatment, Health Systems at Three Levels, Other Health Systems, Guidelines for Standardization, and Needs for the Future.

PRIMARY HEALTH CARE

One of the main conclusions of this article is that medical care for Chagas patients should mainly be provided at a PHC level. According to the authors, the natural evolution of the disease is a key criteria for establishing medical care at primary level. Previously this has occurred with diseases such as diabetes mellitus (DM), hypertension, and more recently, human immunodeficiency virus (HIV) infection. All of these diseases were initially treated by a specialist and later incorporated into PHC services throughout large areas of the world.

Medical care is classically organized in response to the demand, however, following the recent municipalization of health services and models such as the "family doctor", PHC services can potentially provide services which focus on prevention (primary prevention of the infection and secondary for disease development), and adapt medical care for Chagas disease to local specificities, using different approaches based on geographic, social, cultural or other specific characteristics.

To say that the priority for medical care has must given to primary level services does not exclude the important participation of the secondary and tertiary levels of care. It is necessary to identify factors today which may hinder the take over of medical care for Chagas disease as a part of PHC, as well as the positive factors that made this change possible for other diseases some years ago.

Historically it is worth mentioning that over the course of several decades, all available resources and planned activities targeted vector control and that with the arrival of the HIV/AIDS pandemic, this focus was widened monitoring blood transfusions (Dias et al. 2002). These two items, vector control and blood transfusion, are planned at a national or regional level. Paradoxically, the diagnosis and treatment of infected patients (who can be treated) is carried out at municipal level, but this has been delayed even in areas where vector control has been successful.

Also of historic significance is the fact that the few studies which attempted to demonstrate the effectiveness of etiologic treatment were only made during the last decade of the XX century, probably based on the evidence provided by molecular biology which, at that

time, proved that the parasite remained in the targeted tissues, meaning they could no longer attribute the etiopathogeny exclusively to immunological mechanisms (James et al. 2002). Actually, the first study to demonstrate the efficacy of treatment with benznidazole in patients under 12 years of age was not produced until the 1990s (Andrade et al. 1996, Sosa-Estani et al. 1998), neither were the first studies, even though statistically limited, which demonstrated a lower incidence of electrocardiographic changes and less clinical development in the group of treated patients (Viotti et al. 1994, 2006, Villar 2002). At that moment, the significant geographical differences in the response to treatment were already known and were probably related to the *T. cruzi* variety as well as differences in the host, among others. WHO quickly used these findings in two consensus documents; one specifically concerning treatment (PAHO 1998) and another about Chagas disease as a whole (WHO 2002) which included very specific recommendations in the treatment of patients under 12 years of age. This left the criteria as to the decision regarding the pertinence of an etiologic treatment in the adult patient in the hands of the practitioner and patient. Despite these recommendations, neither the diagnosis criteria nor the treatment of patients under 12 years of age were systematically incorporated into health systems in Latin America, probably due to a historic methodology which was embedded in the training and refresher courses of practitioners both during medical training and in post-graduate courses.

A decade later a group of researchers lead by Dr Rassi and Dr Luquetti, in Goiás, Brazil, sounded the alert that in South America confirmation of parasitological cure with seroconversion, in those who had been infected for less than a year, normally occurred within a year of completing ethiologic treatment; in those that were infected for 10 to 15 years, seroconversion took place between 5 and 10 years after completing treatment; in those infected for more than 20 years at least 10 years were needed in order to verify parasitological cure (Luquetti & Rassi 2002). This was most likely another reason which demotivated practitioners to treat patients; owing to the apparent lack of response to treatment or even to the difficulty in explaining treatment efficacy to the patient in the short term.

Another factor of historic significance was the fact that Chagas was a cardiologist's and/or "chagólogos" disease, and not all cardiologists and/or echocardiographists treated Chagas disease. Probably the limited low efficacy spread around, the secondary effects, quantitatively and qualitatively significant (Castro et al. 2006), and the fact that it was a disease not valued by many practitioners (MSF 2005, Maguire 2006) were the main reasons why the disease remained neglected. The complexity of the disease and its natural evolution does not justify the exclusivity of medical care done by specialists in this day and age. As an example, a cardiologist can read an electrocardiogram (ECG), classify patient from the cardiology point of view and make a prognosis from the cardiac alterations found, but even in areas with high morbidity only 15 to 20% of the patients would need to be follow up by them.

SURVEILLANCE SYSTEMS

Everything discussed up to this point in relation to medical care constitutes a proposal that aims to "centrifuge" the disease towards PHC. However, this strategy must go hand in hand with another which needs to be developed with the same intensity but which moves in the opposite direction: an information system that goes from primary health to the other levels of care (centripetal). Worldwide all countries, including those in Latin America, face this as one of their greatest challenges; to install an epidemiological model of surveillance and notification which would make real data and up-to-date figures available in order to evaluate, decide, and plan medical care, including budget planning. According to the authors, national health information systems, vector control strategies, and blood banks are examples of systems which ideally, must have a supra municipal structure and coordination at national or, at least regional level. It is also the responsibility of governments to establish technical and operational regulations, verification of quality, registration, and acquisition of supplies on a large scale, among others.

ACCESS TO DIAGNOSIS AND TREATMENT

Diagnosis is the access point to medical care, without which the Chagas patient cannot receive medical attention. There are at least four possible strategies for diagnosis and consequent points of access to the health system: (a) diagnosis in PHC with filter paper or rapid diagnostic tests (Luquetti et al. 2003); (b) systematic antenatal diagnosis, with screening and diagnosis of children born from infected mothers (Russomando et al. 2005), allowing clinical evaluation and the etiologic and non-etiologic treatment of pregnant women following delivery; (c) confirmed diagnosis of people who were tested during blood bank screening; (d) clinical identification of acute symptomatic patients, including cases of oral transmission, as well as chronic cases presenting with the different forms: cardiac, digestive, neurological, and even those with cerebral vascular accidents. In the Amazon region, another potential entry point could be the identification of *T. cruzi* in blood films prepared for malaria diagnosis.

In this day and age, access to treatment represents another challenge. Following the transfer of technology made by the pharmaceutical company Roche to a public laboratory (Lafepe) in Pernanbuco, Brazil. Lafepe is now responsible for the short term production of benznidazole for the rest of the world. Support by the PAHO will be necessary to ensure quality control, registration, and commercialization of this drug worldwide. It is necessary to avoid delays in these processes in order to prevent the drug being "out of stock" in countries where the infection/disease is endemic.

In addition, pilot experiences (already presented at international forums but not yet published in the treatment of patients under 14 years of age) in countries such as Honduras (MSF) and Colombia (National Health Institute), found surprisingly high percentages of cure rates which could be verified in short periods of time when

compared with studies carried out South of Amazonia. These experiences encourage the replication of similar projects in other regions as well as the expansion of experiences to encompass other age groups.

HEALTH SYSTEMS AT THREE LEVELS

Regarding the different levels of health care, each level has its own attributes.

In PHC, rapid diagnostic tests which could use whole blood without requiring any additional instruments, such as centrifuges, etc. are clearly needed. The objective would be that nurses would perform the screening and diagnostic confirmation, as with other health programs such as diabetes. Ideally, two rapid tests with different technique and different antigen detection would be used. Until this is possible, the collection of samples using filter paper will continue as an excellent method for screening, even in areas with difficult geographic access.

At a medical level, it will be necessary for doctors to be trained in taking a complete history and performing a correct physical examination with the objective of detecting any clinical sign, in acute or chronic phases, and to evaluate the stability or clinical progression of the patient, this would include any reactivation due to immunosuppression or any other cause. The presence of cerebral vascular accidents originating from the cardiac form of Chagas disease is another challenge that should be addressed through proper clinical training prior to graduation from university (Carod-Artal 2006).

With regards to complementary tests, it is unusual to have the option of an ECG or even X-ray at PHC level. When ever possible, clinical screening is particularly important at this level. Assessment of whether an ECG is normal or not will identify at least 60% of the indeterminate forms with an excellent prognosis (Sousa et al. 2001). In a thoracic X-ray it is possible to evaluate whether or not the cardiothoracic index is above normal values. Chest X-ray (right anterior oblique) performed 60 s after swallowing the contrast medium should not demonstrate a diameter exceeding 5 cm in the oesophagus, nor a delay in oesophageal emptying following the Rezende technique (Rezende & Moreira 1988). An abdominal X-ray taken following the introduction by gravity of 1200 ml of barium contrast and water (placed 1 m above the table where the X-ray is being taken), should not demonstrate loss in basal muscular tone; a colonic dilatation greater than 6 cm is also in accordance with the Rezende technique (Rezende & Moreira 1988).

As with other chronic diseases such as tuberculosis or leprosy, medical services require a more pro-active approach with frequent visits to communities and homes when necessary. Experience tells us that early detection is the key to managing the secondary effects of benznidazole and nifurtimox at PHC level and even to prevent the majority of severe secondary effects. When symptoms are mild and there are hospital services at hand, patients can be managed by maintaining a minimum therapeutic dose (5 mg/kg/day) and adding specific treatment for each. When close follow-up of the patient is not an option, and more importantly, when the patient cannot contact the health facility or the practitioner if emergency evacuation is necessary, the decision to initiate treatment should be carefully weighed up.

Regarding diagnosis and bearing in mind the aforementioned entry points, history taking, and physical examination, complementary ECGs and X-rays it is necessary to create and have flow-charts available at the three levels of care. One of the main challenges of the health system is to improve referral and counter-referral procedures.

At secondary health care level, in the same way in which laboratory tests confirm diagnosis in cases with doubtful or inconclusive results (with possible discrepancies between different diagnostic tests), it should be possible to finalise clinical diagnosis in those patients who were not diagnosed at PHC level. The management of referred patients is essential to evaluate, for example, the degree of cardiopathy and if specific cardiological treatment is indicated. Likewise, this also applies to digestive and neurological complications; it is necessary to determine which clinical forms will need the specialist care and which patients could return to PHC level for follow-up in the absence of major complications; which could possibly be at least 75% of cases.

The second level referral and counter-referral process has a unique opportunity to carry out quality control and to identify subjects for ongoing training at PHC level; in the same way laboratories at secondary level will organize quality control at primary level.

The second level would also be responsible for receiving those patients on treatment who present with moderate to severe secondary effects requiring laboratory tests, complementary tests or specialist care in order to recover. As examples, a haematologist may be required for a case of severe medullar depression or a neurologist in event of severe or persistent neuritis.

The tertiary level should be responsible for those clinical cases with cardiac, digestive or neurological presentations of the disease, or with severe secondary complications of treatment such as Steven-Johnson Syndrome. Even if these severe complications are rare, a reference and counter-reference system from primary and secondary levels to tertiary level is vital for these patients.

Here again, as with the laboratory, the third level should constitute part of the quality control of the secondary level as well as the ongoing training of professionals working at that level.

ANOTHER HEALTH SYSTEM

From everything discussed up to this point, and not only exclusively in relation to Chagas disease, it can be deduced that we are advocating for a different health system in order that the established medical system responds to the needs of the population at risk, the infected and ill, regarding prevention and medical care.

Health systems in Latin America and worldwide, will have to carry out the necessary changes to be inclusive of patients with Chagas disease. An exclusive system is one, for example, that does not have diagnostic tests or etiological treatment registered at national level.

A health system which had access to diagnosis and treatment for Chagas disease, integrated and coexisting within other health programs, would always be able to

provide a multi-disciplinary patient approach (Ehrenberg & Ault 2005).

An integrated health system is required in which the patient not only has access to medical care, but also to psychological, social, and occupational components with ongoing IEC at individual, family, and community level. The IEC component should be a part of the actions programmed for the health system involving total collaboration with the education system (Cabrera et al. 2003). This is more evident, for example, when giving a positive result to a patient, above all in the called endemic areas with evidence of other cases of the disease nearby and deaths from the same cause. The anxiety or depression, social rejection, and discrimination in the workplace which also infringes on national legislation, are all too frequent in Latin America. On the other hand, the diagnosis of Chagas infection may contribute to social discrimination in countries where the illness has not been endemic.

Again, the need for the health system to have a significant and ongoing interaction with the education system is reiterated. This not only means the inclusion of Chagas disease as a school subject, but the transformation of students into active participants in the surveillance system; their role would involve the capture and identification of possible vectors in homes and their surroundings. In schools, as well, particularly in rural areas with widespread populations, it is possible to provide etiological treatment in collaboration with a group of teachers. With previous parental consent, over the course of one academic year, one of the best diagnostic and treatment interventions could be carried out at a cost effective level.

It should be emphasized that sustainability must be a condition of any proposal at diagnostic, treatment, management or IEC levels. Bearing in mind that those affected by Chagas disease are usually people with scarce socioeconomic resources, this is more evident. If a proposed measure bears an additional cost for the individual, family or a community, there should at least be some form of long or medium term economic return. Costly interventions will only prove to be effective and continue if there is an improvement in the public health and economy of the community.

GUIDELINES FOR STANDARDIZATION

In order that Chagas disease be incorporated, as any other disease, in the health system of Latin American countries and other territories in the world, it is necessary to produce agreed-upon guidelines to help this become a reality. A healthcare network should be established from local council to national level, with clear criteria. The active participation of the PAHO/WHO and all those institutions who carry out similar identified pilot projects will be essential. In order to produce these guidelines, it will be necessary to bring together all of the parties involved in decision-making; in addition to the diagnostic and medical, economic, logistic and political components, among others. Cost effectivity analysis is seen as one of the most important studies to assist in decision-making. Sadly, until now this has rarely been utilized for the diagnosis and treatment component.

This key fact has already been proven also in locations outside Latin America. When item 36 of the Montevideo document literally specifies: "Countries where Chagas disease/infection is not endemic which receive migration from Latin American countries, should establish a network of centres specialized in subjects related to this infection, aiming to produce standards for healthcare and control strategy protocols" (PAHO 2005). The participation of the PHC system in these countries has also been seen as necessary; not only in the effective medical care for at least 75% of patients, but also in the agreement of protocols, monitoring strategies, the IEC component of health personnel themselves and of the target population: migrants, distributed through national territory, tourists from continents such as Europe with destinations in Latin America-especially those with greater prevalence and higher risk of exposure.

However, none of what has been discussed here would be possible in reality without having the following essential conditions in place.

Firstly, health professionals have to work, more than ever, as a team (Ehrenberg & Ault 2005). A superior/inferior relationship between doctors and nurses, specialists and generalists, people from urban and rural backgrounds, among others, will make true interdisciplinary work impossible. This project is only possible with professionals who are truly at the service of the health system.

Secondly, human resources need to be selected following technical and not political criteria. Unfortunately the political system and local economic authorities have often interfered, consequently damaging the quality of care delivered to the population.

Thirdly, there must be a guarantee of continuity in the human resources selected. Continuity is often limited to local political cycles, meaning no more than four years. With the elections held every four years, particularly at municipal level, employees are renewed and the training of newcomers must be organized and repeated all over again. Another reason for the high turn-over of health professionals is the difficulty for doctors and nurses working in rural areas to be up-dated and to participate in refresher courses; this factor combined with job stability would provide them with a career plan (Gil 2005). These are all significant issues in diseases such as Chagas which require medium and long term planning.

Fourthly, the ultimate goal of health workers should be the patient and not the health system itself. The development of wealthy Western societies has brought with it the organization and regulation of medical care to the minutest detail; the negative side being that health staff may focus more on following written rules rather than providing adequate care to meet the needs of the patient. Another risk, resulting from the current administrative, working, and economic organization of health services, is that health workers are more concerned with pleasing their managers, or even in achieving their institutional goals to ensure job security or getting variable parts of their salaries linked to annual objectives, rather than providing true and quality medical care (Hunter 1998).

Fifthly and finally, the set of values of the Western socioeconomic world has to assess and calculate the

quantity and quality response of the health system according to the real individual and collective service given more than to political or economical parameters. This fact is particularly evident when analyzing neglected diseases. Research and development of new diagnostic tests and drugs for the etiologic treatment of Chagas disease has almost been non-existent when compared with other infectious diseases such as AIDS. Benznidazole and nifurtimox, the only two drugs available for treatment, have been in the market for more than 30 years and the pharmacokinetic characteristics, formulations, efficacy, and secondary effects are far from ideal.

There are two "external" systems which have interfered with the health system: the political and economic one. The need exists for a more autonomous health system which could truly guarantee universal medical care of acceptable quality.

NEEDS FOR THE FUTURE

In order to continue changing the *status quo* it is necessary to become involved today in new challenges that will influence tomorrow's health services.

The marketing of new rapid diagnostic tests with good sensitivity and specificity in the different *T. cruzi* territories is required. A great geographical diversity exists, not only between the large territories of *T. cruzi* II, *T. cruzi* I and zymodeme 3, but also within countries themselves; such as in the Amazon where the number of potential co-infections and cross-reactions increases the challenge to maintain a good positive and negative predictive value.

There is a need to market new rapid diagnostic tests using antigens such as TESA, using the human infective form of the parasite (trypomastigote) achieving higher sensitivity and specificity and being able to diagnose patients in the acute phase of the infection (Umezawa et al. 1996).

A paediatric formulation for benznidazole and nifurtimox is required. For more than 30 years we have been breaking the 100 mg tablets and mixing them with all kinds of liquids in order to administer them in paediatric patients. In this day and age this practice is unacceptable and a solution should be provided from the pharmaceutical industry.

There is a need for new drugs with fewer secondary effects and higher trypanomicidal activity. The advancement in studies with posaconazole, already commercialized for systemic mycotic infections, and ravuconazole, in the animal experimental phase, is urgent. These are two promising drugs for the mid and long term respectively.

Finally, the authors would like to state that the main conclusion of their analysis is that nowadays, even with the endless list of tasks for urgent development in the health sector, after multiple pilot experiences in different settings in Latin America; with the same tools that were available at the beginning of this century, the diagnosis and treatment of Chagas disease is possible, necessary, and from the ethical point of view, unquestionable.

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