Therapeutic Approaches of Acute Thoracic Syndrome in Patients with Falciform Disease

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Abstract

Sickle cell disease (SCD) is an autosomal recessive inheritance disorder that affects the beta-globin gene and results in the replacement of the amino acid glutamic acid by valine at the sixth position of the β chain of the hemoglobin molecule, producing erythrocytes with defective forms and functions. A range of pathological conditions is associated with SCD, however, one in particular stands out by gravity. Acute thoracic syndrome (STA), characterized by the presence of pulmonary infiltrates associated with a clinical symptom such as chest pain, cough, wheezing, tachypnea and fever, is considered a leading cause of death in patients with sickle cell disease. Early diagnosis and introduction of an effective approach to complication are needed to improve outcomes and minimize associated morbidity and mortality.

Keywords: Acute thoracic syndrome; Sickle cell disease; Blood; Therapeutic approach

Introduction

Sickle cell disease (SCD) is an autosomal recessive inheritance pathology that affects the beta-globin gene and results in the replacement of the amino acid glutamic acid with valine at the sixth position of the β chain of the hemoglobin molecule, producing erythrocytes with defective forms and functions [1-5]. As a result, red blood cells are prone to fail and agglutinate in states of low oxygen saturation. A range of complications arising from this condition may occur, such as chronic hemolytic anemia resulting from the premature removal of red blood cells from the circulation, vaso-occlusion caused by erythrocytic deposition in small vessels or bifurcations, increased blood viscosity, predisposition to primary and recurrent infections In addition to advanced stage organ failure [2,6,7]. The occurrence of such events is correlated with the propensity to develop a serious complication, the acute thoracic syndrome (STA). It is characterized by the presence of pulmonary infiltrates associated with at least one clinical or symptom such as chest pain, cough, wheezing, tachypnea, and fever [8-10]. This complication accounts for a quarter of sickle cell deaths (SCD) [11-13], and is also considered the second most common cause of hospitalization of patients with SCD [14]. Considering the clinical relevance of the disease, this article intends to carry out a small bibliographic review on the therapeutic approaches for STA.

Acute thoracic syndrome

Acute thoracic syndrome (STA), a severe complication characterized by pulmonary infiltrates associated with at least one clinical sign or symptom such as chest pain, cough, wheezing, tachypnea and fever [8,14-17]. The clinical characteristics of STA vary with age and can overlap with infectious causes and other pulmonary symptoms, preventing adequate diagnosis [1]. Adults are usually afebrile and prone to shortness of breath, chills, severe pain, bilateral involvement of the lower lobe, and even pleural effusion [10,11,18]. Differently from the symptomatology presented by adults, children younger than 10 years of age usually present with fever, cough, wheezing and involvement of pulmonary lobes [9,10]. A range of risk factors are associated with the occurrence of STA in patients with sickle cell disease (Table 1).

In addition to the above factors, there is small evidence that the SCD genotype is associated with STA, since the frequency of this complication is high in patients who have hemoglobin SC and HbS-β [6,26]. Accordingly, studies suggest that the HLA haplotype of DRB1*130101-DQB1*060101 has been shown to be strongly associated with the development of STA when compared to other [27]. Diagnosis of acute chest syndrome is relatively simple and consists only of the correlation of clinical suspicion with the usual clinical features of the complication, that is, the appearance of suggestive features on a chest X-ray in a patient with sickle cell anemia presenting hypoxia, tachypnea, thoracic signs, fever and chest pain of recent onset is considered a positive case [10]. Despite the importance of the presence of such symptoms, it is quite common to find no physical signs in some young patients, and the same cannot be reliable in the diagnosis of STA, since about 60% of the cases of this complication are undiagnosed because it is not performed radiological examination [28,29]. Thus, a chest X-ray is indicated to confirm the diagnosis of STA and to guarantee the start of treatment in any patient with SCD who presents with fever or chest pain, in addition to respiratory attacks [11]. However, it is important to note that pulmonary infiltrates may not appear on radiographs before 48 to 72 h after the onset of clinical symptoms.

Table 1: Key risk factors for a sickle cell patient.

| Risk factors associated with STA in the SCD |
|-------------------------------------------|
| Abdominal surgery for splenectomy and cholecystectomy [19] |
| Hypersensitivity [20,21] |
| Smoking [20,21] |
| Asthma [22] |
| Infections [9,23-25] |
| Post-Surgical Hypoventilation [9,23-25] |
| Fatty Embolism [9,23-25] |

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Received March 24, 2017; Accepted April 19, 2017; Published April 27, 2017

Citation: Destefani AC, Costa DS, Zanardo TEC, Taufner GH (2017) Therapeutic Approaches of Acute Thoracic Syndrome in Patients with Falciform Disease. J Blood Lymph 7: 165. doi: 10.4172/2165-7831.1000165

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The central focus of treatment in acute chest syndrome is to prevent or reverse acute respiratory failure, however, as the causes of the complication are relatively unknown in the scientific and medical setting, central therapy continues to be supportive and palliative [14]. Once the diagnosis is made, the treatment is directed to limit the progression of the disease in the acute phase, and later, to prevent its recurrence and sequelae that may occur in the long term. All patients with the syndrome are hospitalized and receive intravenous antibiotics, bronchodilators and analgesics [8,30]. And varying from case to case, supportive therapies such as blood transfusion, oxygen supplementation, and spirometer may be needed to aid in breathing [31]. In addition, when the patient is admitted to medical care, a complete blood count is made – mainly of red blood cells and hemoglobin –, a reticulocyte count, blood typing, microbiological culture of blood and sputum [32].

**Antibiotics:** It is generally not possible to distinguish between the different causes of STA, so the presence of virus or micro-organism infection should be closely considered [33]. Therefore all patients with the syndrome should receive broad spectrum parenteral antibiotics consisting of third generation cephalosporins such as penicillin’s and macrolides such as azithromycin [34]. The antibiotic treatment regimen may further be modified depending on the culture results and the clinical condition of the patient [14,34]. For pregnant women at risk or at the beginning of untreated disease, the indicated antibiotic is vancomycin [7]. There are no guidelines available for optimal therapy with antibiotics in STA treatment, but a 10-day course seems to be a reasonable option [31,34].

**Transfusion:** A blood transfusion are a first-line defense for the management of STA in patients with SCD, since the presence of new cells dilutes the number of sickle cells, improves oxygen carrying capacity, and prevents vaso-occlusion and, consequently, ache. In addition, the infused brings many other benefits, as it brings with it several other factors, such as erythropoietin, an important hormone that stimulates the production of red blood cells [33]. Two types of transfusion are used: exchange transfusions and simple transfusions. Acute respiratory failure can develop abruptly, since early blood transfusion of the simple type when hemoglobin levels are less than 50 g/L is extremely important because it aims to achieve an ideal concentration of 100-110 g/L. Although most STA patients respond adequately to simple transfusions, some studies show an efficacy of transfusion transfusions as first-line therapy in STA [33-36]. Blood transfusion does not occur frequently, and your choice should be based on the patient’s clinical status, noting that the patient is deteriorating relatively quickly. For patients with PaO2 less than 9.0 kPa of ambient air a single transfusion should be considered. In addition, it may also be used in cases of severe degrees of hypoxemia depending on the patient’s individual and clinical history or whether the patient’s oxygen needs are increasing. For patients with severe disease characteristics, exchange transfusion is indicated [14,33]. Not yet investigated as a blood transfusion paper background as a clinical approach to an acute chest syndrome, therefore some randomized trials are needed [37,38]. However, there is observational and case-control evidence that the use of this therapeutic approach has an efficacy in STA and can save life in severe cases. Using blood transfusion in STA management can produce rapid and dramatic improvements in patients’ clinical, radiological and oxygenation parameters [9,10,35,39]. Both simple transfusion and exchange transfusion increase oxygenation to desirable levels [10,40].

**Hydroxyurea:** The use of hydroxyurea, a cytotoxic and antineoplastic drug has been studied as a promising therapeutic approach for the treatment of SCD and consequently of STA [39]. This compound, when used for this purpose, acts to stimulate the production of hemoglobin rich in fetal hemoglobin (HbF), consequently suppressing hemoglobin S (HbS). Subsequent laboratory results demonstrate elevation of total HbF and Hb, as well as substantial improvement in red blood cell deformability. These aspects together reduce vaso-occlusive phenomena and consequently STA, hospitalizations and possible deaths [40,41].

**Pain control:** The presence of sickle erythrocytes in the blood circulation results in numerous complications due to vessel-occlusion of vessels and arterioles. The main ones described are alveolar hypventilation that can be aggravated by pulmonary atelectasis and severe pain [41,42]. For the effective relief of pain, the use of the analgesic scale of the World Health Organization [43]. To combat pain, opioid analgesics are often used [44]. However, care should be taken to avoid alveolar hypventilation of overdose, since it increases the risk of STA. Two studies have found that the use of morphine may increase a likelihood of developing STA [45]. However, a small cross-over study does not support these findings [46]. Appropriate analgesia allows for deeper breathing [47], require careful monitoring with frequent review and evaluation of pain and sedation scores, as well as cardiorespiratory monitoring [14]. If the approach of choice is opioids, attention should be given to adequate dosage to avoid excessive sedation and hypventilation. In particular, non-steroidal anti-inflammatory drugs, hyperhydration and overse of opioid analgesics should be avoided because they aggravate STA pain [8]. Intercostal nerve block was attempted and has been shown to relieve chest pain for less than 24 h [8]. For better control of pain and prevention of respiratory depression, patient-controlled analgesia (PCA) can be used, even if use does not decrease episodes of pain, it alleviate nausea related to opiate consumption and constipation compared to the use of analgesics uncontrolled [48]. STA patients should be monitored for exacerbation of pain episodes, and the daily use of pain scores to control the use of analgesia is recommended. In addition, serum sodium levels should be monitored because STA induced nephropathy may lead to sodium loss and hyponatremia, which may be associated with pain. The administration of sufficient sodium may prevent the development of this metabolic complication [48]. As a therapeutic approach to pain, vitamin D is increasingly recognized. Patients with SCD have a high prevalence of vitamin D deficiency. Thus, the correction of low vitamin D may offer a simple and low-cost intervention to help reduce acute vaso-occlusive complications and consequently pain [49].

**Bronchodilators:** Bronchodilators are a class of medications used to treat bronchial complications associated with asthma, acute bronchospasm, and reversible airway diseases such as acute chest syndrome caused by sickle cell disease [50]. Since airway hypersensitivity is a major risk factor for STA development, bronchodilator-based therapies may be used as a therapeutic approach in patients who exhibit wheezing or signs of airflow obstruction [51]. Despite the importance of new clinical approaches, including for bronchal complications, there are no studies that investigate their effects on ACS in depth, and it must be necessary to carry out new well-designed and randomized clinical trials that support this therapeutic modality, for who knows soon it is routinely used [11,50,52,53].

**Corticosteroids:** The use of corticosteroids for long periods is associated with a high risk of avascular necrosis and leukocytosis, a complication that patients with SCD are highly likely to develop due to vaso-occlusive crises [54,55]. The role of corticosteroids,
specifically dexamethasone or prednisone, in the management of STA is controversial, since there is a significant variability in its efficacy [36]. Studies indicate that there is a reduction in the time of hospitalization of patients who use corticosteroids, however, concomitantly other studies show a high rate of readmission of pain 72 h after therapy [31,56,37]. Another central issue is the high risk of corticosteroid-induced fat embolism in patients with SCD, and it is not recommended to administer corticosteroid in these patients [54]. Therefore, routine use of corticosteroids in the treatment of mild and moderate STA should be rethought because of its adverse effects [14].

Conclusion
Acute thoracic syndrome is a common and debilitating complication of sickle cell disease. It accounts for about a quarter of sickling-related mortality. Early diagnosis and introduction of an efficient approach to this complication are needed to improve outcomes and minimize associated morbidity and mortality. The evolution of treatment approaches over the decades to date is satisfactory. There are old management methods allied to new and recent methods, however, treatment of patients developing STA remains exclusively supportive, requiring close monitoring of disease progression and identification of new predictors for the development and severity of the disease. STA that can aid in early diagnosis and improved management of this highly lethal condition.

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