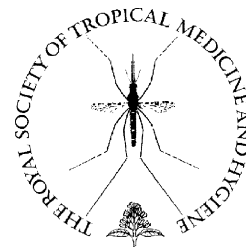




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REVIEW

Managing acute chest syndrome of sickle cell disease in an African setting

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KEYWORDS

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Summary Despite the fact that acute chest syndrome contributes immensely to morbidity and mortality in patients with sickle cell anaemia, its exact aetiopathogenesis is very complex and not yet well understood. Therefore, a high index of suspicion is needed in its diagnosis, and appropriate treatment should be commenced as soon as possible to prevent lethal complications of this condition, especially in Nigeria where appropriate diagnostic and therapeutic facilities may not be readily available. This is very important, as it may even develop on hospital admission. There is a need to further investigate preventive measures such as the use of hydroxyurea and the newly introduced Nicosan, especially in those people with recurrent disease, in order to reduce both short- and long-term complications of this syndrome among sickle cell patients in Nigeria.

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1. Introduction

Pulmonary complications are major contributors to morbidity, and indeed mortality, in patients with sickle cell anaemia (SCA), and in the long run lung involvement constitutes a paramount determinant of survival. Clinical lung involvement in patients with SCA commonly takes two forms: acute chest syndrome (ACS) and chronic lung disease (Weil et al., 1993). This article aims at reviewing ACS, with a view to improving its management in African settings.

Charache et al. (1979) used the term ACS to describe episodes of fever, chest pain and pulmonary infiltrates in

adult sickle cell patients, many of whom seemed to have pulmonary infarction. Currently, the syndrome is defined by the appearance of a new pulmonary infiltrate on chest radiography, fever, cough, chest pain and dyspnoea with hypoxaemia, and leucocytosis (Vichinsky et al., 1997).

2. Incidence and risk factors

Although anecdotal series on ACS are available, there are no firm data on its incidence in Nigeria. It was present in 6% of 102 adolescents and adults in a monocentric study conducted in Lagos, Nigeria (Ibidapo and Akinyanju, 2000). However, studies done elsewhere have shown that it is a common complication that occurs in about 50% of patients with SCA and is recurrent in about 80% of them (Golden et al., 1998; Leong and Stark, 1998). In half of the patients, it is preceded by vaso-occlusive crises affecting the long

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bones, vertebrae and chest wall (Vichinsky et al., 1997). It is a form of acute lung injury that can progress to acute respiratory distress syndrome. It is the second commonest reason for hospital admission for people with SCA and the most common cause of deaths in them, accounting for about 25% of premature deaths among these individuals (Platt et al., 1994). Patients with homozygous or sickle cell β^0 thalassaemia genotypes are more often affected than those with haemoglobin SC or the sickle cell β^+ thalassaemia genotype. Other risk factors include a high sickle haemoglobin concentration, a low fetal haemoglobin concentration, high steady state leucocyte counts, fever, surgery, previous pulmonary events and avascular necrosis of bone (Castro et al., 1994; Vichinsky and Styles, 1996).

3. Pathogenesis of ACS

The pathogenesis of parenchymal lung infiltrates in ACS is incompletely understood. Pulmonary infiltrates may result from either one process or a combination of several interacting processes, which may include atelectasis from splinting due to thoracic pain during vaso-occlusive crises, pulmonary infection, fat embolism, thromboembolism, vascular injury due to cell-cell interactions and inflammatory mediators, and most commonly, in situ microvascular occlusion within the pulmonary vasculature by sickled erythrocytes (Golden et al., 1998; Vichinsky and Styles, 1996; Walker et al., 1979). Secretory phospholipase A2 concentrations are increased in ACS and this phospholipase has been thought to liberate inflammatory free fatty acids from bone marrow lipid, thus contributing to lung injury (Styles et al., 1996). Recent studies also suggest that asthma and bronchial hyper-reactivity are important components of some episodes of ACS in people with SCA (Boyd et al., 2006; Knight-Madden et al., 2005). Excessive narcotic use and excessive hydration have been proposed as two possible iatrogenic causes of ACS; however, both have limited supportive evidence (Haynes and Allison, 1986; Kopecky et al., 2004). Although no available clinical, laboratory or radiographic methods have accurately and reliably distinguished the causes of ACS, it is now believed that the varied causes have in common the ability to create regional hypoxia and lung injury, which are followed by a cascade of events made possible by the inherent pathophysiology of SCA. The regional hypoxia prevents reoxygenation of red blood cells returning to the lung and leaves them in their sickled form. Sickled red blood cells have difficulty passing through small vascular beds both because of the deformed shape and inflexibility and because of expression of adhesion molecules on the cell wall. Thus a vicious cycle develops because of the loss of the lung's role in desickling.

Until recently, there have been controversies as to how the cascade of events that produce the clinical manifestations of ACS develops. Setty and Stuart (1996) and Stuart and Setty (1999) have, however, presented data that provide a unifying hypothesis explaining the pathogenetic mechanisms of the cascade based on nitric oxide (NO). They observed that hypoxia enhances adhesion of red cells to endothelial cells and that this interaction is mediated by binding of vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells to $\alpha 4\beta 1$ on red cells. Under normal conditions NO downregulates endothelial VCAM-1 expression. During ACS,

however, hypoxia and red cell sickling inhibit NO production, while released free radical species inactivate locally produced NO. The depletion of NO results in unopposed VCAM-1 upregulation and increased red cell endothelial adhesion.

4. Diagnosis

Physicians in Nigeria should have a low threshold for diagnosing ACS in patients with vaso-occlusive crisis, especially when they develop chest pain and dyspnoea. ACS may be present at presentation or it may develop on hospital admission (Vichinsky and Styles, 1996; Vichinsky et al., 1997). Clinical findings of patients with ACS developed in a mean of 2.5 d after hospital admission (Vichinsky et al., 1997; Vichinsky et al., 2000). The clinical presentation of ACS is age-dependent. The classic presentation in adults is that of chest pain, limb pain and dyspnoea, with or without cough and fever (Vichinsky and Styles, 1996; Vichinsky et al., 1997). Children, in contrast to adults, were more likely to present with fever, cough and wheeze, with upper and middle lobe opacities present on chest radiographs. These differences may reflect differences in the relative frequencies of aetiology, with children presenting with ACS due to pulmonary infection and adults more commonly presenting with vaso-occlusive crises complicated by subsequent fat emboli and ACS. In this sense, pain is a prodrome of the ACS, indicating the need to monitor for, and try to prevent, its development in those admitted to the hospital for vaso-occlusive crises.

Chest radiography reveals the presence of a new pulmonary infiltrate, which usually progresses rapidly to involve multiple lobes. It is usual to see a drop in haemoglobin concentration of the patient, as well as leucocytosis. Care should be taken in interpreting these results, as most of the patients have a high 'steady state' leucocyte count (Vichinsky and Styles, 1996; Vichinsky et al., 1997). When available, arterial blood gas (ABG) analysis and pulse oximetry should be done. This usually demonstrates hypoxaemia with a widened alveolar-arterial (A-a) oxygen gradient (Emre et al., 1993). Sputum and blood cultures should be done in all patients, despite the low yield documented by most studies. This is to identify bacterial agents when present. Other investigations, such as thin section computed tomography scan of the chest, fibre-optic bronchoscopy (with or without broncho-alveolar lavage) and echocardiography, may yield relevant information, especially in patients that are deteriorating despite adequate treatment; however, they are not readily available in Nigeria.

5. Management of ACS

The emphasis is on supportive care, which includes control of infection and pain, oxygen supplementation, careful hydration and blood transfusion.

5.1. Treatment of underlying factors

Identification and treatment of all the underlying precipitating factors, such as possible bacterial infection, should be treated with i.v. antibiotics, as it is difficult to exclude the

presence of pneumonia or super-infected lung infarction, especially in febrile ACS patients. Macrolide or quinolone antibiotics have been recommended in order to cover atypical pathogens. However, knowledge of the local sensitivity pattern should be taken into consideration.

5.2. Optimal pain control

Prevention of chest splinting and atelectasis is achieved by optimal pain control with narcotic analgesics, continuous positive airway pressure and expiratory positive airway pressure. Care must be taken to avoid excessive sedation, which results in decreased ventilatory effort (Kopecky et al., 2004). Studies that were carried out to compare patient-controlled analgesia to intermittent i.v. analgesia revealed that there was no significant difference in pain control and incidence of adverse effects between regimens (Gonzalez et al., 1991; Perlin et al., 1993).

5.3. Fluid administration

Optimal hydration is essential to maintain a normovolaemic state, but excessive hydration should be avoided because it may worsen pulmonary status (Haynes and Allison, 1986). To date there are no randomized control trials that have assessed the efficacy of different routes, types or quantities of fluid administered to people with SCA during acute episodes (Okomo and Meremikwu, 2007).

5.4. Optimizing blood oxygen

Optimizing blood oxygen requires determination of baseline ABG, which allows estimation of A-a oxygen gradient and the arterial oxygen tension/fractional concentration of oxygen in inspired gas ($\text{PaO}_2/\text{FIO}_2$) ratio. Hypoxic patients should be administered oxygen, and the efficacy of this intervention should be checked by repeating their ABG on oxygen. Subsequent monitoring of the patient can be done with pulse oximetry, which is non-invasive and cost-effective. Clinical assessments of respiratory status should occur hourly, or more frequently in hypoxic patients. Ideally, ABG should be re-examined as needed to monitor the abnormal A-a oxygen gradient, which appears to be the strongest predictor of clinical severity (Emre et al., 1993). Progressively hypoxic patients should be monitored and managed in the intensive care unit for adequate respiratory support and for addressing multi-organ failure (Hassell et al., 1994), which may also develop in this clinical setting. The clinical indicators to monitor in ACS include respiratory rate, pulse rate, blood pressure, temperature, fluid input/output and arterial blood gases or pulse oximetry. Where facilities for ABG or pulse oximetry are not widely available, patients with suspected ACS should be referred to specialist centres early in the course of their illness before they deteriorate.

5.5. Red cell exchange

Decreasing the proportion of sickling red cells in the blood often results in dramatic improvement in clinical condition of the patients (Mallouh and Asa, 1998). Emerging facts

suggest that red cell exchange is preferred to simple or exchange transfusions in ACS because it can provide required oxygen carrying capacity while reducing the overall viscosity of blood (Lawson et al., 1999; Swerdlow, 2006). The use of modern cell separators is safer, more effective, easier and quicker than manual exchange procedures (Lawson et al., 1999). The goal is to prevent progression of ACS to acute respiratory distress syndrome and respiratory failure. It should be initiated at the first signs of hypoxaemia ($\text{PaO}_2 < 70$ mmHg on room air, or a drop of $> 10\%$ from the baseline for patients with chronic hypoxaemia). However, it may not be needed if the abnormal A-a oxygen gradient corrects with optimal analgesia.

Delays in instituting transfusion therapy particularly in rapidly deteriorating patients should be avoided. Possible causes of delays include the following: (1) ascribing an altered mental state to a narcotic overdose, when it may actually be an indication of worsening ACS and impending death; (2) assuming that the pulmonary oedema often described in chest radiographs is due to fluid overload; (3) assuming that patients who are not responding to antibiotics need a trial of different antibiotics (Castro, 1999).

5.6. Other measures

Other treatment modalities are available, but more studies are required to further evaluate their efficacy and safety. Case reports indicate significant improvement in oxygenation and reductions in pulmonary artery pressures during inhalation of NO (Sullivan et al., 1999). It has been noted that sickle haemoglobin binds oxygen more avidly in the presence of NO (Emre et al., 1993). This prevents the haemoglobin molecule from assuming a deoxygenated state, a state associated with sickling and microvascular occlusion. Some researchers have recommended that regardless of the presence or absence of audible wheezes, treatment with bronchodilators should be routine at presentation and continued if a response is noted (Bernard et al., 2007). However, there are no well-designed, adequately powered randomized control trials to assess the benefits and risks of addition of inhaled bronchodilators to established therapies for ACS in SCA patients (Knight-Madden and Hambleton, 2003).

Although steroid has documented efficacy for reducing duration of ACS, studies have shown that it was poorly tolerated (Couillard et al., 2007) and associated with substantial risk of admission for pain (Strouse et al., 2007). Studies have also shown that non-ionic surfactants (Ballack et al., 2004) and anticoagulants (Ahmed et al., 2004) alter the complex interactions between the various agents involved in the pathogenesis of SCA and its complications and as such may have beneficial effect in ACS. Further studies are needed to further assess these agents in SCA patients in ACS.

6. Prevention of ACS

6.1. Good pain control

Although supervised incentive spirometry has been recommended routinely for prophylaxis of ACS in SCA patients in vaso-occlusive crisis (Bellet et al., 1995), it might not be feasible to get patients involved because good pain control

is usually associated with sedation in them. However, good pain control will handle the thoracic splinting that can lead to hypoventilation.

6.2. Hydroxyurea therapy (Charache et al., 1995)

Hydroxyurea (Droxial) is the first widely available agent to show promising activity and to be piloted in Phase III studies in adults. Before the introduction of Nicosan (Iyamu et al., 2002), which was previously called NIPRISAN, it was the least toxic agent investigated in the treatment of SCA (Olujohungbe et al., 1998). The exact mechanism of action is unclear but it appears to increase fetal haemoglobin (Edward, 2001; Olujohungbe et al., 1998), which has been shown to confer some protection on SCA sufferers by binding more strongly to oxygen than haemoglobin A, thus preventing hypoxia and sickling in these patients (Jaja et al., 2000). It may also exact beneficial effects on red cell hydration, vascular wall adherence and suppression of the granulocyte and reticulocyte counts. It is said that white cells and reticulocytes may play a major role in the pathogenesis of sickle cell crisis; their suppression may be an important benefit of hydroxyurea therapy (Edward, 2001). Hydroxyurea has also been found to be oxidized by haem groups to produce NO (Pacelli et al., 1996), and its administration is followed by formation of nitrosyl (heme) haemoglobin and NO metabolites (Glover et al., 1999). The role of NO in ACS has already been mentioned. This may explain why patients taking it report improvements in symptoms before fetal haemoglobin concentrations increase. This drug may have an important role in developing countries, where strategies such as safe transfusion and bone marrow transplantation may not be readily available.

6.3. Institution of long-term red cell exchange programmes (Swerdlow, 2006)

Although patients with recurrent episodes of ACS may benefit from regular red cell exchange for chronic maintenance of low sickle haemoglobin concentration, this may not be feasible in Nigeria because of problems associated with proper screening of blood before transfusion.

6.4. Bone marrow transplantation (Walters et al., 1996)

Even though bone marrow transplantation can provide a definitive cure, it is known to be effective and safe only in children (Edward, 2001). Recent facts also show that transplantation of sibling donor umbilical cord blood has clinical advantages over marrow transplantation in young children, in particular regarding the risk of graft-versus-host disease, a common side effect and the leading cause of death in transplant medicine (Walters et al., 2007). However, it is not likely that it will be readily available to most Nigerian sickle cell patients in the near future because of the present level of development of health care delivery. As bone marrow transplantation and chronic red cell exchange may not be feasible in Nigeria for now, the use of hydroxyurea and Nicosan is recommended for prevention of recurrent ACS.

However, further studies on the efficacy and safety of these drugs in our sickle cell patients are still required.

6.5. Use of Nicosan (Iyamu et al., 2002)

Recently, Nicosan, a non-toxic phyto-pharmaceutical agent, has been introduced for prophylactic treatment of sickle cell disease. It is a herbal mixture consisting of four active agents (*Piper guinense*, *Pterocarpus osun*, *Eugenia caryophyllum* and *Sorghum bicolor*), which have been shown to have anti-sickling effects. Although its precise mechanism of action is not yet confirmed, it has been shown to inhibit cell sickling by increasing solubility of sickle haemoglobin. Results of further studies are needed to confirm or refute claims from earlier studies.

Various other measures (for example, gene therapy and use of agents that block red cell dehydration such as clotrimazole or vascular adhesion such as monoclonal antibodies) are still under trial.

7. Conclusions

Although ACS is an important determinant of survival in sickle cell patients, no available clinical, laboratory or radiographic methods can reliably and accurately distinguish its various causes, even in the developed world. Therefore, Nigerian physicians should have a low threshold for its diagnosis and prompt commencement of appropriate treatments. The use of hydroxyurea and the newly introduced Nicosan should be further investigated in Nigerian sickle cell patients, with a view to their widespread use in those patients with recurrent disease.

8. Practical points

- Physicians in Nigeria should have a low threshold for diagnosing ACS in patients with vaso-occlusive crises.
- Good pain control by analgesics should be used for prophylaxis of ACS in vaso-occlusive crises.
- Sputum and blood cultures should be performed in all patients with ACS, despite low yield documented by most studies.
- Broad-spectrum antibiotics should be administered to patients, as it is difficult to exclude the presence of pneumonia or super-infected lung infarction, especially in febrile ACS patients.
- Clinical assessment of respiratory status should be done at least every hour, or more frequently in hypoxic patients. Any progressively hypoxic patient should be managed in the intensive care unit.
- Where facilities for ABG or pulse-oximetry analysis are not widely available, patients with suspected ACS should be referred to specialist centres early in the course of their illness, before they deteriorate.
- Delays in instituting transfusion therapy, especially in deteriorating patients, should be avoided.

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