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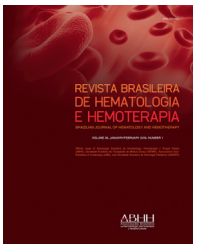

Special article

Guidelines on neonatal screening and painful vaso-occlusive crisis in sickle cell disease: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Project guidelines: Associação Médica Brasileira – 2016

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Introduction

The guidelines project is a joint initiative of the *Associação Médica Brasileira* and the *Conselho Federal de Medicina*. It aims to bring together information in medicine to standardize conduct in order to help decision-making during treatment. The data contained in this article were prepared by and are recommended by the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular* (ABHH). Even so, all possible medical approaches should be evaluated by the physician responsible for treatment depending on the patient's characteristics and clinical status.

This article presents the guidelines on neonatal screening and painful vaso-occlusive crisis in sickle cell disease (SCD).

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Description of the method used to gather evidence

These Guidelines were prepared by elaborating eight clinically relevant questions, two related to neonatal screening for SCD and six related to painful vaso-occlusive crisis in SCD. The questions were structured using the Patient/Problem, Intervention, Comparison and Outcome (PICO) system (Appendix A), allowing the generation of evidence search strategies in the key scientific databases (MEDLINE PubMed, Lilacs, SciELO, Embase, Cochrane Library, Premedline via OVID). The data recovered were critically analyzed using discriminatory instruments (scores) according to the type of evidence – JADAD for randomized clinical trials and the Newcastle Ottawa scale for non-randomized studies. After identifying studies that potentially substantiate recommendations, the level of evidence and degree of recommendation were calculated using the Oxford Classification.[1]

Degree of recommendation and level of evidence

A: Major experimental and observational studies
B: Minor experimental and observational studies
C: Case reports (non-controlled studies)
D: Opinion without critical evaluation based on consensus, physiological studies or animal models

Background

SCD is a group of inherited diseases in which the synthesis of hemoglobin (Hb) is impaired because of a mutation in the beta globin chain of the Hb gene on chromosome 16. This mutation leads to the substitution of a glutamic acid for valine at position 6 of the beta chain, resulting in the production of Hb S whose expression causes sickling of red blood cells, polymerizing Hb with resulting vaso-occlusion, pain and chronic organ damage.[1–3] (D) Hb S is the most common abnormal Hb in Brazil.[2] (D)

Sickle cell anemia occurs when the patient is homozygous for the Hb S gene (Hb SS). Moreover, Hb S can be associated with other abnormal Hb, such as Hb S/beta-thalassemia, Hb SC, Hb SD, persistence of Hb fetal (Hb F) with Hb S, among others. The term SCD defines both sickle cell anemia and these associations. The combination of the Hb S gene with normal Hb (Hb A) characterizes the sickle cell trait (Hb AS).[1–3] (D)

The diagnosis of SCD, a condition with high morbidity and mortality rates, is made at birth with neonatal screening. The pathophysiology is complex and evolves with acute and chronic complications that affect different organs and systems.

Because of the complexity of SCD, many questions were asked during the development of these guidelines and so it was decided to present them in three parts. The first part discusses diagnosis by neonatal screening and aspects of vaso-occlusive crisis, the second part answers questions about splenic sequestration and the central nervous system from diagnosis to treatment and the third part deals with the prevention of infections, diagnosis and treatment of fever, priapism and bone marrow transplantation.

Objective

The aim of the first part of these guidelines is the approach to diagnosis by neonatal screening and subsequent confirmation of SCD and questions related to the diagnosis and treatment of the vaso-occlusive crisis.

What is the prevalence of sickle cell disease and how are the results of neonatal screening for hemoglobinopathies interpreted?

P: All newborn babies
I: Results of neonatal screening
C:
O: Interpretation of the results

The laboratory techniques used to identify hemoglobin in the Newborn Screening Program are high-performance liquid chromatography (HPLC) and isoelectric focusing (IEF) because these tests can quantify small amounts of Hb; the main Hb in the newborn is Hb F.[4–16] (A),[17] (B) Several diseases are investigated during neonatal screening, including SCD, phenylketonuria and congenital hypothyroidism.[4–8,12–16] (A) The Hb with the highest concentration is shown first in the neonatal screening results and so Hb F will always be followed by the other hemoglobins.[4–6,14] (A)[1–3] (D) Table 1 shows how to interpret neonatal screening results. The most common hemoglobinopathies in Brazil are Hb FAS, Hb FS, Hb FSA, Hb FSC, Hb FSD and Hb FSA + Hb Bart's.

The prevalence of Hb S in Brazil is from 1.2 to 10.9% depending on the region of the country,[5,6,13–16] (A),[17–19] (B) while the prevalence of Hb FS (sickle cell anemia) ranges from <0.1 to 0.2%[6,7,13–16] (A)[17,19] (B) and Hb FSC ranges from <0.1 to 0.9%.[5–7,14,15] (A)[17,18] (B) It is noteworthy that the states with the highest number of cases of SCD are Bahia and Rio de Janeiro, while Paraná and Rio Grande do Sul have the lowest rates. The prevalence of Hb C is from 0.15 to 7.4%.[5–7,14,15] (A)[17–19] (B). Hb S/beta-thalassemia has been identified in the states of São Paulo, Minas Gerais, Paraná and Rio Grande do Sul, all with prevalences <0.1%.[5,6,14,16] (A) In the city of Ribeirão Preto, São Paulo the incidence for sickle cell anemia was shown to be 1:7,358 and for Hb SC disease 1:9,365.[7] (A) In Rio Grande do Sul the incidence of SCD (Hb SS, Hb SC, Hb SD and Hb S/beta-thalassemia) was 1:9,120[6] (A) and in Minas Gerais the incidences of Hb FS and Hb FSC were 1:2,800 and 1:3,450, respectively.[14] (A)

In France, SCD prevalence tends to be higher in the population of infants born to parents from Sub-Saharan Africa, the Mediterranean, the Arabian Peninsula, French islands and India compared to the general population (3:10,000 vs. 1:10,000).[20] (B) In Brazil, the USA and the United Kingdom, universal screening is considered ideal due to the population

Table 1 – Interpretation of neonatal screening test for hemoglobinopathies[3] (D).

Result	Interpretation	Clinical condition
FA[a]	Normal	Asymptomatic
FAS	Sickle cell trait	Asymptomatic
FS	Sickle cell anemia (Hb SS) or Hb S/Beta^0-thalassemia or Hb S/HPFH	Hemolytic anemia
FSA or FS[b]	Hb S/Beta$^+$-thalassemia	Hemolytic anemia
FSC	Hb SC	Hemolytic anemia
FSD	Hb SD	Hemolytic anemia
FSA + Hb Bart's	Hb S/alpha-thalassemia	Hemolytic anemia
FSE	Hb SE	Hemolytic anemia
FSV[c]	Hb SV	Hemolytic anemia
FAC	Hb C trait	Asymptomatic
FC	Hb C or Hb C/beta^0-thalassemia	Hemolytic anemia
FCA	Hb C/beta$^+$-thalassemia	Hemolytic anemia
FAD	Hb D trait	Asymptomatic
FD	Hb D	Hemolytic anemia
FDA	Hb D/beta$^+$-thalassemia	Hemolytic anemia
FA + Hb Bart's (1–5%)	Silent carrier of alpha-thalassemia	Asymptomatic
FA + Hb Bart's (5–10%)	Alpha-thalassemia trait	Mild anemia
FA + Hb Bart's (25–50%)	Hb H disease	Hemolytic anemia
F	β^0-thalassemia (thalassemia major) – by high-performance liquid chromatography	Hemolytic anemia

HPFH: hereditary persistence of fetal hemoglobin.

[a] FA because fetal Hb is predominant at birth; the result of thalassemia minor is also Hb FA.

[b] Hb FSA is Hb S associated with beta-thalassemia. However, if the percentage of Hb A is very low, the phenotype in neonatal screening may be Hb FS.

[c] FSV indicates Hb variants different from Hb A, Hb S, Hb C, Hb E, Hb D and Hb Bart's. The following Hb variants have been identified in Brazil: Hb Woodville, Hb Chad, Hb G-Phil, Hb E-Saskatoon, Hb Richmond, Hb O-Arab, Hb Beckman, Hb Hope.

characteristics.[4,10] (A),[2] (D) Screening is also universal in Belgium.[11] (A)

After the diagnosis of SCD, children and their families should be provided special care, as there is a possibility of other cases of SCD in the family.[4,8,11,13,15] (A),[21,22] (C)

The interpretation of newborn screening for sickle cell anemia depends on the initial tests and the confirmation method used. The proper interpretation and use of these results depends on the implementation experience of neonatal screening programs.[8] (A)

The Neonatal Screening Program for hemoglobinopathies in Brazil has had a great impact on SCD mortality and morbidity rates, as early diagnosis permits the use of prophylactic antibiotic therapy, special vaccinations and the training of parents and caregivers about the clinical characteristics of SCD, such as spleen palpation for splenic enlargement.[23] (D)

Recommendation: The results of neonatal screening for hemoglobinopathies should be interpreted based on tests made using HPLC or IEF. As Hb is expressed in decreasing order of concentration, HbF will always be the first to be reported in the results, followed by at least one other Hb.

Is there evidence for the need to perform a confirmatory electrophoresis exam after the sixth month of life?

P: Over 6-month-old patients and abnormal hemoglobin results in neonatal screening
I: Blood collection for hemoglobin electrophoresis
C: Results of neonatal screening
O: Interpretation of the results

The diagnosis of hemoglobinopathies needs to be confirmed when the child is about six months old and, in some situations, a study of the parents or molecular analysis (DNA) of the child should be made.[1,2] (D),[4,6–8,10,11,14–16] (A)

Positive results should always be confirmed.[4,5,10–12,24] (A) The combination of methods (IEF and HPLC) reduces the possibility of false negative results for SCD, which can occur in cases of red blood cell transfusions prior to sample collection or prematurity.[4,9] (A) False positive results for sickle cell anemia can be found in the rare combination of Hb S and Hb Hope detected by IEF. In France, two cases in 42 infants with suspected Hb SS, actually had Hb S/Hb Hope.[25] (B)

A Brazilian study of 4,635 children from Minas Gerais diagnosed with Hb AS, Hb AC or Hb AD in neonatal

screening showed 0.6% of discordant results between the initial screening and an IEF exam after six months of life. Seven cases had had blood transfusions before blood collection, seven cases had problems in blood collection or in the transcription of the exam results, there was difficulty to differentiate between Hb S and Hb D in eight cases and the reason was not identified in five cases.[14] (A)

Recommendations: All children identified as having hemoglobinopathies during neonatal screening should be retested by hemoglobin electrophoresis after six months of life.

Is there evidence on the factors that cause a vaso-occlusive crisis?

P: Patients between 0 and 18 years old with sickle cell anemia and painful crisis
I: Fever, dehydration, infection, metabolic disorder, exposure to extreme cold and heat, alcoholism, osteomyelitis, illegal drugs (marijuana, cocaine)
C: Without symptoms
O: Triggers of vaso-occlusive crisis

Several factors have been associated with the vaso-occlusive crisis in patients with SCD, such as infections, climate change, psychological factors, altitude, acidosis, sleep apnea, stress, dehydration, hypoxia and physical exhaustion. However, in most cases the triggering factor is not identified.[26] (D)

Pain crises in these patients have variable intensities and frequencies, being higher in winter. Higher temperatures during winter were associated with less pain intensity and frequency.[27] (B) However, another study did not confirm the association between changes in temperature and pain frequency.[28] (B) Moreover, the hospitalization rate for pain crisis increases with the intensity of wind and air humidity.[29,30] (B)

Some factors increase the likelihood of hospitalization for painful crisis in patients with SCD. In a multivariate analysis of factors associated with crisis, increased risk of hospitalization was observed in subjects with Hb SS (hazard ratio: 3.1), in those exposed to smoking (hazard ratio: 1.9) and those with a history of asthma (hazard ratio: 1.3).[31] (B) Another study demonstrated the importance of respiratory symptoms and asthma in pain crisis.[32] (B) An assessment of nocturnal O_2 saturation and painful crisis in 90 patients with sickle cell anemia concluded that a nocturnal O_2 saturation <90% (p-value <0.0001), Hb below 8.8 g/dL (p-value <0.01) and a hematocrit below 28% (p-value <0.0012) are associated with the onset of symptoms.[33] (B)

Other clinical situations are associated with pain crisis in patients with SCD, including high blood viscosity[34] (B) and menstruation (61.5% of cases of crisis in women occur during menstruation).[35] (C)

Recommendation: Factors associated with pain crisis can be environmental, such as temperature, wind and humidity or clinical such as respiratory diseases, increased blood viscosity, anemia and menstruation. Smoking increases the risk of hospitalization and some infections increase the risk of having a painful vaso-occlusive crisis.

Is there evidence that the use of pain assessment scales is a good method to monitor pain related to vaso-occlusive crisis?

P: Patients between 0 and 18 years old with sickle cell anemia and painful crisis
I: Following up treatment using pre-established pain scales
C: Following up treatment without using pre-established pain scales
O: Adequate pain control

There are several challenges to pain management in sickle cell anemia, such as disregarding the level of pain felt by patients, the difficulty to 'quantify' this pain, the best instrument to assess pain, the discrepancy between pain and patient behavior, the inadequate prescription of analgesia and the fear that the patient becomes dependent on opioids. Only by evaluating the true intensity of the pain, is it possible to offer the best treatment.[36] (B)

Three methods are used to evaluate pain intensity. The African-American Oucher scale is designed for children between 3 and 12 years and gives scores of 0–100 for the intensity of pain; it consists of a series of pictures of children expressing different levels of pain. The Wong-Baker FACES scale uses pain scores between 0 and 5, and can be used in over 3-year-old children; it is comprised of a series of drawings of faces expressing different levels of pain. The visual analog scale (VAS) uses a horizontal 10-cm line on paper, where one end is designated as no pain and the other is designated as extreme pain; the patient indicates at what level his/her pain is on a scale of 0–10.[37] (B)

A critical issue in the management of pain in sickle cell anemia is precisely which scale is most appropriate. An assessment of the pain of 100 children with sickle cell anemia and vaso-occlusive crisis using the three methods (African-American Oucher scale, VAS and the Wong-Baker FACES scale) showed that the FACES and Oucher scales were equally valid and reliable as instruments to evaluate pain, but 56% of children and adolescents preferred the FACES scale. The visual analog scale had the lowest degree of reliability.[37] (B)

A retrospective study of 3- to 21-year-old patients used the VAS to compare 152 episodes of pain due to vaso-occlusion in 77 patients with SCD versus 221 episodes of pain in 219 patients with long bone fracture. The pain scores were significantly higher in the children with painful vaso-occlusive crisis (7.7 ± 2.5 vs. 6.7 ± 3.0; p-value = 0.005). In SCD patients, there was no relationship between any pain assessment scale and time to analgesic administration.[38] (B)

A retrospective study of 279 episodes of painful vaso-occlusive crisis (initially treated with one dose of morphine) in 105 over 8-year-old children with SCD found that application of the Wong-Baker FACES pain scale (0–5) can guide analgesia management. The initial score was higher in hospitalized compared to non-hospitalized children (4.4 vs. 3.9; p-value = 0.002). The FACES scale allowed a more accurate assessment of the necessity of hospitalization in over 8-year-old SCD children with painful crisis who were being treated with morphine.[39] (B)

A prospective study of 232 over 16-year-old SCD patients who self-reported pain every day during six months using a pain scale between 0 and 9, reported that the mean pain intensity increased as the percentage of days with pain increased (p-value <0.001). Pain was reported on 56% of the total patient-days; pain crises without attending a medical service was reported on 13% of the days and medical care was used only in 3.5% of the days. About 30% of patients reported pain on more than 95% of the days. Based in the scale, the use of opioids was higher on days with more pain (p-value <0.001). Thus, the pain scale also allows control of pain out of the hospital without the indiscriminate use of opioids.[40] (B)

The medication quantification scale (MQS) associated with a pain scale applied in 27 SCD children hospitalized for painful crisis, allows monitoring regarding the use of analgesics and pain intensity. In this prospective study, 59.3% described the onset of pain as sudden and that pain continued to be constant for 70.4% of patients from the time of onset until admission to the hospital. Using the African-American Oucher scale, the mean score of pain intensity on the day of hospitalization was 84 ± 9.9 (range: 63.8–100), and the initial mean score of the MQS was 15.7 ± 4.9 (range: 6–24). After drug therapy (morphine was the most frequent), this score dropped 1.2 ± 0.5 points for each day of hospitalization (range: 0.9–2.5; p-value <0.0001). There was a correlation between the pain level and drug dose; the MQS proved to be a sensitive and useful tool to quantify the utilization of analgesics in SCD.[41] (B)

The pain level measured using the VAS (scores of 0–100) in 74 SCD adults with vaso-occlusive crisis identified a mean score of 80 [95% confidence interval (CI): 75.99–82.95] on arrival at hospital. The reduction in pain following the use of analgesics was monitored using the VAS. In patients reporting a significant improvement in pain, the change in the VAS was 23.4 (95% CI: 15.4–31.4), while it was only 13.5 (95% CI: 11.25–15.74) in those in whom the improvement was minimal. The study concluded that the minimum clinically significant score to assess improvement in pain during treatment with analgesia was 13.5; this also allows an evaluation of pain relief in adults with SCD.[42] (B)

A pain intensity scale (numeric rating scale) was used to predict hospitalization of 65 patients aged between 13 and 53 years old (mean: 23 years) with SCD and vaso-occlusive crisis and 80 acute events that resulted in 49 hospitalizations. The mean initial score for pain was 8.5 in hospitalized patients and 5.1 for those who were discharged (p-value <0.001). When considering a score of 6.5 as the cutoff point, the sensitivity was 0.886 and specificity was 0.762, with positive and negative predictive values of 0.886 and 0.760, respectively. Therefore, the pain score allows an indication for hospitalization.[43] (B)

In the assessment of pain in 17 SCD children using the FACES scale, the level of pain predicted the length of hospitalization. Children with a high score (>2) 24 h after receiving medications spent more time in hospital.[44] (B)

Recommendation: The use of pain scales in SCD patients with vaso-occlusive crisis can guide treatment, monitor response and predict hospitalization.

What is the best sequence of medications to control painful vaso-occlusive crisis?

P: Patients between 0 and 18 years old with sickle cell anemia and painful crisis
I: Treatment with morphine versus meperidine
C: Treatment with paracetamol or dipyrone
O: Adequate pain control

The treatment of painful vaso-occlusive crisis in SCD patients involves correcting triggering factors, such as hypoxia, infection, acidosis, dehydration, physical exhaustion and exposure to extreme cold. The management of painful crisis is based on non-randomized clinical studies[45,46] (A),[47] (B), and mainly consists of hydration and analgesia.[48] (A) Thus, many guidelines have been written to provide support in the treatment of pain in sickle cell anemia.[49,50] (D)

The proper use of analgesics is important and the prescription should suit the intensity of pain, with a fixed dose at specific intervals, and not using medications 'as necessary.'

The use of medications for pain management in over 12-year-old children and adults should follow the three steps of the analgesia scale (Table 2) recommended by the World Health Organization (WHO)[51,52] (D).

For under 12-year-old children, the use of drugs for the management of pain is a little different because the analgesia scale, as recommended by WHO guidelines published in 2012, has only two steps (Table 3)[53] (D).

The two-step approach considers the use of low doses of strong opioid analgesics for the treatment of moderate pain because it is not safe to use codeine in children due to problems related to genetic variability in biotransformation and insufficient data from clinical studies in children using other intermediate opioids such as tramadol.[53] (D)

Treatment of mild to moderate pain in over 12-year-old children and adults should start with a non-opioid drug at the recommended dose and frequency together with adjuvant medications as necessary. If the pain does not stop, add a weak opioid. If the weak opioid combined with a non-opioid drug does not control the pain, the weak opioid should be replaced by a strong opioid.[48] (A)[49,52] (D)

In under 12-year-old children with mild pain, treatment should start with a non-opioid drug at the recommended dose and frequency; if pain does not improve, a low dose of a strong opioid should be added with the dose being increased only if the pain does not improve. After a starting dose according to the dosages recommended in Table 3, the dosage should

Table 2 – Steps of pain management listed in the analgesia scale as recommended by the World Health Organization – over 12-year-old children and adults[51,52] (D).

Mild pain Visual pain scale (1–4)	Moderate pain Visual pain scale (5–7)	Severe pain Visual pain scale (8–10)
Non-opioid	Weak opioid	Strong opioid
Aspirin 30–60 mg/kg/day PO every 4 h maximum 3.6 g/24 h OR Acetaminophen 10–15 mg/kg/dose PO every 4 h maximum 635 mg/kg/day OR Dipyrone 5–10 mg/day PO every 4 h	Codeine 0.5–0.75 mg/kg/dose PO every 4 h	Codeine 0.75–1 mg/kg/dose IV or PO every 4 h OR Morphine 0.1–0.2 mg/kg IV or SC every 3 h or 4 h OR Tramadol 0.1–0.25 mg/kg/h IV
Ibuprofen 5–10 mg/kg PO every 6 h to 8 h	Tramadol 0.5 mg/kg IV maximum 5 mg/kg/day every 6 h	

PO: *per os*; IV: intravenous; SC: subcutaneous.

Table 3 – Steps of pain management listed in the analgesia scale recommended by the World Health Organization – under 12-year-old children[53] (D).

Mild pain (non-opioid)	Moderate/severe pain (strong opioid)
Acetaminophen 10–15 mg/kg/dose PO every 4 h, maximum 635 mg/kg/day (WHO: maximum 1 g each dose) OR Dipyrone 5–10 mg/day PO every 4 h OR Ibuprofen 5–10 mg/kg PO every 6–8 h (max. 40 mg/kg/day)	Morphine 0.1–0.2 mg/kg IV or SC every 3 h or 4 h

PO: *per os*; IV: intravenous; SC: subcutaneous.

be adjusted to the level that is effective (with no maximum dose). The maximum increase in dosage is 50% every 24 h in outpatient settings.[53] (D)

Do not use meperidine because, besides having one tenth of the analgesic power of morphine, it is associated with serious adverse events, such as seizures and physical dependence.[49,50,54,55] (D)

Intravenous morphine is considered the treatment of choice for the severe pain crisis in sickle cell anemia, but it is associated with several adverse events including acute chest syndrome. Patient-controlled administration of morphine compared to continuous use was no more effective in respect to pain management and length of hospital stay, but it significantly reduced opioid consumption and produced fewer adverse events.[56] (B)

A randomized, double blind, parallel-group study compared the use of oral versus continuous intravenous morphine. Initial pain management used intravenous morphine (up to 0.15 mg/kg). Subsequently, a comparison between oral morphine (1.9 mg/kg every 12 h) and continuous intravenous morphine (0.04 mg/kg/h) was made for the management of pain episodes in sickle cell anemia patients; there was no difference in the resolution of pain nor the time of analgesic administration. The need for rescue analgesia was similar, as were the adverse effects. Oral morphine may be an alternative to the use of continuous intravenous morphine.[57] (B)

The use of oral or intravenous methylprednisone at a dose of 15 mg/kg in two doses in the first 24 h combined with morphine can produce benefits to reduce the time needed to resolve pain in episodes of severe pain. However, the use of corticosteroids is associated with a rebound effect with the worsening of pain when its administration is stopped, and its indication must be carefully considered.[58] (B) The use of corticosteroids favors painful crisis when used in acute chest syndrome.[59] (D)

The use of nitric oxide in the treatment of painful vaso-occlusive crisis of hospitalized sickle cell anemia patients does not shorten the time required for crisis resolution, does not reduce the length of hospitalization, does not affect the intensity of pain or chest pain, and does not reduce the use of opioids.[60] (A)

Recommendation: Pain management of vaso-occlusive episodes in sickle cell anemia patients should be designed according to the intensity of the pain. Oral or intravenous morphine should be used in cases of severe pain, with intravenous administration being intermittent. The use of methylprednisolone should be avoided. There is no indication for the administration of nitric oxide in this clinical situation.

Is there evidence for the use of adjuvant medications such as non-steroidal anti-inflammatory drugs, antihistamines, antidepressants, benzodiazepines, anticonvulsants or corticosteroids in the management of painful vaso-occlusive crisis?

P: Patients between 0 and 18 years old with sickle cell anemia and painful crisis
I: Treatment with non-steroidal anti-inflammatory drugs (diclofenac, nimesulide, aspirin, COX 1 inhibitors and COX 2 inhibitors), antihistamines, antidepressants, benzodiazepines and anticonvulsants
C: Treatment with paracetamol or dipyrone
O: Adequate pain control

There are few randomized clinical trials on the treatment of the painful crisis in sickle cell anemia[45] (A),[46] (B), so that most of the treatment is based on data from non-randomized studies.[49,55,61,62] (D)

Five studies with non-steroidal anti-inflammatory drugs (NSAIDs) as adjuvant pain medications for children and adults with SCD were reviewed. Oral diflunisal was similar to placebo. Two studies with intravenous ketorolac in hospitalized adults were favorable to ketorolac for pain control, while two others were not. The small sample sizes and the heterogeneity of the methods preclude any conclusion in the use of NSAID to treat pain in SCD and make any meta-analysis on this subject unrealistic.[45] (A) A phase III trial, double blind, randomized, placebo-controlled of 66 episodes of painful vaso-occlusive crisis concluded that ketorolac was not effective to control the pain and the use of morphine when compared to a placebo. The authors do not recommend the systematic use of ketorolac in these patients.[63] (A) No studies were found in the literature on other NSAIDs, such as acetaminophen.[45] (A)

A double-blind randomized placebo-controlled study in Brazil showed no benefit with the use of piracetam in children and young adults with sickle cell anemia and painful vaso-occlusive crisis in relation to the use of opioids, pain intensity and hospitalization.[64] (A) Piracetam is ineffective in the prevention of vaso-occlusive pain crisis.[64] (A) These data were confirmed in a meta-analysis with three studies, including the Brazilian study, where it was concluded that there are insufficient data to indicate piracetam for painful crisis in SCD patients.[65] (A)

Methylprednisolone or intravenous dexamethasone suggest benefits in relation to pain management, but patients who received a single dose of corticosteroids had a higher risk of pain reactivation.[45] (A)

Magnesium is a vasodilator that enhances the hydration of red blood cells. For this reason it was investigated in a randomized, double-blind, placebo-controlled study of 104 children with SCD hospitalized to receive intravenous analgesia for painful crisis. Intravenous magnesium sulfate had no effect on reducing the length of hospital stay, improvements in pain or reductions in the cumulative dose of analgesics.[66] (A)

Adjuvant medications have been used to enhance the analgesic effect of opioids in patients with cancer and to decrease their adverse events. Antihistamines (chlorpheniramine 0.15 mg/kg/day orally every 6 h with a maximum dose of 12 mg/day), antidepressants (amitriptyline 10–20 mg orally at night), benzodiazepines (the dose depends on the benzodiazepine) and anticonvulsants (carbamazepine 5–10 mg/kg/day once or twice a day) have mild analgesic effects. When indicated, these medications should be used carefully.[49,51,52] (D)

Recommendations: There is no consistent evidence supporting the use of antidepressants, benzodiazepines and anticonvulsants in the management of painful vaso-occlusive crisis in sickle cell anemia. There are no benefits with piracetam or magnesium sulfate use in painful vaso-occlusive crisis.

Is there evidence for the use of oxygen therapy or hyperhydration in the management of painful vaso-occlusive crisis?

P: Patients between 0 and 18 years old with sickle cell anemia and painful crisis
I: Treatment with oxygen therapy or hyperhydration
C: Treatment without oxygen therapy or hyperhydration
O: Adequate pain control

Although inhaled oxygen therapy (50% oxygen) in patients with SCD reverses the sickling of red blood cells, there is no evidence in the literature that its use in vaso-occlusive pain crisis provides benefits by reducing the pain, the use of opioids or hospitalization.[67,68] (B)

Dehydration is an important factor in the sickling process. The decreased ability to concentrate urine, a characteristic of SCD patients, results in inadequate control of hydration. Thus, during painful crisis, patients receive intravenous or oral hydration, regardless of their state of hydration. However, care is necessary not to cause cardiac or pulmonary volume overload. No randomized controlled trials report benefits in respect to improving or resolving pain with the infusion of intravenous fluids as adjuvant treatment in sickle cell anemia patients with painful vaso-occlusive crisis, regardless of the state of hydration.[47] (A)

Hydration in patients with sickle cell anemia should be carried out with caution. Hypotonic solutions may be used to establish baseline hydration, maximum 1–1.5 times the maintenance volume including the medications volume.[49,55,61,69,70] (D) Care should be taken to avoid excessive hydration because it decreases the plasma oncotic pressure and increases the hydrostatic pressure, with risk of pulmonary edema (especially in patients with kidney disease, heart disease or previous lung disease).[70] (D)

Recommendations: There is no published evidence on the benefits of oxygen therapy or excessive hydration in sickle cell anemia patients with painful vaso-occlusive crisis.

Is there evidence that bone scintigraphy is a good test to differentiate the painful vaso-occlusive crisis from osteomyelitis? Is there any test that allows this differentiation?

P: Patients between 0 and 18 years old with sickle cell anemia and doubts between painful crisis and osteomyelitis
I: Bone scintigraphy
C: Clinical diagnosis
O: Differential diagnosis between painful vaso-occlusive crisis and osteomyelitis

In sickle cell anemia, bone infarction is about 50 times more common than osteomyelitis.[71] (B) However, the differentiation between osteomyelitis and bone infarction is difficult. In both situations the patient can have pain, fever, edema, erythema, and leukocytosis and imaging tests (X-ray, computed tomography) are nonspecific.[72,73] (B)

A prospective study of 42 episodes of bone pain in children with SCD showed that in most cases the diagnosis of bone infarction is clinical. However, scintigraphy with technetium can help in cases where there is doubt about osteomyelitis. When bone marrow scintigraphy with technetium is made within ten days of onset, the uptake is normal at the injury site in the case of osteomyelitis (100% of cases) while in bone infarction the uptake is diminished (93% of cases). Bone scintigraphy with technetium has proven effective to identify osteomyelitis in 100% of cases due to the higher uptake, but it is not specific for bone infarction.[74] (B)

Combination of sequential bone and bone marrow scintigraphy with technetium showed benefits in the differential diagnosis of bone infarction and osteomyelitis in 39 children with SCD and bone pain. These exams should be performed within 72 h of the onset of pain. Decreased bone marrow uptake associated with normal or reduced bone uptake in scintigraphy suggests a diagnosis of bone infarction, whereas increased bone uptake suggests infection.[75] (B)

Scintigraphy images of 79 children with SCD performed within 24 h of the onset of pain were retrospectively analysed. Bone marrow scintigraphy with technetium was performed followed by bone scintigraphy. Reduced uptake by the bone marrow and abnormal bone uptake suggested bone infarction and normal uptake by the bone marrow with increased bone uptake suggested osteomyelitis. Seventy cases of bone infarction were diagnosed with 66 being successfully treated without antibiotics. Four cases were diagnosed as osteomyelitis, in which three cultures were positive; no false negative results were observed.[73] (B)

A retrospective study of 22 episodes of suspected osteomyelitis in SCD children showed that the combination of bone scintigraphy with gallium and technetium can help in the differential diagnosis of bone infarction and osteomyelitis. The best data for diagnosis are obtained within 24 h after the onset of symptoms.[72] (B) The use of bone marrow scintigraphy with gallium and technetium was also effective for this differential diagnosis in a study of 18 episodes of pain.[76] (C)

A prospective study of 53 SCD children with the need to differentiate between vaso-occlusive crisis and osteomyelitis found ultrasound changes of the soft tissue suggestive of osteomyelitis in 17 patients; pus was drained from all patients. The authors suggest that ultrasound should be considered as the first option to investigate osteomyelitis.[77] (B) The overall sensitivity of soft tissue ultrasound in the diagnosis of osteomyelitis was 74% with a specificity of 63%.[78] (C) The ultrasound was normal in cases of bone infarction, and periosteal elevation, subperiosteal or intramedullary abscesses and cortical bone erosion can be observed in osteomyelitis.[77] (B)[78] (C) The diagnosis of osteomyelitis by ultrasound can be enhanced by investigating reactive protein C serum levels and leukocyte counts, as these values are significantly increased in osteomyelitis.[79] (B)

Magnetic resonance imaging (MRI) is a good imaging exam to evaluate the bone marrow and to detect bone infarction. However, in SCD, it is difficult to differentiate between infarction and osteomyelitis with MRI.[80] (D)

Although imaging tests can help to differentiate between bone infarction and osteomyelitis, a clinical diagnosis is always better.[73,74,81] (B)

Recommendation: Differentiating bone infarction and osteomyelitis remains a challenge because the clinical presentation is similar in both cases and laboratory tests are still of limited use. Bone scintigraphy with technetium does not help to differentiate bone infarction in sickle cell anemia patients with bone pain. Thus, the combination of bone and bone marrow scintigraphy with technetium can assist in the differentiation between osteomyelitis and bone infarction, as can scintigraphy using gallium and ultrasound of the soft tissues. MRI may play a role and be sought wherever possible in cases of fever and prolonged pain.

Conflicts if interest

The authors declare no conflicts of interest.

Appendix A.

PICO 1

What is the prevalence of sickle cell disease and how are the results of neonatal screening for hemoglobinopathies interpreted?

((Anemia, Hemolytic, Congenital AND screening AND neonatal)) OR (((screening AND neonatal)) AND (Hemoglobinopathies))

PICO 2

Is there evidence for the need to perform a confirmatory electrophoresis exam after the sixth month of life?

(Anemia, Sickle Cell OR Hemoglobinopathies OR Hemoglobins) AND (Electrophoresis) AND (Neonatal OR Newborn)

PICO 3

Is there evidence on the factors that cause vaso-occlusive crisis?

Sickle cell anemia AND (veno-occlusive disease OR veno-occlusive syndrome OR pain OR vaso-occlusive OR vascular disease OR crisis) AND (fever OR dehydration OR infection OR metabolic syndrome OR cold OR heat OR alcohol OR osteomyelitis OR cocaine OR marihuana OR etiology OR risk)

PICO 4

Is there evidence that the use of pain assessment scales is a good method to monitor pain related to vaso-occlusive crisis?

Sickle cell anemia AND (veno-occlusive disease OR veno-occlusive syndrome OR pain OR vaso-occlusive OR vascular disease OR crisis) AND (Severity of Illness Index OR scale OR score OR VAS OR measurement)

PICO 5

What is the best sequence of medications to control painful vaso-occlusive crisis?

(Therapy/broad[filter] AND Sickle cell anemia AND (veno-occlusive disease OR veno-occlusive syndrome OR pain OR vaso-occlusive OR vascular disease OR crisis))

PICO 6

Is there evidence for the use of adjuvant medications such as non-steroidal anti-inflammatory drugs, antihistamines, antidepressants, benzodiazepines, anticonvulsants or corticosteroids in the management of painful vaso-occlusive crisis?

(Therapy/broad[filter] OR anti-inflammatory OR Histamine Antagonists OR anticonvulsant OR Benzodiazepines) AND Sickle cell anemia AND (veno-occlusive disease OR veno-occlusive syndrome OR pain OR vaso-occlusive OR vascular disease OR crisis)

PICO 7

Is there evidence for the use of oxygen therapy or hyperhydration in the management of painful vaso-occlusive crisis?

Sickle cell anemia AND (veno-occlusive disease OR veno-occlusive syndrome OR pain OR vaso-occlusive OR vascular disease OR crisis) AND (oxygen therapy OR OXYGEN OR Fluid Therapy OR Infusions, Parenteral OR HYDRATION OR DEHYDRATION)

PICO 8

Is there evidence that bone scintigraphy is a good test to differentiate painful vaso-occlusive crisis from osteomyelitis? Is there any test that allows this differentiation?

((Radionuclide Imaging)) AND (sickle cell anemia)

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