

# Surgical Therapy and DH-II-90 Protocol in the Treatment of Hodgkin Disease in Young Adults: an Ecological Study

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*A Terapêutica Cirúrgica e o Protocolo DH-II-90 no Tratamento da Doença de Hodgkin em Jovens e Adultos: um Estudo Ecológico*  
La Terapia Quirúrgica y el Protocolo DH-II-90 en el Tratamiento del Linfoma de Hodgkin en Jóvenes y Adultos: un Estudio Ecológico

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## ABSTRACT

**Introduction:** Hodgkin disease (HD) is a pathology that starts in the lymph nodes, develops in the neoplastic tissues and manifests, mainly, in young adults. **Objective:** To correlate the results of the surgical therapy and the DH-II-90 protocol in young adults affected by HD, and to associate them with the epidemiological profile, the mortality data by the disease and the distribution of physical resources in Brazil. **Method:** Exploratory ecological study with information collected from the Informatics Department of the National Health System (DATASUS), the National Cancer Institute José Alencar Gomes da Silva (INCA), the National Registry of Health Establishments (CNES) and the SUS Outpatient Information System (SIA/SUS) between 2013 and 2021. The study, therefore, compares the results of surgical therapy and the DH-II-90 protocol associated with epidemiological data, and the protocol is considered the most efficient method, as it produces better results when compared to more invasive methods. **Results:** The Southeast Region concentrates high number of beds and procedures and stands out due to more expressive numbers of patients diagnosed from 0 to 29 years. In short, crude mortality rates per HD decreased since 1990, the period where the DH-II-90 protocol was applied. **Conclusion:** This study provides a relevant view on the epidemiological profile of HD and contributes for the comparison between surgical therapy and the DH-II-90 protocol, being possible to conclude that after the application of the protocol, there was a reduction of the mortality rate by HD in Brazil and worldwide.

**Key words:** Hodgkin disease/epidemiology; drug therapy; radiotherapy; mortality.

## RESUMO

**Introdução:** A doença de Hodgkin (DH) é uma patologia que se inicia nos linfonodos, desenvolve-se nos tecidos neoplásicos e manifesta-se, majoritariamente, em jovens adultos. **Objetivo:** Correlacionar os resultados da terapêutica cirúrgica e do protocolo DH-II-90 em jovens adultos acometidos pela DH, e associá-los ao perfil epidemiológico, aos dados de mortalidade pela doença e à distribuição de recursos físicos no Brasil. **Método:** Estudo ecológico exploratório, com informações coletadas do Departamento de Informática do Sistema Único de Saúde (DATASUS), do Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), do Cadastro Nacional de Estabelecimentos de Saúde (CNES) e do Sistema de Informações Ambulatoriais do SUS (SIA/SUS), entre 2013 e 2021. O estudo, portanto, compara os resultados da terapêutica cirúrgica e do protocolo DH-II-90 associados a dados epidemiológicos, sendo o protocolo considerado o método mais eficiente, por apresentar melhores resultados quando comparado a métodos mais invasivos. **Resultados:** A Região Sudeste concentra maior número de leitos e procedimentos com números mais expressivos de pacientes diagnosticados de 0 a 29 anos. Em resumo, as taxas de mortalidade bruta por DH reduziram-se a partir de 1990, período no qual o protocolo DH-II-90 foi aplicado. **Conclusão:** O presente estudo fornece uma visão relevante sobre o perfil epidemiológico da DH e contribui para a comparação entre a terapêutica cirúrgica e o protocolo DH-II-90, sendo possível concluir que, após a aplicação do protocolo, houve redução da taxa de mortalidade por DH no Brasil e no mundo.

**Palavras-chave:** doença de Hodgkin/epidemiologia; tratamento farmacológico; radioterapia; mortalidade.

## RESUMEN

**Introducción:** El linfoma de Hodgkin (LH) es una patología que inicia en los ganglios linfáticos, se desarrolla en los tejidos neoplásicos y se manifiesta mayoritariamente en adultos jóvenes. **Objetivo:** Correlacionar los resultados de la terapêutica quirúrgica y del protocolo DH-II-90 en jóvenes adultos acometidos por el LH, y asociarlos al perfil epidemiológico, a los datos de mortalidad por la enfermedad y a la distribución de recursos físicos en Brasil. **Método:** Estudio ecológico exploratorio, con información recolectada del Departamento de Informática del Sistema Único de Salud (DATASUS), del Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), del Registro Nacional de Establecimientos de Salud (CNES) y del Sistema de Informaciones Ambulatorias del SUS (SIA/SUS), entre 2013 y 2021. El estudio, por lo tanto, compara los resultados de la terapêutica quirúrgica y del protocolo DH-II-90, asociados a datos epidemiológicos, siendo el Protocolo considerado el método más eficiente, por presentar mejores resultados cuando comparado a métodos más invasivos. **Resultados:** La Región Sudeste tiene más camas y procedimientos y presenta mayores números de pacientes diagnosticados de 0 a 29 años. En resumen, las tasas de mortalidad bruta por LH disminuyeron a partir de 1990, período en el que se incorporó el protocolo DH-II-90. **Conclusión:** El presente estudio proporciona una visión relevante sobre el perfil epidemiológico del LH y contribuye a la comparación entre terapêutica quirúrgica y el protocolo DH-II-90, concluyendo que, tras la inserción del protocolo, hubo reducción de la tasa de mortalidad por LH en Brasil y en el mundo.

**Palabras clave:** linfoma de Hodgkin/epidemiología; quimioterapia; radioterapia; mortalidad.

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## INTRODUCTION

The World Health Organization (WHO) defines Hodgkin's disease (HD) as a pathology that begins in the lymph nodes, develops in neoplastic tissues with small quantity of tumor cells surrounded by lymphocytes T and in most of the cases, it manifests clinically in adolescents and young adults<sup>1,2</sup>, preferentially of European descent<sup>2</sup>. Nowadays, it has one of the highest rates of cure among non-cutaneous neoplasms<sup>3</sup>. In relation to the epidemiology of HD, according to *PAINEL-Oncologia Brasil*<sup>4</sup>, it is a pathology diagnosed in 7,905 children, youngsters and adults from 0 to 29 years from 2013 to 2021. In USA in 2018, nearly 8,500 new diagnosis of the pathology have been reported<sup>5</sup>.

Surgery and combination of chemotherapy and radiotherapy, namely, protocol DH-II-90, are, currently, the treatment for HD with satisfactory results. Initially, laparotomy and splenectomy were the surgery modalities utilized<sup>7</sup>; however, these procedures are associated with risks to the patients due to post-operative infections and elevated mortality rate<sup>8,9</sup>.

Surgery is restricted to specific situations when other staging methods were proven as ineffective<sup>10</sup>. According to *PAINEL-Oncologia Brasil*<sup>4</sup>, 302 cases of youngsters and adults were treated surgically between 2013 and 2021, with high prevalence in the Southeast region where oncologic surgical resources are concentrated.

As medical science advances, more knowledge about the physiopathology of the disease and chemotherapy and radiotherapy methods are acquired, the risk-centered protocol of combined therapy was developed<sup>11</sup> and determined as the most effective treatment because of favorable outcomes when compared to more invasive methods<sup>12,13</sup>. Protocol DH-II-90 is defined as combined chemotherapy and radiotherapy with the prevalence of the regimen adriamycin, bleomycin, vinblastine, dacarbazine (ABVD)<sup>12</sup>. The results were beneficial for the patients<sup>14,15</sup>, which can be proven by the direct effects over the mortality rate of individuals affected by HD.

The combined therapy for HD is also applied by European countries and North America<sup>16</sup>, the latter with a survival of 88.3% of the cases<sup>5</sup>. Both therapies have discrepancies on the outcomes and impacts on the treatment of these patients. The purpose of this study is to analyze the results of surgery and protocol DH-II-90 in youngsters and adults further to epidemiological data about how these therapies are applied in Brazil and relating to the physical resources available at the geographic regions based in the analyzes of the Health Information Systems (SIS) of SUS' Computer System (DATASUS).

## METHOD

Retrospective, ecological, exploratory study with information collected from DATASUS<sup>4</sup>, of the National Cancer Institute (INCA)<sup>17</sup>, of the National Registry of Health Clinics (CNES)<sup>18</sup> and of the Outpatient Information System of SUS (SIA/SUS)<sup>19</sup>, regarding the epidemiology, morbidity, vital statistics and physical resources. DATASUS is a public domain database and open access offered by the Ministry of Health from where INCA data were extracted<sup>17</sup> for a 40-years period (1979-2019) and showing the crude mortality rate by HD in patients from 0 to 29 years of age.

From *PAINEL-Oncologia Brasil*<sup>4</sup>, patients of different age-ranges were analyzed which allowed a better visualization of the most affected groups based in a pre-review of the relation incidence/age and mortality. The diagnoses from 2013 to 2021 were distributed per Federation Unit considering all the analyzes. In addition, the chemotherapy and radiotherapy treatments and both combined were evaluated, further to SUS outpatient consultations of neoplasms. The analysis was restricted because it was based in percentage but when population density was included, it was revealed that the Southeast has a much larger population than the North which does not necessarily mean that the diagnosis is regional.

At INCA<sup>17</sup> platform patients diagnosed with HD submitted to therapy between 2013 and 2021 were found. On the other hand, CNES<sup>18</sup> databases show the number of surgical beds utilized per region for oncologic treatment of HD. In addition, the information from SIA/SUS<sup>19</sup> contribute to SUS outpatient consultations based in clinical procedures related to oncologic treatment in March 2021 for specific age-ranges (0 to 19; 20 to 24; 25 to 29).

The evaluation of the mortality for each specific region was based in the calculation of the number of deaths per 100 thousand inhabitants, place and period, allowing to estimate the risk of death by the cause selected. The calculation consisted in the number of deaths by specific therapy at a certain place and period divided by the number of deaths multiplied by 100 thousand. The analysis was made with frequencies and percentages of the categorical variables.

## RESULTS

Table 1<sup>4</sup> shows the distribution of patients affected by HD from 0 to 29 years of age per Federation Unit in the period 2013 to 2021 with 7,905 cases. The Southeast region had more expressive results with 3,349 cases reported (42.45 %), the Northeast with 1,988 (25.24 %)

diagnosed, the South region with 1,573 (19.90%), the Midwest region with 534 (6.64%) and the North region with 461 (5.74%), the lowest numbers of cases.

Table 2 shows the distribution of the individuals diagnosed with HD from 0 to 29 years of age according to FU of treatment submitted to surgery, chemotherapy and radiotherapy from 2013 to 2021. 7,757 individuals were treated, 302 with surgery (3.89%), 7,455 (96.10%) with chemotherapy and radiotherapy. Chemotherapy is the most utilized therapy in comparison with radiotherapy.

In April 2021, there were 4,943 oncological surgical beds per region according to CNES<sup>18</sup> with the greatest concentration in the Southeast region with 2,046 beds, accounting for 41.39% of all the beds available in the country. The second was the Northeast region with 1,356 beds, 27.43% of the total followed by the South region

with 889 beds, 17.9% of the total. The Midwest region counts with 353 beds (7.14%), and the North, 299 beds, 6.04% of the total.

In Brazil, 326,867 oncological clinical procedures were reported in March 2021 according to SIA/SUS<sup>19</sup>. The Southeast had substantial results with 150,283 procedures, 45.96% of the country, followed by the Northeast with 75,915, corresponding to 23.22%, the South with 71,479 procedures, 21.86%, the North had the lowest numbers with 11,994, a percentage of 3.66% of Brazil's total.

Graph 1<sup>17</sup> portrays crude mortality rates by HD adjusted per age, world and Brazilian population per 100 thousand men and women between 1979 and 2019. Following a general parameter, it was noticed a drop of the mortality by HD in Brazil since 1990 when the protocol DH-II-90 was inserted.

**Table 1.** Distribution of patients with HD from 0 to 29 years of age per Federation Unit, 2013-2021

Federation Unit	C81 – Hodgkin Disease
Acre	20
Alagoas	116
Amapá	6
Amazonas	136
Bahia	382
Ceará	392
Distrito Federal	126
Espírito Santo	200
Goiás	217
Minas Gerais	764
Maranhão	172
Mato Grosso	116
Mato Grosso do Sul	75
Pará	199
Paraíba	197
Paraná	617
Pernambuco	411
Piauí	110
Rio Grande do Norte	161
Rio Grande do Sul	535
Rio de Janeiro	515
Rondônia	61
Roraima	4
São Paulo	1,870
Santa Catarina	421
Sergipe	47
Tocantins	35
<b>Total</b>	<b>7,905</b>

Source: PAINEL-Oncologia<sup>4</sup>.

## DISCUSSION

The reference of the current study are the data collected by DATASUS<sup>4</sup> for the age-range from 0 to 29 years old, which shows that the Southeast region has expressive results of HD with 42.31% of the cases. This can be justified by the greatest population density of this region according to the National Household Sample Survey (PNAD)<sup>20</sup>. This target age-range is the one where more volume of data is found and for which scientific discussions have been held although HD can affect individuals of any age<sup>17</sup>. As HD survivorship is high, there are concerns about the effects and toxicity of the treatment for this population<sup>21</sup>. The aim is to investigate surgery and protocol DH-II-90 and correlate them to epidemiological findings regarding mortality.

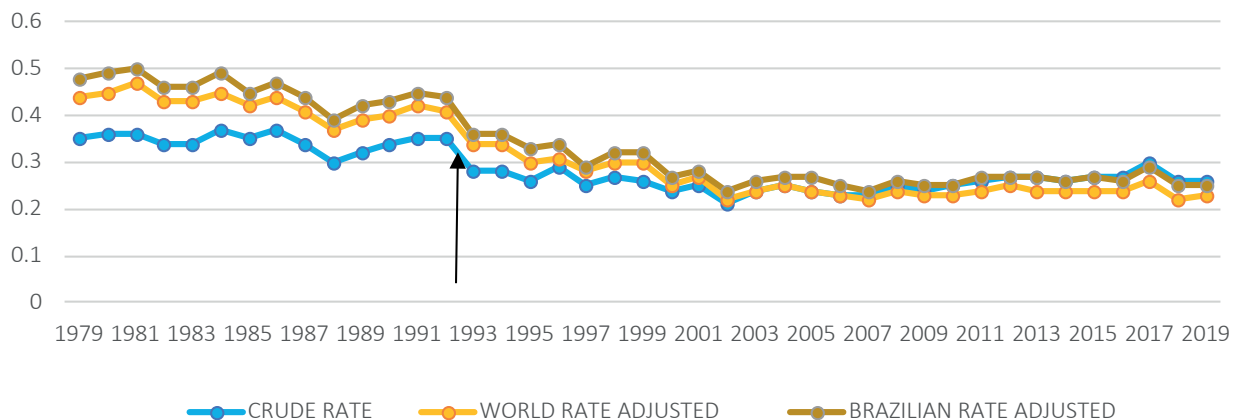
Laparotomy and splenectomy were utilized as effective tools to evaluate intrabdominal diseases in 1965 and were applied as staging method<sup>7</sup>, which represents a clinical evaluation of the results obtained from the pathological analysis of a tissue sample after surgical excision. But this model caused harms to the patient due to more risks of post-splenectomy infections with high mortality<sup>8,9</sup>. With advances in the treatment of HD and the introduction of practices as imaging diagnosis and chemotherapy, surgery became obsolete<sup>10,12-15,21,22</sup>, and in 1989, this method was nearly discontinued. Currently, surgery for staging is limited to specific situations when clinical staging, physical exams or biopsies are ineffective to evaluate the cancer<sup>10</sup>.

Based in data collected from DATASUS<sup>4</sup>, surgery has not been utilized in Brazil as before, reaching only 3.89% of the therapies from 2013 to 2021 for the target age-range. The Southeast region presents the higher number of this therapy, 58.94%, due to highest incidence and surgical beds for oncologic procedures (41.39%).

**Table 2.** Distribution of therapeutic modalities according to diagnosis of HD in patients from 0 to 29 years of age per Federation Unit, 2013-2021

Federation Unit	Surgery	Chemotherapy	Radiotherapy	Total
Acre	-	17	3	20
Alagoas	-	104	10	114
Amapá	-	6	-	6
Amazonas	-	101	35	136
Bahia	12	362	8	382
Ceará	4	365	19	388
Distrito Federal	4	119	3	126
Espírito Santo	10	174	12	196
Goiás	7	165	27	199
Minas Gerais	50	658	44	752
Maranhão	-	152	20	172
Mato Grosso	5	108	2	115
Mato Grosso do Sul	-	69	4	73
Pará	3	156	17	176
Paraíba	4	181	10	195
Paraná	13	587	13	613
Pernambuco	26	362	18	406
Piauí	5	102	1	108
Rio Grande do Norte	1	152	7	160
Rio Grande do Sul	21	484	19	524
Rio de Janeiro	12	459	44	515
Rondônia	1	58	2	61
Roraima	-	4	-	4
São Paulo	106	1,635	78	1,819
Santa Catarina	16	383	16	415
Sergipe	2	40	5	47
Tocantins	-	35	-	35
<b>Total</b>	<b>302</b>	<b>7,038</b>	<b>417</b>	<b>7,757</b>

Source: PAINEL-Oncologia<sup>4</sup>.



**Graph 1.** Mortality rates by HD crude and adjusted per age, world and Brazilian population of 2020, per 100 thousand men and women. Brazil, 1979-2019

Source: Online Mortality Atlas<sup>17</sup>.

In order to reduce the practice of surgical staging, protocol DH-II-90 was developed, a combined chemotherapy and radiotherapy method<sup>23</sup>. The discontinuation of more invasive practices increased the survivorship of these patients since the rate of cure from current approaches is 85% of the cases<sup>14,15,24</sup>. Combined therapy allows the reduction of toxicity for both therapies when isolated and the treatment is effective for the local control of the tumor, inhibiting the growth of tumor cells<sup>6,23</sup>.

The most utilized chemotherapy method is regimen ABVD<sup>21</sup> consolidated since 1990 as golden-standard for HD treatment because of better results and low toxicity compared to the others<sup>12,13</sup>. The number of cycles and intensity of radiotherapy are determined according to the disease's staging<sup>12</sup>. Specimen collected from clinical trials and individual treatment sites show that two to three ABVD chemotherapy cycles followed by radiotherapy sessions have nearly 95% of cure for limited-stage patients<sup>25,26</sup>.

HD's mortality rate per 100 thousand inhabitants between 1979 and 2019 as shown in Graph 1<sup>17</sup>, has significantly dropped since 1990, a reduction of 0.2 from 1991 until 2019, a variation of 44.4% with less 200 deaths for a population of 100 thousand inhabitants. The remarkable reduction of these numbers is justified by the discontinuation of invasive practices and the implementation of the protocol DH-II-90. It has been seen the reduction of postoperative complications and mitigation of isolated treatments-related toxicities<sup>27</sup>, further to the rate of cure for HD reaching considerable results<sup>14</sup>, which significantly reduced the mortality of these patients and reiterated by DATASUS.

As more is known about the disease's physiopathology and side effects of both therapeutic approaches, HD treatment is patient-centered and matched to the risk to the individual<sup>11</sup>. Several targeted strategies created by renowned American clinical research sites are available and continuously developed to combined therapy adjusted to risk of HD<sup>24</sup>.

Likewise in the last decade, the use of new technologies has been discussed mainly in developed countries in patients with advanced HD, such as immunotherapy, positron emission tomography/computed tomography (PET/CT), in addition to hematopoietic stem-cells transplantation<sup>28,29</sup>. There is still no robust ground able to ensure that these approaches affect considerably the survivorship of these patients at population level<sup>30</sup>.

In order to improve the prognosis of HD, new methods of radiotherapy have been tested as modulated intensity radiation and image-guided radiation which, if effective, can lead to local control of the tumor and reduce

the damage to the tissues affected<sup>29</sup>. The implementation of chemotherapy associated with advances of the radiation techniques makes Hodgkin's lymphoma a pathology with favorable cure prospects<sup>31</sup>. With improved knowledge about HD biology associated to more effective and safe therapies, the management of this pathology has improved considerably in the last 50 years<sup>32</sup>.

Based in the epidemiological collections of *PAINEL-Oncologia Brasil*<sup>6</sup>, the use of chemotherapy is substantially greater when compared to radiotherapy to treat HD, revealing that chemotherapy alone is still strongly considered. For more than two decades, a debate about the use of chemotherapy alone in contrast to combined modality<sup>33</sup> is still taking place. However, non-combined treatment exposes the patient to greater doses of chemotherapeutics which may result in harms to the patient's health because of the toxicity, indicating that radiotherapy is not to be rejected during great part of the therapy<sup>12</sup>.

Studies prove that therapy doses typically applied in the past, mostly alone, are considerably high when compared with current doses<sup>34</sup>, which reinforces still more the importance of this association. However, other initial studies concluded that after three cycles of treatment with negative PET radiotherapy may not be necessary<sup>35</sup>. Radiotherapy has high costs and implies in bureaucracy by the ruling entities, which prevents its dissemination across the country notwithstanding its relevance in the therapeutic setting of oncologic pathologies<sup>36</sup> as HD. Although essential for patients diagnosed with HD, Brazil's socioeconomic context do not favor its regular use.

Tables 1 and 2 are related to the number of cases diagnosed (7,905) and to the number of patients submitted to oncologic therapies (7,757) and based in the same periods, places and age-ranges, with discrepancies of the number of patients with HD who did not submit to the treatments (148 individuals). This might be justified by specific conditions of each case or non-access to the treatment, very common in many regions, standing out the Southeast region. Although Brazil is a country in development, there are strong structures to treat oncologic diseases, however, the access is still challenging due to investments issues.

By analogy, regardless of low general incidence of HD in the cases diagnosed, the prevalence is bigger in youngsters and adults of European descent<sup>2</sup>. In 2018, 8,500 individuals were diagnosed in USA, corresponding to approximately 220 thousand individuals affected by this pathology<sup>5</sup>. In addition, the relative survivorship of HD in the United States accounts for 88.3% of the cases which added to the drop of the mortality rate of 4.5%/year from 2010 to 2019<sup>5</sup> adjusted by age confirms the high rate of cure<sup>3</sup>. Typically, the commonly therapies for

HD applied in Europe and in the United States initiate with chemotherapy followed by radiotherapy<sup>16</sup>.

There is a clear discrepancy between the prevalence of HD in USA and in Brazil, justified by the USA's higher population density and higher European descendants corresponding to 72.4% of the total population according to the 2010 Census<sup>37</sup>. Furthermore, developed countries count with high number of SIS<sup>38</sup>, favoring better notification and status of HD.

Epidemiological data collection tend to be flawed in countries in development<sup>38,39</sup>. There are obstacles for the objective evaluation of the number of individuals diagnosed and therapy-related procedures. This gap was more evident at the North region with lower numbers registered for the variables, possibly due to less development and poor access to health services, with less surgical beds and less oncologic procedures. Another obstacle to the collection of data about specific procedures and physical resources for the treatment of HD is the number of surgical beds and oncologic procedures attributed to a single group of the disease at DATASUS platform<sup>4</sup>.

In developed countries as USA, more accessible, wide and complete information systems are available because of more investments in data quality<sup>38</sup>. An objective analysis of the HD status depends on diagnostic data, mortality rate and survivorship and development of studies for screening and therapeutic. It is essential to revise the errors found at the data collecting institutions for a proper elaboration of health interventions, improved quality-of-life and future researches<sup>5,38,39</sup>.

## CONCLUSION

This study attempted to compare surgical therapy with protocol DH-II-90 in youngsters and adults. The protocol is less invasive and was developed to reduce surgical practice. Based in data collected at DATASUS, it has been shown the scarce use of surgery because is riskier for the development of post-surgical complications and infections.

The protocol consists in a combined chemotherapy and radiotherapy allowing the treatment of the pathology disseminated and localized control of the tumor. In addition, the Southeast region is more expressive in regard to the disease, possibly because of higher populational density.

The epidemiological profile of HD has been clearly demonstrated and helps to compare surgery with the protocol DH-II-90. The findings compatible with the literature support the analyzes for the elaboration of policies to be implemented to more vulnerable regions as it was concluded that upon the application of the protocol, mortality rate by HD dropped in Brazil and worldwide.

## CONTRIBUTIONS

All the authors contributed to the study design, acquisition, analysis and/or interpretation of the data, wording and critical review. They approved the final version to be published.

## DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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