

# Pulmonary Complications in Children with Sickle Cell Disease Followed at the Pediatric Department of Gabriel Toure University Hospital

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## Abstract

**Objective:** To study the pulmonary complications of major sickle cell syndromes in children aged 6 months to 15 years followed at the Department of Pediatrics of Gabriel Toure University Hospital. **Materials and methods:** This was a retrospective study from January 1<sup>st</sup>, 2017 to February 28, 2018 and a prospective study from March 1, 2018 to December 31, 2019, concerning sickle cell disease children followed at the Gabriel Tour  University Hospital. All children with sickle cell disease confirmed by hemoglobin electrophoresis, aged 6 months to 15 years with a pulmonary complication and admitted to pediatrics were included. Were not included: 1) Infants and children with sickle cell disease not presenting a pulmonary complication coming only to their routine follow-up. 2) Sickle cell patients over 16 years of age and those whose parents do not consent. 3) Those who have not done electrophoresis. **Results:** During the study period, we were able to include 45 sickle cell children with a pulmonary complication. The frequency of pulmonary complications was 13.76%, involving homozygotes in 91.11% of cases. The age group 6 - 10 years predominated with 46.66% and the sex ratio was 0.45. Vaso-occlusive crisis was the most frequent reason for consultation with 35.56%. Respiratory distress (80%), fever (66.67%), crepitus rales (64.44%) and chest pain (60%) were the most frequent clinical signs. The main pulmonary complication was acute chest syndrome with 86.67%. Treatment was based on hydration (91.91%), analgesics (91.91%) and antibiotics (73.33%). Lethality was 4.44%. **Conclusion:** Pulmonary complications of sickle cell disease are serious and constitute the main cause of mortality in our context.

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## Keywords

Sickle Cell Disease, Children, Lungs, Complications

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### 1. Introduction

Every year, nearly 300,000 children are born with a major hemoglobin abnormality, including more than 200,000 cases in Africa [1] [2].

In Mali, according to Center of management and research of Sickle cell disease called “Le Centre de Recherche et de Lutte contre la Drépanocytose (CRLD)”, there are 5000 to 6000 sickle cell births each year with a prevalence of 12%, including 3% for the major form [3]. They are subject to complications that can affect all organs, which makes sickle cell disease a disabling disease, with a 5-year probability of hospitalization for painful vaso-occlusive crisis (VOC) of 63%, for acute chest syndrome (ACS) of 45%, and for acute anemia of 30% [4]. Pulmonary disorders are of particular importance because of their frequency and severity. They represent 20% to 30% of the causes of mortality [5]. Recent publications show that asthma represents an unfavorable comorbidity in major sickle cell syndromes (MDS) in children. Its presence increases the risk of occurrence of vaso-occlusive attacks (VOC) and acute chest syndrome (ACS) [6] [7].

The difficulties in the management of pulmonary complications and the absence of previous studies in the pediatric setting in Mali motivated the realization of this work, which aims to study pulmonary complications in children with sickle cell disease followed up in the pediatric department of the Gabriel Toure University Hospital.

### 2. Materials and Methods

Our study took place at the Gabriel Toure University Hospital Center. It was a retrospective study from January 1, 2017 to February 28, 2018 and prospective from March 1, 2018 to December 31, 2019. All children with sickle cell disease confirmed by hemoglobin electrophoresis, aged 6 months to 15 years with a pulmonary complication and admitted to pediatrics were included. Were not included:

- Infants and children with sickle cell disease not presenting a pulmonary complication coming only to their routine follow-up.
- Sickle cell patients over 16 years of age and those whose parents do not consent.
- Those who have not done electrophoresis.

During the study period we were able to include 45 sickle cell children with a pulmonary complication. Sociodemographic, clinical and paraclinical variables were analyzed.

Data collection was carried out by means of a questionnaire form filled in

from the patients' hospitalization records and the sickle cell disease follow-up booklet. The data collected were entered and analyzed using Microsoft Word 2007 and SPSS version 17.0 software. We used the Chi-square test for the comparison of categorical variables. The value of  $p < 0.05$  was considered statistically significant. Informed consent was requested and obtained from the parents or caregivers before including the patient. Confidentiality of data was respected during the study. Authorization from the head of the department was obtained for the use of medical records.

### 3. Results

Our study concerned children with sickle cell disease under the age of 16 with a pulmonary complication in the pediatric department of Gabriel Toure University Hospital.

#### Limits of our study

As any retrospective study presents difficulties, we encountered difficulties related to:

- Missing information in the files;
- The non-feasibility of spirometry in children under 5 years old;
- The unavailability of spirometry inside the hospital and its high cost.

#### 3.1. Frequency

From January 01, 2017, to December 31, 2019, we collected 45 records of children who presented a pulmonary complication out of 327 sickle cell children followed at the Department of Pediatrics of the Gabriel Touré University Hospital, *i.e.* a frequency of 13.76%.

#### 3.2. Sociodemographic Parameters

The age range of 6 to 10 years represented 46.66% and the sex-ratio was 0.45. (**Figure 1** & **Figure 2**)

The children were from consanguineous marriages in 22.22% of cases. The fathers were shopkeepers in 42.22% of cases and civil servants in 22.22% of cases while the mothers were housewives in 60% of cases and civil servants in 26.66% of cases. Non-educated children represented 55.55% of the mothers and 40% of the fathers.

#### 3.3. Clinical and Paraclinical Parameters

The children had a history of hospitalization in 53.33% of cases and a history of chest pain or dyspnea in 24.4% of cases. The discovery (of sickle cell disease) was made between 6 months and 5 years of age in 64.44%, 40% of whom had osteoarticular pain (**Table 1** and **Table 2**).

Vaso-occlusive crisis (VOC) represented 35.56% of the reasons for consultation (**Table 3**).

On admission, 89% of the children had fever, 71.11% had tachypnea, and

66.67% had a pulsed saturation below 95%. The most common clinical signs were respiratory distress (80%), crepitus (64.44%), of which one third was bilateral, and chest pain (60%) (Table 4).

Complications were dominated by acute chest syndrome with 86.67% (Table 5).

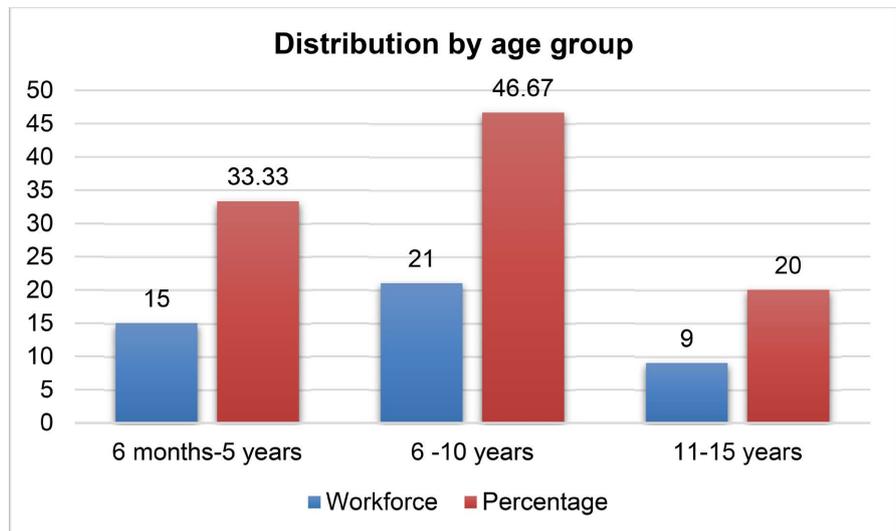


Figure 1. Distribution of patients according to age.

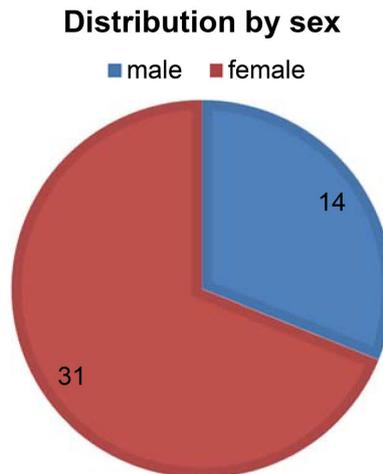


Figure 2. Distribution of patients by sex.

Table 1. Distribution of patients according to the number of previous hospitalizations.

Number of previous hospitalizations	Effective	Percentage
1	15	33.33
2	6	13.33
3	2	4.44
>3	1	2.22
Total	24	53.33

**Table 2.** Distribution of patients according to the circumstance of discovery of sickle cell disease.

circumstance of discovery	Effective	Percentage
Osteoarticular pain	18	40
Systematic assessment	12	26.66
Anemia	9	20
Hand-foot syndrome	6	13.33
Total	45	100

**Table 3.** Distribution of patients according to reason for consultation/referral.

Reason for consultation/referral	Effective	Percentage
vaso-occlusive crisis	16	35.56
Acute thorac syndromes + Pneumonia	14	31.11
Respiratory distress	8	17.78
Anemia	3	6.67
Other* (see below)	4	8.88
Total	45	100

\*Other: Convulsion = 2, coughing + vomiting = 1, Desaturation = 1.

**Table 4.** Distribution of patients according to clinical signs.

Clinical Signs	Effective	Percentage
Respiratory distress	36	80
Crackling rales	29	64.44
Chest pain	27	60
Mucocutaneous pallor	24	53.33
Matter	15	33.33
Conjunctival jaundice	13	28.89
Hepato-Splenomegaly	13	28.89
Heart murmur	04	8.88
Skin lesions	02	4.44

**Table 5.** Distribution of patients according to the types of pulmonary complications.

Pulmonary complications	Effective	Percentage
Acute thorac syndromes	39	86.67
Acute thorac syndromes + pulmonary hypertension	1	2.22
Pneumonia	5	11.11
Total	45	100

There was hyperleukocytosis in 97.77% of cases, anemia in 93.33% of cases and opacity (on radiography) which was bilateral basal in 26.67% of cases, right basal in 20% and left basal in 17.78% of cases. One case of pulmonary hypertension was found on cardiac Doppler ultrasound. Management was based on hydration, taking into account the child's needs and the risk of pulmonary overload (*i.e.* 1.5 to 2 liters/m<sup>2</sup>/24hours without exceeding 2 liters/24hours), broad antibiotic therapy active spectrum on intracellular germs and pneumococcus (amoxicillin, amoxi-clavulanic acid and cefotaxime or Ceftriaxone), oxygen therapy to maintain arterial oxygen saturation > 95%. The antibiotic of choice is Amoxicillin in sufficient dose (100 mg/kg/day) due to its good bioavailability. Thus the management focused on hydration (with isotonic solution) in 91% of cases, level II analgesics in 91% of cases, antibiotic therapy in 100% of cases, oxygen therapy in 80% of cases. Blood products were transfused in 51.31% of the children, phenotyped red blood cells in 31.31%, non-phenotyped red blood cells in 17.78% and non-phenotyped whole blood in 2.22% of children. Incentive spirometry was prescribed in 84.44% of children and 13.33% of children were put on hydroxycarbamide. We recorded two deaths, *i.e.* a mortality rate of 4.44%.

There are significant relationship between the type of hemoglobin and the reasons for consultation or referral ( $P = 0.02$ ) on the one hand and between the type of hemoglobin and the type of complication ( $P = 0.001$ ) on the other (**Table 6** and **Table 7**).

**Table 6.** Distribution of patients according to the reason for consultation and the type of hemoglobin.

Reason for consultation/Reference	Type of hemoglobin			Total
	S $\beta^0$ thalassemia	SC	SS	
Anemia	0	0	3	3
CVO	1	1	21	23
Pulmonary complications	1	1	17	19
Total	2	2	41	45

$\chi^2$ :  $P = 0.02$ .

**Table 7.** Distribution of patients according to the type of pulmonary complication and the type of hemoglobin.

Type of hemoglobin	Type of complications			Total
	Acute thorac syndromes	Pneumonia	Acute thorac syndromes+ pulmonary hypertension	
SS	36	4	1	41
SC	1	1	0	2
S $\beta^0$ thalassémie	2	0	0	2
Total	39	5	1	45

$\chi^2$ :  $P = 0.001$ .

## 4. Discussion

### Frequency

From January 1, 2017 to December 31, 2019, we collected 45 records of sickle cell children with pulmonary complications out of the 327 sickle cell children followed at the sickle cell unit of the pediatrics department of the Gabriel Touré University Hospital, *i.e.* a frequency of 13.76%.

### Sociodemographic parameters

The age group of 6 to 10 years was the most represented with 46.66%, the same observation was made by Berthold S *et al.* [8] who, in a study of respiratory complications in children in Brussels, found 39.7%.

The average age was 7.4 with extremes ranging from 14 months to 15 years. These data are comparable to those of Berthold S *et al.* [8] who found a mean age of 8 years with extremes ranging from 5.6 to 10 years. The female sex was the most represented, with a sex ratio of 0.45. Our results are different from those of Berthold S *et al.* [8] who respectively found a sex ratio of 2.12. For the moment, the predominance of one gender cannot be explained. The occupation of the fathers was dominated by traders (42.22%), followed by civil servants with 22.22%. Diakité AA *et al.* [9] also observed a predominance of traders with 35.7% followed by civil servants with 25.7%. This result was due to the fact that civil servants and shopkeepers have an acceptable standard of living that allows them to bring their children to consultations. The majority of mothers (60%) were housewives; other authors in Mali, such as Diakité AA *et al.* [9], found this predominance of housewives with 80%. This result could be explained by the low schooling rate of girls in Mali. We observed 22.22% of children born of a consanguineous marriage. This could be explained by the practice of endogamy in Mali. Our results are lower than those of Belala A *et al.* [10] who found consanguinity in 45% of cases.

### Clinical and paraclinical parameters

The most common age of discovery was 6 months to 5 years (64.44%). This could be explained by the high susceptibility to infections at this age and the appearance of the first symptoms in relation to the disappearance of fetal hemoglobin. The most frequent circumstances of discovery were osteoarticular pain with 40%. Douamba S *et al.* [11] found that the first circumstance of discovery was infections with 24.8%. More than half of the children (53.33%) had a history of hospitalization. Infections were the most noted reason for hospitalization with 34.21%. Our results are superior to those of Bertholdt *et al.* [8] and Douamba S *et al.* [11] who found respectively 8% and 21.8% of previous hospitalization. This repetition of hospitalization could be explained by the vulnerability of sickle cell children. Chest pain/dyspnea was found in 24.4% of children. The main reason for consultation was vaso-occlusive crisis (35.56%), the same observation was made by Bertholdt S [8] who had 40% vaso-occlusive crisis as the main reason for consultation. This could be explained by the fact that the vaso-occlusive crisis represents a triggering factor of a pulmonary complication (acute thoracic syn-

drome) or contemporary with it. More than half of the children (66.67%) had a fever on entry. This result is lower than that of Douamba S *et al.* [11] who had 95.5%. This frequency of fever would be related to the extreme susceptibility of sickle cell patients to infection. More than half (66.67%) of the children had a saturation of less than 95%. Bertholdt S *et al.* [8] found 50% of patients with saturation < 95%. The hypoventilation observed in acute chest syndrome would be the cause of the poor oxygen saturation. In this study, clinical signs were dominated by respiratory distress (80%), followed by crepitus and chest pain with 64.44% and 60% respectively. Bertholdt S *et al.* [8] found 58.33% chest pain and 50% respiratory distress. This could be explained by the symptomatology of acute chest syndrome which is made of respiratory distress and chest pain. Almost three quarters (71.11%) of our patients had presented with intercostal pulling and 60% presented with subcostal pulling. This was a respiratory struggle observed in young children in respiratory distress with the presence of bilateral crackles in 33.33% of cases. The crackles were bilateral in 33.33% of our patients, located on the left in 17.78% and on the right in 13.33%. The complications observed were acute chest syndrome (86.67%), pneumonia (11.11%) and pulmonary arterial hypertension + acute chest syndrome (2.22%). These results are superposable to those of Bertholdt S *et al.* [8] who found acute chest syndrome as the main complication with 75%.

In our study the SS form predominated with 91.11% followed by the SC and S $\beta^{\circ}$  thalassemia forms with 4.44% each. These results are comparable to those of Bertholdt S *et al.* [8] who had found a predominance of SS with 95.45%. This is due to the high prevalence of SS in the Sahelian zone in general and to the predominance of the SS form among the children followed up at the sickle cell disease unit of the Gabriel Touré University Hospital. Hyperleukocytosis was noted in 97.77% of our patients, with an average of 31,856/mm<sup>3</sup> leukocytes and extremes ranging from 11,500 to 78,300/mm<sup>3</sup> Douamba S *et al.* [11] found that 84.9% of patients had hyperleukocytosis with a mean leukocyte count of 22,945/mm<sup>3</sup> with extremes ranging from 6400 to 78,600/mm<sup>3</sup>. This could be explained by the presence of hyperleukocytosis in sickle cell patients without any infection and the extreme susceptibility of these children to infection. A hemoglobin level of less than 10 g/dl was found in 93.33% of the patients with an average of 6.53 g/dl and extremes ranging from 2.6 g/dl to 10.8 g/dl. Our results are comparable to those of Douamba S *et al.* [11] who in their study in Burkina Faso found a mean hemoglobin level of 6.7 g/dl with extremes ranging from 2.5 g/dl to 10 g/dl, but lower than those of Bertholdt S *et al.* [8] who found a mean hemoglobin level of 8.3 g/dl with extremes ranging from 7.3 g/dl to 9.5 g/dl. Indeed, anemia is constant in sickle cell patients due to chronic hemolysis and can worsen in acute situations. Of 97.78% of patients who had a thick blood drop, about half (44.44%) were positive. In the study by Douamba S [11], it was done in all patients with 12.8% of positive results. Mali being a malaria endemic area, malaria remains one of the triggers of the attacks. Chest X-ray was abnormal in 64.44%

of cases (n = 29). This result is lower than that of Douamba S [11] who found 76.5% (n = 50) of abnormalities on the chest X-ray. This difference can be explained by the delay of the imaging compared to the clinic. Repeat radiography was often necessary, but insufficient financial resources limit the performance of chest x-rays. Cardiac Doppler ultrasound was abnormal in two of the six children who had the examination. In the study by Douamba S [11], cardiac ultrasound was performed in 36 patients with 73.5% (n = 26) of anomalies.

### **Management and outcome**

Hydration with Ringer Lactate (RL) and 0.9% saline (SS) was used to reduce pain in 91.11% (n = 41) of patients. Our results are superior to those of Diagne I *et al.* [12] who found 66.6% of cases of hyperhydration. These high rates of hyperhydration can be explained by the importance of hydration in the management of pain in sickle cell patients. A level I and II analgesic had been used in 91.11% of patients. Diagne I *et al.* [12] found that 66.6% of the patients had received level I and II analgesics during their vaso-occlusive crises. While Bertholdt S [8] had used morphine in 33.33% of these patients for pain relief. This could be explained by the intensity of pain in the sickle cell patient. In our context the availability and handling of morphine explains the use of levels I and II. Nearly three quarters of our patients (73.33%) received treatment with third generation cephalosporins, followed by vancomycin (55.56%), gentamycin and the combination of amoxicillin and clavulanic acid in 51.11% (n = 23) each. Our results are close to those of Douamba S [11] who used ceftriaxone (64.6%), gentamicin (48.9%), amoxicillin-clavulanic acid combination (16%). Antibiotics were combined in 86.66% (n = 39) of cases. This same observation was made by Douamba S [11] in 71.4% of his patients. The majority of our patients (68.89%) were put on oxygen. Our results are superior to those of Bertholdt S *et al.* [8] who used oxygen therapy in 50% of their patients. The oxygen flow rate was greater than or equal to 3l in 44.44% of cases. Weaning occurred between 3-4 days in 33.33% of cases (n = 15). This oxygen use is explained by desaturation which is frequently observed in pulmonary complications of sickle cell disease. Non-phenotyped packed red blood cells were transfused in 31.31% of patients. Bertholdt S *et al.* [8] had transfused 44% of their patients with packed red blood cells. Ideally, phenotyped red blood cells should be transfused, but the availability of phenotyped blood in emergency situations is lacking in our context. Incentive spirometry was advised in 84.44% of patients. Ideally, spirometry should have been performed in all patients over 5 years of age, but the lack of financial means, the non-availability and the high cost of this examination in the hospital were lacking in our study. Half of our patients (51.11%) were relieved of their attacks between 6 and 10 days. The average length of hospitalization was 7.5 days with extremes ranging from 2 to 30 days. Our average length of hospitalization is comparable to that of Bertholdt S *et al.* [8] who found 7 days with extremes ranging from 4.5 to 11 days. We recorded two deaths (4.44%) all in the context of acute chest syndrome. This result is lower than that of Douamba S

[11] who had in Burkina Faso 7.5% (n = 10) of cases of death in major sickle cell syndromes and associated infections in children.

There are significant relationship between the type of hemoglobin and the reasons for consultation or referral (P = 0.02) on the one hand and between the type of hemoglobin and the type of complication (P = 0.001) on the other. These relationships are linked to the specifics of each form of sickle cell disease, which is why there has been more reference due to anemia in the homozygous form.

## 5. Conclusions

Sickle cell disease is a source of pulmonary complications. In our study, we noted 13.76% of pulmonary complications in the children followed. They are determined by the acute thoracic syndrome (87.67%) hence the need to repeat the chest X-ray for follow-up. His mortality rate was 4.44% (n = 2).

At the end of our study, we recommend to:

- Make spirometry accessible at a lower cost;
- Strengthen the training of sickle cell specialists;
- Provide the imaging in pediatrics department with a mobile x-ray machine.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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