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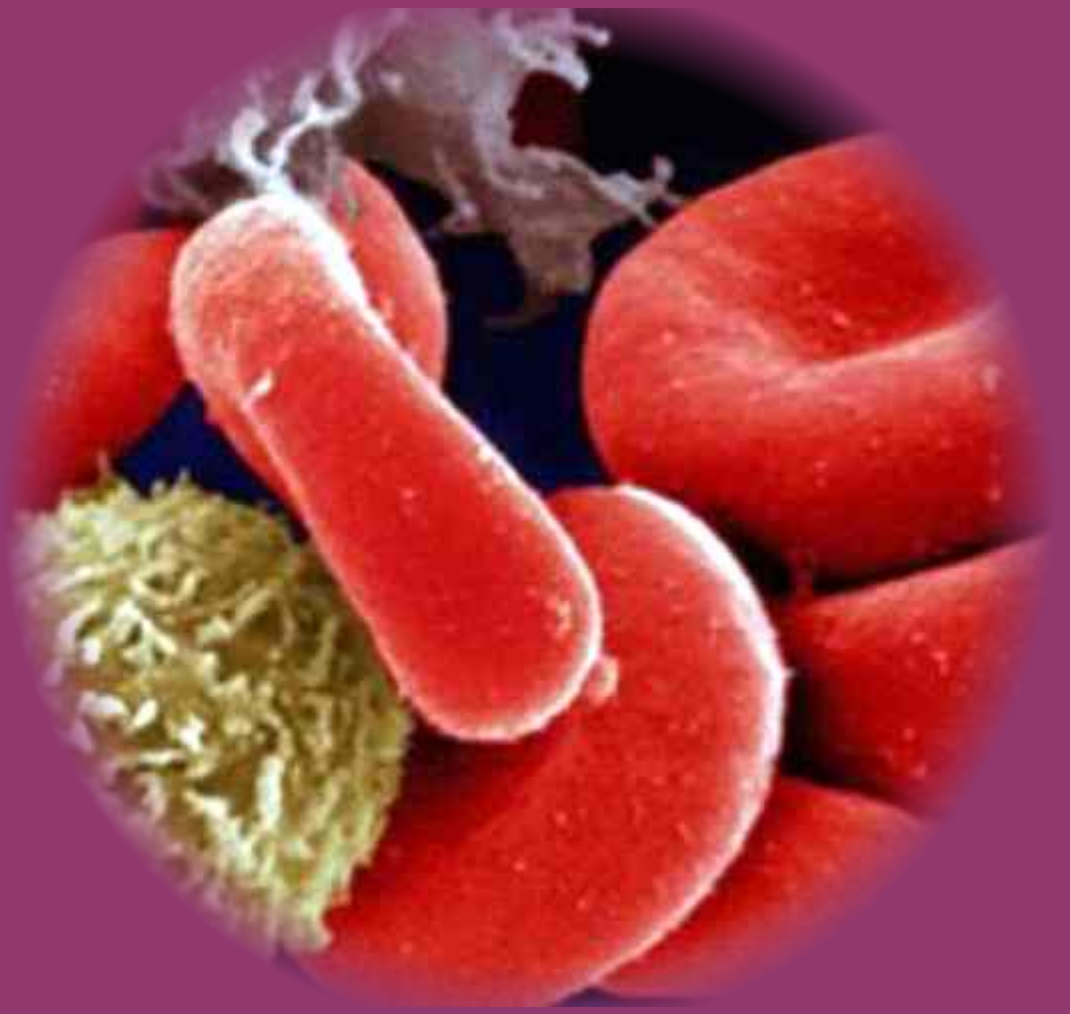
Journal of the Nigerian Society for Haematology & Blood Transfusion



ISSN: XXX - XX - XXX

VOL. 1 NO 1, AUGUST, 2017

REVIEW ARTICLE

Acute Chest Syndrome: A Leading Cause of Death in Sickle Cell Disease

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ABSTRACT

Acute chest syndrome (ACS) is a leading cause of mortality in sickle cell disease (SCD), and is one of the numerous complications of sickle cell disease. The aetiological factors associated with the development of ACS could either be either infectious or non-infectious. ACS develops insidiously or suddenly, during admission for vaso-occlusive crises, or after surgery particularly abdominal surgery. Diagnosing and managing it may be challenging in in-experienced hands. The outcome of ACS depends on rapid diagnosis (clinical, radiological and laboratory), as well as institution of appropriate management, which aims to reduce the incidence of respiratory failure, and death. Therefore, this review article aims to elucidate on ACS in order to improve on the diagnostic and management skills of Emergency Physicians/ Surgeons, Pediatricians, Family Physicians, Internists and Haematologists who manage SCD patients, thus reducing associated mortality.

The following search engines were used in this review article: Google, Pubmed and UpToDate. Key words used in the search were: Acute chest syndrome and Sickle cell disease. The number of articles initially obtained was 53; however 41 articles were included in this review. Literature search for this review article was conducted over a period of four (4) months from June 2016 to October 2016.

Keywords: acute chest syndrome, sickle cell disease.

INTRODUCTION

Sickle cell disease (SCD) is a genetic abnormality involving a single point mutation which causes the replacement of adenine with thymine on deoxyribonucleic acid (DNA) structure. The mutation leads to the substitution of glutamine on the 6th position of the globin chain by valine. Sickling of the red blood cells (RBC) occurs as a consequent of the mutation. The red blood cells become polymerized consequent on the sickling. Polymerized red cells encounter difficulty in passing through small vascular beds. This difficulty is as a result of deformed shape and inflexibility of the red blood cell causing micro-vascular occlusion, hypoxia, pulmonary infarction and ACS.

A leading cause of mortality in sickle cell disease (SCD) is ACS [1] particularly in low-income countries because of late diagnosis due to poor facilities and delay in treatment by attending Physicians. ACS is associated with the following types of SCD in order of occurrence Hb SS, Hb SC, Hb S $^{+}$ thalassaemia and Hb S $^{\circ}$ thalassaemia. [2] Acute chest syndrome is associated with increased risk in patients with previous history of ACS and asthmas. Haematologic risk factors for the development of ACS include high steady state white blood cell count and haemoglobin concentration and a low steady state haemoglobin F level. [2] ACS is frequently preceded by painful events. [3] Post-operatively, the average time to developing ACS is three days. [4]

METHODS OF LITERATURE SEARCH

The following search engines were used in this review article: Google, Pubmed and UpToDate. Key words used in the search were: acute chest syndrome and sickle cell disease. The number

of articles initially obtained was 63; however 41 articles were included in this review.

Definition

Acute chest syndrome is defined as an acute illness associated with fever, respiratory symptoms and the development of a new pulmonary infiltrate on chest X-ray. [5,6] Although, traditionally not part of the definition, the presence or otherwise of hypoxia is relevant in clinical practice because it is a predictor of severity and outcome. [7]

Aetiology:

Aetiology could be infectious or non-infectious (Table I). The latter is responsible in 62% of cases in adults unlike commoner infectious causes in children. [7] Infectious causes may be associated with seasonal variation being common in the cold season when respiratory infections are commoner. [3] Non-infectious causes may be due to complications of pathophysiology of Hb SS like fat embolism syndrome, hypoventilation resulting from rib/sterna bone infarction or iatrogenic causes from over-hydration causing pulmonary oedema and excessive narcotic use causing hypoventilation and poor respiratory efforts.

Infectious Causes of ACS

Chlamydia and *Mycoplasma Pneumoniae* are considered the most common infectious agents [8] followed by viruses like *adenovirus, influenza virus, para-influenza viruses, respiratory syncytial virus, parvovirus B19,* cytomegalovirus [9] followed by bacteria like *Streptococcus* and *Klebsiella Pneumoniae, Haemophilus influenza* and *Staphylococcus aureus*. [7]

Non-infectious Causes of ACS

There is a high frequency of fat embolism in ACS as documented by Vichinsky *et al* (1994) who reported 12 of 27 episodes of ACS presented with evidence of fat embolism as the cause. [10] There is an association between fat embolism syndrome of trauma patients and ACS. [11] Fat droplets were recovered from cells obtained from bronchoscopy and bronchoalveolar lavage in ACS. Similarly, elevated levels of the enzyme secretory phospholipase A2 and serum levels of free fatty acids are seen in both fat embolism syndrome and ACS. Vichinsky *et al* (1994) also found fat embolism on autopsy studies and fat-laden macrophages in bronchoalveolar fluid and induced sputum in ACS. Bone vaso-occlusion may be responsible for bone marrow necrosis and release of fat emboli. The emboli migrate into the blood stream, lodge in the pulmonary vasculature causing acute hypoxia.

Other non-infectious common causes of ACS are infarctions of the ribs and other bones of the thorax causing localized splinting, atelectasis, radiographic infiltrates and ACS. [12] Alveolar hypoventilation secondary to opiate over dosage and excessive use of intravenous fluids in aggressive hydration strategies during treatment of VOC are common iatrogenic causes of ACS. [13,14]

Boyd *et al* reported an increased incidence of ACS in patients with pre-existing diagnosis of asthma. Patients with asthma had almost twice as many episodes of ACS compared with SCA patients without asthma. [15]

Pathophysiology

Hypoxia is the pathophysiological hallmark in ACS. It causes lung injury by preventing re-oxygenation of haemoglobin in the lung ensuring they are permanently sickled. Polymerized haemoglobin in the sickle red cell is unable to pass through small vascular beds. The difficulty in passing through is as a result of deformed shape and inflexibility of the red blood cell. [16]

Hypoxia and fat embolism also up regulate adhesion molecules like VCAM 1 on the vasculature endothelium resulting in adhesion of sickle red blood cells to the endothelium. [17] Release of inflammatory mediators, vascular stasis and failure to re-oxygenate enhance further sickling of red cell, microvascular occlusion and pulmonary infarction. All these factors contribute to the development of ACS from hypoxia and atelectasis.

Clinical Features

Cough, chest pain and fever are seen in almost all patients irrespective of age (Table II). [7]

Wheezing, shortness of breath and bloody sputum are other symptoms patients could present with. Physical examination may reveal normal findings; however, reduced air entry, bronchial breath sounds, rhonchi, pleural rub and tachypnoea may be elicited. Crepitation is the most common physical finding followed by a normal physical examination. Half of all patients diagnosed with ACS have been admitted for other diagnoses particularly vaso-occlusive crises and develop ACS in average of two and half days of admission. [7]

Diagnosis

As important as a chest radiograph is, in making a diagnosis of ACS, it may be normal in severely ill patients Clinical severity and degree of hypoxia may not correlate with chest radiograph findings. [18] Usually a lower lobe new infiltrate may be seen or commonly it may be multi-lobular. A serial radiograph is indicated in all patients to monitor therapy because radiographic changes may lag behind clinical findings. [19] Other features of a chest radiograph are pleural effusion particularly in adults, while children are more likely to have upper and middle lobe disease. [20]

Chest CT and CT pulmonary angiography may be considered in strong suspicion of ACS with unexplained hypoxia and no radiological signs on chest x ray. These may elucidate lung parenchyma and pulmonary vasculature pathologies. Bhalla *et al* (1993) reported that unlike a chest radiograph, chest CT strongly correlated with degree of hypoxia and disease severity with a specificity and sensitivity of 97% and 84% respectively. [18] A nuclear ventilation and perfusion (V/Q) scan may provide information on defective perfusion which is suggestive of ACS. [21] Thrombo-embolism and early ACS before the development of radiographic changes on chest radiograph may also be diagnosed by a V/Q scan.

Laboratory Investigations

Samples should be collected for haemato-logical, biochemical and microbiological tests (Table III).

Haematological

These include a full blood count, in which a drop in haemoglobin level and platelet count below steady state is expected. This may be as a result of bone marrow infarction and necrosis. A rise in total white blood cell count, an acute drop in haemoglobin level by 0.7g/dl and platelet count to below 200×10^9/L signify bad prognosis. Reticulocytosis confirms haemolysis associated with sickle cell disease and rules out parvovirus B 19–induced red cell aplasia because of the acute drop in the packed cell volume. [3] Grouping and cross-matching should be done for all SCD patients presenting with vaso-occlusive crises, in whom there is a high index of suspicion for the development of ACS.

Biochemical

Biochemical tests include urea, creatinine, liver function tests and C-Reactive protein because of the risk of multi-organ failure following systemic fat embolism. Other biochemical tests are arterial blood gas measurement. A pO2 less than 8kPa should be considered as severe hypoxia and a pCO2 greater than 6kPa as hypercapnia. [22] Secretory phospholipase A2 (sPLA2) assay level is elevated and has a positive predictive value of 24% in ACS. [23]

Microbiology

Infectious screening test should include sputum for microscopy, culture and sensitivity test sample collected by bronchoscopy yields a better quality than sputum, however, the procedure is associated with a complication rate of 13% in ACS. [11] Bronchoscopy sample could also be used to diagnose pulmonary fat embolism in which case the sample may contain fat-laden macrophages.

Antibody screen for *Mycoplasma Pneumonia*, *Chlamydia* and *Legionella* species and nasopharyngeal/sputum sample for PCR/immunoflurescence testing for viruses screen like *influenza A* and *B*, *parainfluenza, adenoviruses* and *Epstein-Barr* virus.

Management

Success of the management is dependent on prompt diagnosis and early intervention.

Effective treatment reduces the risk of respiratory failure and mortality. Management could be supportive or specific.

Supportive management

This includes, administration of intranasal oxygen, adequate analgesia which prevent thoracic splinting, thus encouraging deeper breathing [24]. Opiod overdosage must be avoided to prevent hypoventilation that may worsen the risk of ACS. Buchanan *et al* (2005) reported increased likelihood of developing ACS on morphine. [25] Intravenous fluids administration should not be excessive in order to prevent pulmonary oedema and worsen pulmonary status. Monitoring of pulse rate, blood pressure, respiratory rate, SPO_2 and arterial blood gases 4 hourly. Use of non-invasive ventilation and /or mechanical ventilator may be necessary.

Bronchodilators

Routine use of bronchodilators in all patients with history suggestive of asthma, acute bronchospasm and demonstrable reversible airway disease is desirable. The chest X-ray should be repeated if the clinical condition is not improving; daily evaluation of full blood count, urea and creatinine, liver function tests and thrombo-prophylaxis is recommended. [22]

Table 1. Aetiology of ACS

Infectious	Non Infectious
Bacterial	
Chlamydia Pneumoniae	Fat Embolism
Mycoplasma Pneumoniae	Opiod Overdosage
Steptococcus Pneumoniae	Aggressive hydration
Klebsiella Pneumoniae	strategies
Staphylococcus aureaus	Bone infarctions
Viruses	
Adenovirus	
Influenza Virus	
Parainfluenza Virus	
Respiratory syncytial virus	
Parvovirus B19	
Cytomegalovirus	

Table II. Clinical Features of ACS

Symptoms	Signs
Cough	Normal findings
Chest pain	Reduced air entry
Fever	Bronchial breath sounds
Wheezing	Ronchi
Shortness of Breath	Pleural rub
Bloody sputum	Tachypnoea
	Crepitations

Antimicrobial

Irrespective of blood or sputum culture results, every patient should be placed on antibiotics such as third generation cephalosporin against *Streptococcus pneumonia, Haemophilus Influenza* and *Klebsiella pneumonia* and macrolide which covers atypical respiratory organisms like *Mycoplasma* and *Chlamydia species.* [7] Antiviral drugs should be used if there is clinical suspicion of H1N1 subtype of Influenza A virus infection.

Transfusion Therapy

Use of transfusion therapy should be considered, keeping in mind the risk of allo-immunisation, transfusion transmissible infections, transfusion reactions and hyperviscosity vis-à-vis benefits associated with transfusion therapy. Emre *et al* (1995) reported increment in both the partial pressure of arterial oxygen and oxygen saturation following transfusion therapy. [26] Transfusion of haemoglobin phenotype AA blood either by exchange or simple transfusion lowers haemoglobin S concentration, thus promoting blood flow through the pulmonary vasculature and improving oxygenation effect that is similar in both simple and exchange transfusion. [7]

The merits of exchange transfusion are to reduce haemoglobin S concentration, thus preventing their further participation in vaso-occlusive process, and reducing the adverse consequences of haemolysis without increasing blood viscosity. [27] However, simple transfusion should be considered if there is concomitant severe anaemia, or if the PaO_2 less than 9.0kPa on room air and avoided if its use will raise the packed cell volume to 35% and above in order to prevent hyperviscosity syndrome. Red cell allo-immunisation could be reduced by 4% by the

use of phenotypically matched red cells. [7] For a full exchange transfusion which could be manual or automated, eight units of packed red cells may be needed in an adult or 40mls/kg in children less than 50kg to reduce the percentage of Hb S to between 30-40% and increase Hb concentration to between 10-11g/dl.

Corticosteroids

Use of corticosteroids is controversial; a report favours its use in children in which a reduction in hospital length of stay and reduction in the need for oxygen and opiod was reported [28] while some discouraged its use in both children and adults because of rebound sickling and higher rate of readmission. [29,30,31] Exception to the controversy is its use in children and adults with a co-morbidity of acute asthma with ACS. [32]

Nitric Oxide

The use of inhaled nitric oxide has been published in some case reports although no clinical trials have been reported [33,34] Nitric oxide has theoretical benefits of improving haemoglobin saturation, decreasing expression of adhesion molecules, reducing pulmonary pressure and improving oxygenation.

Prevention

The goal of prevention is to prevent occurrence and a recurrence of ACS. Every episode of ACS predisposes the patient to lung injury, pulmonary hypertension, cor pulmunale, scarring, chronic sickle lung disease, pulmonary fibrosis, pulmonary failure and death. [35] ACS should be anticipated in all patients admitted for vaso-occlusive crises. In managing these patients, intravenous fluids and analgesia should be used judiciously and patients closely monitored. [3]

Prevention strategies include use of prophylactic antibiotic such as Penicillin V till the age of 5 years [36], to prevent *S. pneumonia* infections [37], administration of vaccination against *S. pneumoniae*, *H. Influenza and N. Meninigitdis* infections such as influenza virus, pneumococcal conjugate vaccination, pneumococcal polysaccharide vaccination, haemophillus influenza type B and meningitis C vaccination.

Charache *et al* (1995) reported that use of hydroxycarbamide significantly reduces incidence of ACS in patients presenting with recurrent severe pain. [38] Similarly, long-term blood transfusion also decreases incidence of ACS in the stroke prevention [39] and silent cerebral infarct [40] studies. Sickle cell anaemia patients booked for elective surgery particularly abdominal surgery should be given pre-operative blood transfusion, Howard *et al* (2013) reported a lower incidence of ACS in this cohort of patients. [41] Secretory phospholipase A2 (sPLA2) assay could be monitored if the facility is available because of its positive predictive value of 24% in ACS. [23] Lastly, avoidance of smoking is necessary in all SCD patients.

Table III. Laboratory Investigations

Haematology	Biochemistry	Microbiology
Full Blood Count	Urea/Creatinine	Sputum M/C/S
Reticulocyte Count	Liver function test	Antibody Screening for
Grouping and cross-matching	Arterial Blood Gases	M. Pneumoniae
	Secretary Phospholipase A2	C. Pneumoniae

Keys: M/C/S- Microscopy /Culture/ and Sensitivity.
M. Pneumoniae- Mycoplasma Pneumoniae
C. Pneumoniae—Chlamydia Pneumoniae

CONCLUSION

Acute chest syndrome is a medical emergency, high index of suspicion is required to make the diagnosis because of a close diagnostic similarity with pulmonary embolism, lobar pneumonia, asthma among others, and efforts should be made to prevent it and its recurrence. Once the diagnosis is suspected, it should be attended to promptly and appropriately in order to reduce morbidity and mortality associated with it.

Conflict of Interest: No Conflict of interest was declared.

Authors' Contributions. All authors contributed to writing and reviewing this paper.

Acknowledgment: The authors thank Miss Oluwatosin Soetan for editorial assistance

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