Antibiotic prophylaxis in sickle cell disease: a cross-section study of adherence and associated costs

Antibiotico profilaxia na doença falciforme: um estudo transversal de adesão e custos associados

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ABSTRACT
Objective: To assess adherence to antibiotic prophylaxis and to describe the cost of prophylactic antibiotics in Sickle Cell Disease (SCD). Methods: Cross-sectional study with 115 children. Adherence was assessed through caregiver interviews and medical records. Costs and posologies were assessed through the Brazilian SCD Guidelines. Results: 50.4% of the patients were male. The mother was responsible for answers (83.5%) and the main caregiver (86.1%). Maximum adherence was achieved in 45.2%. There was no statistically significant association between adherence and the studied variables. The total cost was US$ 102,824.50. The average annual cost per adherent patient was US$ 196.41. Conclusion: Adherence to prophylactic antibiotics was low and actions are needed to increase it, even though the costs of this action are low.

Keywords: sickle cell disease, antibiotic prophylaxis, medication adherence, costs and cost analysis.

RESUMO
Objetivo: Avaliar a adesão à profilaxia antibiótica e descrever os custos desta terapia em crianças com Doença Falciforme (DF). Métodos: Estudo transversal com 115 crianças. Adesão foi avaliada através de entrevistas com cuidadores e prontuários médicos. Os custos e a posologia foram retirados do Protocolo Clínico e Diretrizes Terapêuticas para DF. Resultados: 50,4% dos pacientes eram do sexo masculino. A mãe foi a principal responsável por responder as entrevistas (83,5%) e a principal cuidadora (86,1%). Adesão máxima foi encontrada em 45,2% dos pacientes. Nenhuma das variáveis analisadas obteve diferença estatística. O custo total da terapia profilática foi de US$ 102,824.50. O custo médio anual por paciente aderente foi de US$ 196.41. Conclusão: A adesão à antibioticoterapia profilática foi baixa e ações são necessárias para melhorá-la, apesar do baixo custo desta ação de saúde.

Palavras-chave: anemia falciforme, aderência à medicação, custos e análise de custo, antibioticoprofilaxia.

1 INTRODUCTION

Hemoglobinopathies represent the most prevalent genetic diseases in the population, the set of hemoglobin combinations SS, SC, SD, S/Beta Thalassemia, S/Alpha Thalassemia is called Sickle Cell Disease (SCD), which is a public health problem with great clinical, social and epidemiological impact[1]. According to data from the National Newborn Screening Program (PNTN), about 3,500 children/year are born with SCD in Brazil, corresponding to 1/1,000 live births. In the state of Minas Gerais, where this study was conducted, SCD with homozygous

SS, or Sickle Cell Anemia (SCA), has an incidence of 1:1400[2,3]. In Brazil, the PNTN was first implemented in Minas Gerais in 1998 and consolidated in all units of the federation in 2012[2].

Infectious complications are an important cause of mortality in SCD worldwide, improvements in medical care in the past decades have been increasing the survival of children and allowing more patients to reach adulthood, in Brazil, around 37.5% of all deaths in SCD happen before the patient reaches nine years[4,]. These measures include early diagnosis in newborns through the heel prick test, immediate referral to specialized centers for outpatient control of these children, additional vaccination, prescription of folic acid and prophylactic penicillin therapy for regular use[4,5]. In countries where newborn screening for hemoglobinopathies was instituted, mortality decreased from 8% to 1.8%, due to earlier diagnoses and immediate monitoring of patients in specialized centers[6].

In Minas Gerais, the mortality rate in children with SCD is 5.6%, with the most common cause of death being an episode of pneumonia/acute chest syndrome followed by sepsis[7]. According to Branco (2007), patients with chronic diseases have serious difficulties in adhering to recommendations suggested by the health team, and low adherence can be identified as the main cause for increased morbidity in SCD patients[9,10].

The criteria for analyzing treatment adherence are complex, and there is insufficient knowledge of the necessity for antibiotic prophylaxis among parents and healthcare professionals[9-11]. This makes low adherence a common problem in outpatient clinics, requiring greater efforts to identify patients at higher risk for non-adherence[12,13]. SCD represents an important cost for the Brazilian Public Health System (SUS), due to continuous use of medications, regular multidisciplinary consultations, expanded immunization schedule, periodic hematological examinations; blood transfusions and frequent hospitalizations[2].

The objectives of this study were to assess adherence to prophylactic antibiotics in children with SCD, to analyze factors that may influence adherence, and to describe the cost of prophylactic antibiotics for SUS.

2 METHODS

Quantitative cross-sectional retrospective study in a sample of 126 children born between March 1998 and April 2007 diagnosed with SCA or heterozygous SCD (SC, Sβtal^{o}, Sβtal^{+} and SD).

Inclusion criteria were: being diagnosed with SCD by a standardized methodology adopted (isoelectric focusing followed by high performance liquid chromatography) by the Federal University of Minas Gerais (UFMG), having outpatient follow-up at Fundação

Hemominas Juiz de Fora (JFO), and having signed the Informed Consent Form (ICF). Exclusion criteria were: diagnosis by another methodology, non-adherence to the JFO follow-up protocol, death and transfers.

In total, 11 patients were excluded, 4 due to death before signing the ICF and 7 due to loss of follow-up. The final study population was 115 children. The variables studied were: sex, type of SCD, maximum adherence, education of the main caregiver and socioeconomic profile.

Medical records were reviewed to obtain clinical data, and a semi-structured interview composed of eight questions adapted from Bitarães *et al* (2008)[14] was performed to assess adherence[15]. The interviews were carried out individually with the main caregivers at JFO. Maximum adherence was defined through regularity of medication intake (daily use with 12 hour intervals) and adequate dosage.

For the socioeconomic profile, a questionnaire from the National Institute of Educational Studies and Research (INEP) was applied [16]. All of the patient's caregivers signed the ICF before data collection.

The total number of phenoxymethylpenicillin vials used by the child was assessed using the Brazilian Ministry of Health's Clinical Protocol and Therapeutic Guidelines for SCD[17]. The price of phenoxymethylpenicillin was extracted from the Brazilian Medicines Market Regulation Chamber (CMED) [18]. This study adopted the Maximum Consumer Price (MCP) from CMED's latest version, and a Tax on Circulation of Goods and Services rate of 18%. The total cost for each patient was calculated multiplying the total number vials used and the unit value of each item[18].

We considered the version of the phenoxymethylpenicllin dispensed by our institution's pharmacy, the 60 milliliters reconstituted solution bottle of oral Penicilin 80,000 IU/ml, with a MCP of US $ 4.79 for each vial [18].

The prophylactic regimen recommended from diagnosis to 5 years of age (oral) is[2]:

• Children up to 3 years old: 125 mg (equivalent to 200,000 IU or 2.5 mL) every 12 hours (250 mg/day);

• Children aged 3 to 5 years: 250 mg (equivalent to 400,000 IU or 5 mL) every 12 hours (500 mg/day).

The Total Average Cost (TAC) of Phenoxymethylpenicillin was calculated as follows: The total number of vials needed was a result of the number of days each child lived until the moment of the interview, considering maximum adherence to the medication schedule, multiplied by the daily dosage recommended in each age group. Then, this total number of vials was multiplied by the unit price of the medicine, finding the total cost for each individual. The

TAC was found through the average of all total costs in the research. For the average annual cost, the TAC of each child was divided by their age at the moment of the interview.

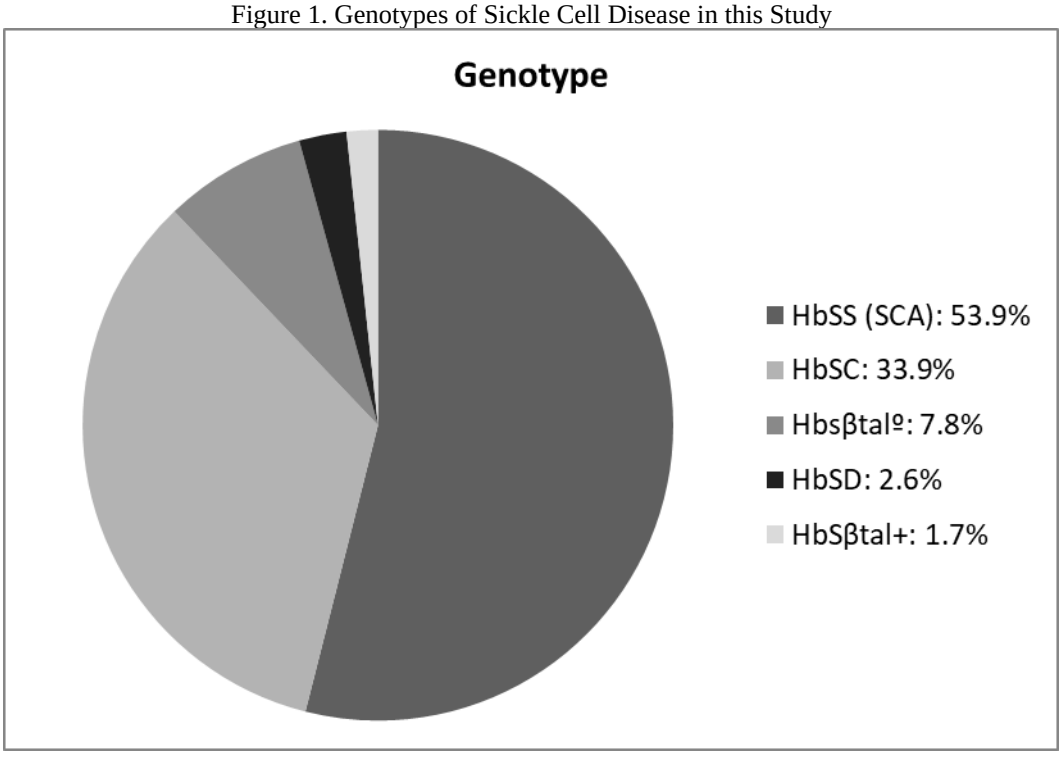
The cost perspective adopted is that of SUS paying for the SCD treatment to service providers and reference centers. The methodology used is Bottom up, in which we start from unit values to estimate the total values. The costs are presented in US dollars (exchange rate 1 US = BRL 5.47 on February 1, 2022).

Quantitative data were stored in Excel 2003® and subjected to statistical analysis using SPSS14®. The research was approved and registered with the Research Ethics Committee under No. 3.489.059 and No. 419.415.

3 RESULTS

Of the 115 children in this study, 50.4% were male and 53.4% had SCA (Figure 1). The mother was the main responsible for the answers (83.5%) and the main caregiver who administered the medication (86.1%).

Figure 1. Genotypes of Sickle Cell Disease in this Study



Source: The Authors

Maximum adherence was defined through regularity of medication intake (daily use with 12-hour intervals) and adequate dosage. In this study, maximum adherence was identified in 45.2% of the sample, and 26.1% of children missed taking the medication at least 5 times.

Table 1 shows the frequencies regarding the number of abstentions in the administration of medication by the caregivers. The association between factors that influenced adherence is shown in *Table 2*.

Table 1. Abstaining from prophylactic penicillin administration in children with SCD followed at JFO.

Abstentions	Frequency (%)
None	45.2
1 or 2 times	16.5
3 to 4 times	12.2
5 times or more	26.1
Total	100

Source: Semi-structured interview adapted from Bitarães et al. (2008)

Table 2. Adherence to prophylactic treatment of children with SCD accompanied at JFO, depending on the factors considered.

Factors	Treatment adherence		Total	P-value
	Yes (n,%)	No (n,%)		
Difficulty taking the medicine				0,07
No	38 (48.1%)	41 (51.9%)	79	
Yes	11 (30.6%)	25 (69.4%)	36	
Understands medical guidelines				0,26
Yes	36 (46.1%)	42 (53.9%)	78	
No	13 (35.1%)	24 (64.9%)	37	
Understands reason for the use of medication				0,87
Yes	32 (42.1%)	44 (57.9%)	76	
No	17 (43.6%)	22 (56.4%)	39	
Mother's education level				0,15
< Fourth grade	22 (51.2%)	21 (48.8%)	43	
> Fifth Grade	27 (37.5%)	45 (62.5%)	72	

Source: Semi-structured interview adapted from Bitarães et al. (2008)

In 79 interviews, there were no reports of difficulty in administering the medication, with a maximum adherence of 48.1% in this group. In 36 interviews, complaints about the administration of penicillin were identified, determining an impact on maximum adherence, which was 30.6%., the data showed a tendency for statistical significance (p = 0.07). The main difficulty for caregivers was the taste of the medication and forgetfulness.

When asked about if they understood the instructions given the multidisciplinary team, 78 respondents answered that they understood, in this group 46.1% of the children had maximum adherence to treatment. Among the 37 respondents who answered negatively, maximum adherence was 35.1% (p=0.26).

When asked about if they understood the reason for the use of antibiotic prophylaxis (functional asplenism), 76 parents responded positively, with 42.1% maximum adherence. In the 39 interviews with negative answers, maximum adherence was 43.6% (p = 0.87).

Regarding the mothers' education, in the group that studied up to the fourth grade of elementary school, maximum adherence was 51.2%. Of the 72 mothers with education above fifth grade, maximum adherence was 37.5% (p = 0.15).

Family income was less than minimum wage in 37.4% of the sample, between one and two minimum wages in 35.7%, and between two and ten minimum wages in 26.9%. This variable was not significant for maximum adherence (p = 0.98).

Taking into account what was recommended by the Ministry of Health, the total expenditure with phenoxymethylpenicillin in the sample was US $ 102,824.50 (Table 3). Considering only those who had maximum adherence (45.2%), this value was 47,922.65.

The Total Average Cost (TAC) per patient in the sample was US $ 901.97 (PD ± 230.97) and the average annual cost per patient was US $ 194.49 (PD ±19.26). Considering only those who had maximum adherence, the total average cost per patient was US $ 921.59 (PD ± 229.58) and the average annual cost per patient was US $ 196.41 (PD ± 17.91). *Table 3* shows the average total and annual costs per patient in the age groups where there is a change in the dosage of the medication.

Table 3: Average costs of antibiotic prophylaxis per patient

Age	Average Total Cost (US dollar)	Pattern-deviation (PD)	Average Annual Cost (US dollar)	Pattern-deviation (PD)
< 3 years	297.31	± 117.19	145.97	± 0.00
3 to 5 years	736.29	± 181.85	180.37	± 18.19
> 5 years*	1021.76	± 0.00	204.35	± 0.00
Total	901.97	± 230.97	194.49	± 19.26

Source: Agência Nacional de Vigilância Sanitária - Anvisa. Câmara de Regulação do Mercado de Medicamentos (CMED) adapted by the Authors

4 DISCUSSION

Adherence is a complex multifactorial behavior, influenced by social and economic factors (age, sex and socioeconomic level), factors related to the patient (knowledge, attitudes

and beliefs), conditioning factors and treatment-related factors (the severity of symptoms and diseases, the complexity of the medical treatment regime, the duration of treatment and adverse effects), characteristics of the healthcare provider (communication, skills, training and resources) and configuration (coverage of medicines, sharing of drug costs, access to medication and clinical care)[10].

Although there are no totally reliable methods for assessing adherence, the use of questionnaires is common in health research, as it is easy to apply and low cost, even though it is not the most specific method for quantification[20]. In the present study, the following parameters were defined to quantify adherence: regularity in the administration and dosage of the medication, with maximum adherence being characterized the child who never stopped receiving the medication at the posological intervals. An analysis of the difficulties faced when administering the drug was also performed.

Bitarães *et al*.[14] (2008) and Rodrigues *et al*.[17] (2020) discussed that the information obtained from medical records should be considered an imprecise method for assessing adherence[16,17,21,22]. The review of medical records in our study showed a maximum adherence to prophylactic penicillin of almost 80%, which was not confirmed through the analysis of interview data.

Assessing adherence is complex and difficult to quantify precisely, either by direct methods (observing medication intake and administration) or indirect methods (questionnaires, interviews, home visits and active search). Some authors report that methods of estimating adherence, such as pill counts, drug withdrawal counts in pharmacies, or the measurement of serum or urine drug levels, tend to overestimate adherence[23-25].

The number of children studied (n = 115) was higher than in most studies with similar objectives[15,26,27], and Teach et al.[16] (1998) was the only one with a larger sample (123 children). All of the sample was diagnosed with a single methodology, which enabled a homogeneous sample.

In our study, 36 caregivers reported having difficulties administering the prophylactic penicillin. According to Bitarães *et al*.[14] (2008) and Walsh *et al*.[23] (2014), the main causes of non-adherence were: beliefs about safety, medication effectiveness, taste of medication, administration errors at home, forgetfulness of the caregiver and daily occupations as an impediment.

In accordance to the literature, there was no significant association between adherence, sex, education of the caregiver or family income. Understanding the medical guidelines and the reasons behind the use of the medicine also showed no statistical significance, which was also

observed by Bitarães (2008) *et al.* [14]. The mothers' education level did not guarantee a difference in relation to non-adherence.

In our study, prophylaxis with phenoxymethylpenicillin did not represent a high economical burden, costing the public health system annually US $ 196.41 (PD ± 17, 91) per patient with maximum adherence. Acute conditions, such as invasive pneumococcal disease, are the main economic burden in children with SCD, due to their frequency and resources needed for adequate treatment[28], a meta-analysis that included 880 children in three trials showed that the use of prophylactic penicillin decreases the incidence of pneumococcal septicaemia in children under the age of five years and the medication had a favorable safety profile[11]. A. Brazilian study showed that the antibiotic prophylaxis in children with SCD had a cost-effectiveness that exceeded the expenses resulting from hospitalizations due to complications of the disease[30]. Therefore, prophylaxis with oral penicillin is a proven way to avoid deaths in children with sickle cell disease.

The inclusion of oral penicillin (phenoxymethylpenicillin) in the national guidelines for SCD, as an alternative to the injectable form, humanizes care for children with SCD, since they must be administered this drug until five years of age[2]. However, even with the use of oral penicillin, maximum adherence still did not surpass 50% in our study.

Robust studies evaluating the economic burden of SCD are rare, making it difficult for a consensus to be reached in the literature. Inadequate adherence to antimicrobial prophylaxis is common and can contribute to an unsatisfactory clinical control of the disease, increasing the morbidity, mortality and costs due to infectious complications. The issue of “non-adherence” is an opportunity for discussion among the multidisciplinary team involved in healthcare.

5 CONCLUSION

Actions to strengthen adherence are necessary, as they help to improve the quality of life and increase life expectancy in SCD, while also reducing disease-related costs since phenoxymethylpenicillin is relatively cheap and its use is not dependent on sophisticated technology, contrary to the treatment of infectious complications. Increasing adherence may involve factors such as better caregiver education, monitoring, access to pharmacy, family support and/or the relationship with health professionals and training in the Health Care network.

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REFERENCES

1- Ducatti RP, Teixeira AEA, Galão HA, Bonini-Domingos CR, Fett-Conte AC. Investigação de hemoglobinopatias em sangue de cordão umbilical de recém-nascidos do Hospital de Base de São José do Rio Preto. Revista Brasileira de Hematologia e Hemoterapia 2001; 23(1): 23-29.

2- BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Secretaria de ciência, tecnologia e insumos estratégicos. Portaria conjunta nº 05, de 19 de fevereiro de 2018. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Doença Falciforme. Brasília (Distrito Federal), 2018.

3- Cançado RD, Jesus JA. A doença falciforme no Brasil. Rev. Bras. Hematol. Hemoter 2007; 29 (3): 204-206.

4- Miranda JF, Matalobos, ARL. Prevalência da anemia falciforme em crianças no Brasil. Brazilian Journal of Health Review 2021;4(6):26903-26908.

5- Streetly A, Sisodia R, Dick M, Latinovic R, Hounsell K, Dormandy E. Evaluation of newborn sickle cell screening programme in England: 2010-2016. Arch Dis Child 2018;103(7):648-653.

6- Fernandes APPC, Januário JN, Cangussu CB, Macedo DL, Viana MB. Mortalidade de crianças com doença falciforme: um estudo de base populacional. Jornal de Pediatria 2010, 86(4):279-284.

7- Branco CM. Adesão ao tratamento anti-retroviral por cuidadores de crianças e adolescentes soropositivos de uma unidade de saúde do Estado do Pará. [Tese de Mestrado] Programa de Pós-Graduação em Teoria e Pesquisa do Comportamento. Belém, 2007.

8- Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, Rosen DL, Sista P, Lohr KN. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med. 2012; 157(11):785-95.

9- Patel NG, Lindsey T, Strunk RC, DeBaun MR. Prevalence of daily medication adherence among children with sickle cell disease: a 1-year retrospective cohort analysis. Pediatr Blood Cancer 2010; 55(3):554-6.

10- Duncan N A, Kronenberger WG, Hampton KC, Bloom EM, Rampersad AG, Roberson CP, Shapiro AD. A validated measure of adherence to antibiotic prophylaxis in children with sickle cell disease. Patient preference and adherence 2016; 10:983–992.

11- Rankine-Mullings AE, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease (Review). Cochrane Database of Systematic Reviews 2021:3. Art. No.: CD003427

12- Reeves SL, Tribble AC, Madden B, Freed GL, Dombkowski KJ. Antibiotic Prophylaxis for Children With Sickle Cell Anemia. Pediatrics March 2018, 141 (3):e20172182.

13- Yee ME, Bakshi N, Graciaa SH, Lane PA, Jerris RC, Wang YF, Yildirim I. Incidence of invasive Haemophilus influenzae infections in children with sickle cell disease. Pediatr Blood Cancer 2019; 66(6):e27642.

14- Bitarães EL, Oliveira BM, Viana MB. Adesão à antibioticoterapia profilática em crianças com anemia falciforme: um estudo prospectivo. Jornal de Pediatria 2008; 84(4):316-322.

15- Babiker MA. Compliance with penicillin prophylaxis by children with impaired splenic function. Trop Geogr Med 1986; 38(2):119-22.

16- Teach SJ, Lillis KA, Grossi M. Compliance With Penicillin Prophylaxis in Patients With Sickle Cell Disease. Arch Pediatr Adolesc Med. 1998;152(3):274–278.

17- Rodrigues DOW, Teixeira MTB, Ribeiro LC, Santos OF, Sudário LC, Sana DEM, Campos EMS. Adesão ao uso de penicilina profilática em crianças com Doença Falciforme acompanhadas na Fundação Hemominas Juiz de Fora. Pediatria – Experiências Profissionais e Relatos de Casos. 2020; 1(1):1-13.

18- BRASIL. Agência Nacional de Vigilância Sanitária - Anvisa. Câmara de Regulação do Mercado de Medicamentos (CMED). Disponível em <https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/precos>.

19- MINAS GERAIS. Secretaria de Estado de Fazenda. Evolução anual da arrecadação. Disponível em <http://www.fazenda.mg.gov.br/governo/receita_estado/evolucao_anual/evolucao_anos_anterioresef.html>.

20- Matsui DM. Drug compliance in pediatrics. Clinical and research issues. Pediatr Clin North Am. 1997; 44(1):1-14.

21- Lasmar LMLBF, Camargos PAM, Costa LF, Fonseca MTM, Fontes MJF, Ibiapina CC, et al. Compliance with inhaled corticosteroid treatment: rates reported by guardians and measured by the pharmacy. Jornal de Pediatria 2007; 83(5):471-476.

22- Tebbi CK. Treatment compliance in childhood and adolescence. Cancer 1993;71(10 Suppl):3441-9.

23- Walsh KE, Cutrona SL, Kavanagh PL, Crosby LE, Malone C, Lobner K, Bundy DG. Medication adherence among pediatric patients with sickle cell disease: a systematic review. Pediatrics 2014;134(6):1175-83.

24- Pegelow CH, Armstrong FD, Light S, Toledano SR, Davis J. Experience with the use of prophylactic penicillin in children with sickle cell anemia. J Pediatr 1991;118(5):736-8.

25- Leite SN, Vasconcellos MPC. Adesão à terapêutica medicamentosa: elementos para a discussão de conceitos e pressupostos adotados na literatura. Ciência & Saúde Coletiva 2003; 8(3):775-782. 26- Elliott V, Morgan S, Day S, Mollerup LS, Wang W. Parental health beliefs and compliance with prophylactic penicillin administration in children with sickle cell disease. J Pediatr Hematol Oncol. 2001;23(2):112-6.

27 - Buchanan GR, Siegel JD, Smith SJ, DePasse BM. Oral penicillin prophylaxis in children with imparied splenic function: a study of compliance. Pediatrics 1982;70(6),926-3029- Silva-Pinto AC, Costa FF, Gualandro SFM, Fonseca PBB, Grindler CM, Souza HCR, et al. Economic burden of sickle cell disease in Brazil. 2022:17(6): e0269703.

28- Pereira BT, Souza GS. Anemia falciforme: letalidade, agravos e fatores epidemiológicos. Brazilian Journal of Health Review. 2022;5(2):5000-7.

29- Silva-Pinto AC, Costa FF, Gualandro SFM, Fonseca PBB, Grindler CM, Souza HCR, et al. Economic Burden of Sickle Cell Disease in Brazil. 2022:17(6): e0269703

30- Motta FVR, Souza SPS, Fonseca LANS, Chaoubah A, Rodrigues DOW. Analysis of the costs of the basic care line for sickle cell disease in Brazilian children under 5 years of age. Hematol Transfus Cell Ther. 2023;45(S2):S113−S118.