

Description of a disease management service for children newly diagnosed with sickle-cell disease

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Abstract

Objective: To assess the results of the health condition management service provided for children with sickle cell disease (SCD). **Methods:** a cross-sectional study of the health condition management service offered to newly diagnosed children with SCD treated between January 2016 and December 2019 at the Blood Center in Belo Horizonte, Brazil. The service was provided by a clinical pharmacist and an academic from the pharmacy course, with data from the initial consultation (start of drug use) performed in a pharmacist's office and telephone contact carried out eight days later. All children seen at the service were evaluated, and their demographic characteristics, compliance with the beginning of the use of prophylactic drugs for sickle cell disease (phenoxymethylpenicillin and folic acid) according to the protocol of the Ministry of Health (within 90 days after birth), and documented reason in case of non-compliance. The doubts regarding the medications and the standardized interventions of the service to the children's guardians were also described. The difference in the distribution of variables in the adequacy and non-adequacy group to the MS protocol was assessed using Pearson's chi-square test (categorical) and Mann-Whitney (numerical). **Results:** In the SCD condition management service, all children together with their guardians (N = 298) had their first consultation with the pharmacist (initial dispensation day), however, only 185 (62.1%) participated in the pharmaceutical service by telephone (eight days after the initial dispensing). Approximately 88.3% of children started using drugs for sickle cell disease according to the protocol of the Ministry of Health; the most frequent reason for non-compliance was the late diagnosis in the complementary health system (22.9%). The guardians pointed out 63 doubts about the medications, highlighting their non-acceptance by the child (28.6%), and for all doubts standard pharmaceutical guidelines were provided in the service. **Conclusion:** It was identified that the health condition management service provided is relevant, since most of those responsible for the children with SCD had doubts about their medication after the administration of medications began. The pharmacist contributes positively to the pharmacotherapeutic management of SCD, promoting empowerment about the correct use of medicines.

Keywords: sickle cell, pediatrics, pharmaceutical services, telemonitoring, telepediatrics.

Descrição do serviço de gestão da condição da saúde voltado a crianças recém-diagnosticadas com doença falciforme

Resumo

Objective: To assess the results of the health condition management service provided for children with sickle cell disease (SCD). **Methods:** a cross-sectional study of the health condition management service offered to newly diagnosed children with SCD treated between January 2016 and December 2019 at the Blood Center in Belo Horizonte, Brazil. The service was provided by a clinical pharmacist and an academic from the pharmacy course, with data from the initial consultation (start of drug use) performed in a pharmacist's office and telephone contact carried out eight days later. All children seen at the service were evaluated, and their demographic characteristics, compliance with the beginning of the use of prophylactic drugs for sickle cell disease (phenoxymethylpenicillin and folic acid) according to the protocol of the Ministry of Health (within 90 days after birth), and documented reason in case of non-compliance. The doubts regarding the medications and the standardized interventions of the service to the children's guardians were also described. The difference in the distribution of variables in the adequacy and non-adequacy group to the MS protocol was assessed using Pearson's chi-square test (categorical) and Mann-Whitney (numerical). **Results:** In the SCD condition management service, all children together with their guardians (N = 298) had their first consultation with the pharmacist (initial dispensation day), however, only 185 (62.1%) participated in the pharmaceutical service by telephone (eight days after the initial dispensing). Approximately 88.3% of children started using drugs for sickle cell disease according to the protocol of the Ministry of Health; the most frequent reason for non-compliance was the late diagnosis in the complementary health system (22.9%). The guardians pointed out 63 doubts about the medications, highlighting their non-acceptance by the child (28.6%), and for all doubts standard pharmaceutical guidelines were provided in the service. **Conclusion:** It was identified that the health condition management service provided is relevant, since most of those responsible for the children with SCD had doubts about their medication after the administration of medications began. The pharmacist contributes positively to the pharmacotherapeutic management of SCD, promoting empowerment about the correct use of medicines.

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Introduction

Sickle-cell disease (SCD) is characterized by the presence of hemoglobin S in the red blood cells. It is diagnosed through the neonatal screening test. In Brazil, it is spread in a heterogeneous manner, being more prevalent where the proportion of black-skinned people is higher. In Minas Gerais, the incidence of SCD is of 1 every 1,400 live births, according to data of the National Neonatal Screening Program (*Programa Nacional de Triagem Neonatal*, PNTN).^{1,2}

Children up to five years old present even higher chances of death and development of severe health conditions resulting from infections, and this is the main cause of death among these patients.³⁻⁵ To avoid SCD complications, in Minas Gerais, immediately after confirming the diagnosis, the patients with SCD are referred to the medium-complexity reference center – Hemominas Foundation – for monitoring and adequate disease management.⁶

The adequate management of SCD mainly includes the use of prophylactic antimicrobials, and phenoxymethylpenicillin, a penicillin, is the medication chosen to prevent infections mainly related to *Streptococcus pneumoniae*. Folic acid is also used to prevent hemolytic anemia, since the exogenous source of folate is necessary for the synthesis of nucleoproteins and maintenance of adequate erythropoiesis. It is recommended that initiation of these medications occurs before the child is 90 days old. Some patients with disease progression may require the use of analgesic and anti-inflammatory drugs for pain crises, as well as of iron chelators and hydroxyurea for greater counts and higher quality of red blood cells.¹

In the initial appointment in the reference centers, the children are seen by a multidisciplinary team and the first standardized information about the disease is shared with those responsible for the care of the children. In the appointment with the clinical pharmacist, dispensation of the prophylactic treatment for complications associated with SCD and interventions with the children's caregivers are conducted in order to reduce complications, such as pneumonia, pain crises, and hemolytic anemia.^{2,3,7} This disease management service is extremely important as it has standardized interventions and coordinated care communications for people with specific health conditions in order to ensure compliance with the guidelines.⁷

In this scenario, the pharmacist plays an important role, mainly regarding the monitoring of drug use for the global clinical management of this disease⁷ and the impact on the quality and increase of life expectancy in patients with SCD.¹ Thus, this study aims at assessing the results of the disease management service directed to children newly diagnosed with SCD assisted in the Blood Center of Belo Horizonte (BCBH), Minas Gerais, Brazil, as well as the factors associated with the adequacy of the pharmacotherapy of these children to national guidelines.

Methods

A cross-sectional study carried out in the pharmacy sector at the outpatient clinic of the Blood Center of Belo Horizonte (BCBH - *Hemocentro de Belo Horizonte*) with all children with SCD in partnership with the Ministry of Health, the State Health Secretariat of Minas Gerais and the Federal University

of Minas Gerais (*Universidade Federal de Minas Gerais*, UFMG). The BCBH outpatient clinic of the Hemominas Foundation is a reference in the diagnosis and treatment of coagulopathies and hemoglobinopathies, including SCD. When an abnormal hemoglobin (Hemoglobin S) is detected in the neonatal screening test, which indicates the diagnosis of SCD, all patients assisted in the Brazilian public Health System (*Sistema Único de Saúde – SUS*) or in the complementary health system are referred to the BCBH by the Center for Diagnostic Support Actions and Research (*Núcleo de Ações e Pesquisa em Apoio Diagnóstico*, NUPAD) of the UFMG Medical school.

In the unit, after the diagnosis, the children are assisted by a pediatric hematologist, who prescribes medications for prophylactic and adjuvant treatments and refers the patients to the pharmacy sector. The medications prescribed in compliance with the Ministry of Health guidelines are phenoxymethylpenicillin and folic acid and their doses vary according to the children's age.⁸

After receiving the first prescription from the pediatric hematologist, all children with SCD are referred to the pharmacy sector of the BCBH and have their first pharmaceutical consultation when the medications prescribed are dispensed. The first consultation is carried out in an office with a pharmacist and a pharmacy student, who provide the child's guardian with information about all medications dispensed, including guidelines about the indication, dosage, method of preparation, way of administration, adequate location for storage, validity of prescription, and expiration date of the medications. These pharmaceutical interventions are reinforced upon delivery to the child's guardian of an educational material (booklet and dosage chart) prepared by the pharmacists responsible for the service. This first pharmaceutical consultation lasts approximately twenty minutes.

Eight days after the first consultation, the patients' guardians are contacted by telephone to verify their understanding of the information provided during dispensation and also to identify and elucidate possible questions based on some of the standardized questions in the service about indication, method of preparation, storage and acceptance of the medications, expiration date after reconstitution of penicillin, validity of the prescription, and date for the next dispensation. The interval established for the telephone contact was determined taking into account the fact that the potassium phenoxymethylpenicillin dispensed by the service expires up to seven days after its reconstitution. Therefore, this day is strategic for addressing the date of a new dilution. In case of failure in the initial telephone contact, another three attempts are made on different days. The guardian can also contact the pharmacist by telephone to ask questions or to schedule an additional appointment. The teleappointment lasts a mean of ten minutes depending on the doubts of those responsible for administering the children's medications. For each question presented, an intervention is conducted, and these interventions are already standardized in the service. In this study, only the results referring to the service's initial consultations (first pharmaceutical consultation and first telephone contact) will be presented.

The population included in the study consisted of all pediatric patients diagnosed with SCD assisted by the clinical pharmacist and by a pharmacy student from the disease management service of the BCBH outpatient clinic of the Hemominas Foundation from January 1st, 2016, to December 31st, 2019



(N=298). It is noteworthy that all the children went through the first pharmaceutical consultation, but it was not possible to contact all of their guardians by telephone.

During all the pharmaceutical consultations, either in person or by telephone, information on the patient's pharmacotherapy was collected, which was later recorded in a spreadsheet in the Microsoft Excel® software. After each appointment, the evolution is also recorded in the patient's electronic medical chart. The variables selected in the study were extracted from the medical records and indicators of the service and included the following data: age (in days old), gender, and time elapsed between birth and first appointment (in days). Compliance of medication use by the child with SCD was also evaluated according to the Ministry of Health guidelines (yes versus no), which recommends its initiation 90 days after the birth of the child with SCD;⁸ as well as the documented reason for non-compliance. Data on telephone contacts made, time elapsed between the initial appointment and the call (in days), as well as questions and adverse events related to medications reported by the guardian (description of the answers when there were questions about the occurrence of adverse events or other questions) and the demographic data of filtered water availability in the residence (yes versus no) were also collected.

Descriptive data analysis consisted of frequency distributions for the categorical variables, and of measures of central tendency and dispersion for the continuous variables. The difference in the distribution of variables in the "adequacy to the Ministry of Health guidelines" and "non-adequacy to the Ministry of Health guidelines" groups was evaluated using Pearson's chi-square test, in the case of categorical variables, and by means of the Mann-Whitney test for continuous non-parametric variables. In relation to normal distribution, the variables were evaluated using the Kolmogorov-Smirnov test.

The information not provided by the patients was treated as missing data and excluded from the analysis. All the analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 25.0.

The project entitled "Dispensation of Medications for the Care of Children with Sickle-Cell Disease" was approved by the Research Ethics Committee of the Hemominas Foundation on August 21st, 2018, under CAAE registration No. 94238718.6.0000.5118.

Results

In the SCD management service, all the children together with their guardians had their first consultation with the pharmacist (day of initial dispensation) from January 2016 to December 2019 and were included in the study (N=298). Most of the children were male (n=164, 55.0%) and presented a median age of 42 days old (15 to 1,448 days old) and an interquartile range (IQR) of 27 (Table 1).

Telephone contacts were successfully established with 185 (62.1%) of the guardians. The median of the time elapsed between the initial appointment and the telephone contact was 10 days (IQR=7).

In the first consultation, standardized guidelines were provided by the service regarding the use of the medications dispensed for all those responsible for administering the medications for children with SCD. As for the telephone contact, standardized guidelines were provided for the questions presented. The most frequently identified question was about how to increase the child's acceptance to medication use (n=18; 28.6%). The standardized guidelines provided in the first appointment and in the telephone contact and the questions presented by the guardians are shown in Table 2. During the telephone contact, it was also identified that a minority (n=9; 3.02%) of those responsible for the children reported some adverse event related to the use of SCD medications, with diarrhea being the main reaction reported (n=7; 77.8%).

As for adequacy to the Ministry of Health guidelines, it was identified that 88.3% (n=263) of the children who participated in the study started using the medications for SCD up to 90 days after being born. When comparing the two groups (adequacy and inadequacy to the Ministry of Health guidelines) a significant association was identified only for the age variable.

For children in whom inadequacy to the Ministry of Health guidelines was identified (n=35; 11.8%), the reasons (Table 3) for non-compliance with the guidelines were identified, with late diagnosis in the complementary health system being the most frequent (n=9; 25.7%).

Table 1. Sickle-cell disease management in children assisted in the Hemominas Foundation and adequacy to the therapeutic guidelines. Belo Horizonte (MG).

Information	All N=298	Adequacy to the treatment guidelines ¹		p-value
		Adequate N=263 (88.2)	Inadequate N=35 (11.8)	
Sociodemographic				
Male gender n (%)	164 (55.0)	141 (53.6)	23 (65.7)	0.176*
Age (days old) Median (IQR)	42 (27)	38 (22)	136 (148)	<0.001**
Clinical condition management service				
Telephone contact made n (%)	185 (62.1)	163 (61.9)	22 (62.8)	0.920*
Adverse event reported n (%)	9 (3.0)	9 (3.4)	-	0.320*
Having filtered water to dilute the medications at home n (%)	121 (40.6)	105 (39.9)	16 (45.7)	0.749*
Doubts about the treatment n (%)	52 (17.4)	48 (18.3)	4 (11.4)	0.318*

*Dichotomous variable for which the Chi-square Test was performed. **Numerical variable in which the Interquartile Range (IQR) was presented and the Mann-Whitney test was performed. ¹Clinical and Therapeutic Guidelines for Sickle-cell disease.⁸

Table 2. Standardized pharmaceutical information provided during the first pharmaceutical consultation and phone contacts made by the sickle-cell disease (SCD) management service to the children assisted in the Hemominas Foundation, and adequacy to the therapeutic guidelines. Belo Horizonte (MG).

Standardized pharmaceutical guidelines ¹	Types of doubts identified in the telephone contact	Frequency n (%) N=63
Children starting to use the medication are in the adaptation phase; persist with administration. Do not repeat the dose if they do not take all the medication. Folic acid can be administered in the bottle.	Non-acceptance of the medication by the child	18 (28.6)
After being diluted, the oral phenoxymethylpenicillin suspension no longer has the validity indicated in the box and is valid for 7 days. Always on the same day of the week, the old flask must be discarded and a new one must be prepared.	Expiration date of the medication after dilution	15 (23.8)
Phenoxymethylpenicillin must be administered twice a day, with a 12h-interval. Folic acid is administered once a day together with the morning dose of phenoxymethylpenicillin.	Dosage	15 (23.8)
Phenoxymethylpenicillin is an antimicrobial used to avoid infections in children with SCD who present predisposition to some infections. Folic acid assists in the production of blood cells, slightly reducing anemia.	Indication of the medications	8 (12.7)
In the Blood Center, the prescription is valid for six months or until the date of medical return.	Validity of the medical prescription	5 (7.9)
Keep the medications in a dry and ventilated place. Do not store in the bathroom or in the kitchen. Keep out of the reach of children.	Storage location of the medications	2 (3.2)

¹All the studied patients had their first consultation with the pharmacist and received all the standardized information regarding medication use.

Table 3. Reason for inadequacy to the guidelines according to age at initiations of the sickle-cell disease management treatment in children assisted in the Hemominas Foundation. Belo Horizonte (MG).

Reasons for inadequacy to the guidelines	Frequency n (%) N=35
Reason not documented	14 (40,0)
Late diagnosis in complementary health system	9 (25.7)
Transfer from other service	5 (14.3)
Delay in first appointment	3 (8.5)
Refusal by the guardian	2 (5.7)
Late diagnosis due to sample lost	1 (2.9)
Late diagnosis in the Brazilian Public Health System	1 (2.9)

¹Clinical and Therapeutic Guidelines for Sickle-cell disease.⁸

Discussion

Disease management services are focused on a specific disease, which, in the case of this study, was pediatric SCD. In these services, it is sought to provide information and promote actions and appointments with a focus on the empowerment of those responsible for administering the medication.⁷ They are very applicable to the reality of the SCD diagnosis moment, when the child often has this single health condition. Thus, to the authors' knowledge, this study is the first to describe this type of service offered to children newly diagnosed with SCD and is relevant because it can be reproduced in other scenarios similar to the one presented, with the potential to improve medication use at this critical moment in the child's life.

The study has the limitation of having been carried out in only one unit of the Hemominas Foundation and presenting only the data of the initial appointments of the disease management service. In addition to that, the impact of the service on the patients' clinical evolution or mortality was not evaluated, which, although relevant, has limitations in its analysis, since multiple clinical factors inherent to the gestational period and after birth can influence them.

It is noteworthy that the proportion of treatments in accordance with the Ministry of Health guidelines for SCD was high (88.3%).⁸ This fact can be explained by the inclusion (in 1998) in the state of Minas Gerais of SCD in the list of exams performed by the Neonatal Screening Program.⁹

The main reason identified for non-compliance with the Ministry of Health guidelines was delay in diagnosis by the complementary health system, confirming the importance of consolidating an integrated care network. The patients who underwent the heel prick test in the complementary health system took longer to be referred to the treatment center and, therefore, started using medication later. There is lack of knowledge on the part of the health professionals about SCD diagnosis and treatment,⁴ which may have contributed to this late referral, the training of these professionals being important.

However, it is to be noted that, even late, adequate prophylaxis is extremely important, as it reduces the incidence of infection by *Streptococcus pneumoniae*, the main cause of death among patients with SCD in the first five years of life.^{5,9,10} The high risk of developing severe and recurrent infections in patients with SCD is due to the abnormal function of the spleen, which compromises the immune system. Thus, prophylaxis, especially when instituted in the first 90 days of the patient's life, tends to minimize such risk.^{11,12}



The disease management service focused on SCD provided by the pharmacist plays an important role in the empowerment of those responsible for patients with SCD, since the degree of unsatisfactory knowledge among patients/guardians after receiving information on the drugs prescribed during the medical consultation is documented in the literature.¹³ In the study locus, the initial appointment at the disease management service is the occasion in which the pharmacist, in a duly individualized way according to the reality of the patient/guardian, provides information on pharmacotherapy management.

The reassessment of knowledge about prophylaxis is carried out by means of a telephone contact with the person responsible for the patient which, according to the internal procedure defined in the unit, must be made on the eighth day after the date scheduled for initiation of the medications.

However, the relevance of the telephone approach was reinforced when it was identified that a considerable part of those responsible for the patients had questions about chemoprophylaxis. The problems related to acceptance of the medications by the children were highlighted. The palatability of the medication is an important point for its acceptability, and oral penicillin is constantly not accepted by the children due to its unfavorable taste to their palate.^{14,15} It is necessary to conduct studies and produce medications with greater palatability for children for better results in treatment.¹⁵

As for access to filtered water in the homes, which is essential for reconstitution of the powder for oral phenoxymethylpenicillin solution, it was identified that there is still a difficulty in accessing water suitable for consumption, which can be understood due to the socioeconomic fragility of the families assisted in the blood center services.^{4,16} As an alternative to this adversity, the guardians are instructed to boil water as recommended by the Ministry of Health.^{17,18}

It was identified that a minority of patients reported some adverse event related to the use of SCD medications, and this is due to the fact that this information was spontaneously reported. Common adverse reactions caused by phenoxymethylpenicillin are diarrhea, epigastric discomfort, nausea, vomiting; and those caused by folic acid are bad taste in the mouth, loss of appetite and nausea.¹⁹ In this study, diarrhea was the main reaction observed.

Finally, as the study was carried out only in only one Hemominas unit, its data cannot be generalized, further studies being needed to explore the magnitude of SCD in children at drug treatment initiation.

Conclusion

The proportion of treatments initiated in accordance with the period proposed by the Ministry of Health guidelines in children with SCD was high. The most frequent reason for non-compliance was late diagnosis in the complementary health system. The relevance of the disease management service was identified, since most of those responsible for children with SCD had questions after initiation of drug administration and all the questions presented were answered by the pharmacist. The pharmacist has the potential to contribute positively to the pharmacotherapeutic management of SCD, promoting the empowerment of those responsible for the correct use of medications. Further studies are needed to assess the impact of the pharmacist's role in the clinical management service in patients with SCD.

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Collaborators

EFD, FTD and MGN participated in the design and elaboration of the project. RCGV and MGN performed data analysis. EFD, RCGV and MGN participated in the writing and review of the article.

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Conflict of interest statement

The authors declare no conflict of interests regarding this article.

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