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Paediatric Association of Nigeria Guidelines on the Management of Acute Chest Syndrome in Children with Sickle Cell Disease (2023)

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Executive Summary

Background

Acute Chest Syndrome (ACS) is a major cause of hospitalisation, a potentially life-threatening complication and a leading cause of mortality in children with Sickle Cell Disease (SCD). The affected child commonly presents with respiratory symptoms such as cough, breathlessness, chest pain, jitteriness, and confusion, with or without fever. The cause of this condition is multifactorial and sometimes unidentified, but the majority are due to infection, infarction, and fat embolism. ACS and its related complications may be minimised by prompt intervention and appropriate therapy, including the use of incentive spirometry and blood transfusion.

Objective

The development of a national guideline on the management of ACS in children with SCD under 18 years in Nigeria is meant to enhance early diagnosis and prompt treatment of ACS to improve the quality of care and clinical outcome and prevent death from ACS. It is intended to enhance the clinician's diagnostic capability and ensure that children with ACS receive the best available care.

Methods

This evidence-based guideline was adapted from the British Society of Haematology (BSH) and the American Society of Hematology (ASH) guidelines using the ADAPTE (Resource tool kit version 2.1) and AGREE II methods.

Results

The PAN Guideline Panel reached a consensus on 25 recommendations, three of which were modified and adapted for local use. The recommendations reflect a broad definition of

ACS and a management approach, including blood transfusion and incentive spirometry, such as blowing latex balloons in the absence of a spirometer.

Conclusions

Most recommendations are conditional because of low-certainty evidence and closely balanced benefits and harms (benefits of therapy to patients and availability of such therapy). Patient preferences should drive clinical decisions. Randomised controlled trials and comparative-effectiveness studies are needed for optimal management of blood transfusion, fluid therapy, and use of oxygen.

Summary of key recommendations

- ACS is an acute illness characterised by fever and respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray. Severe hypoxia is a valuable predictor of severity and outcome (1B).
- ACS has a multifactorial aetiology, and an infective cause is common, especially in children, and this should be considered in treatment algorithms (1B).
- Malaria caused by *Plasmodium falciparum* should be considered a significant co-morbidity in children from malaria-endemic regions (1C).
- Patients with sickle cell disease (SCD) can present with ACS, which may develop after the onset of severe pain. Therefore, vigilance should be maintained throughout hospital admission (1B).
- Clinicians should maintain a high index of suspicion of ACS in children with chest symptoms and signs, especially if hypoxic, even in the presence of a normal chest radiograph (1C).
- The non-availability of chest radiographs should not delay the commencement of treatment in children with signs and symptoms suggestive of ACS (1C).
- Pulmonary embolism, fluid overload, opiate narcosis and hypoventilation may cause or trigger ACS. It should be considered when a diagnosis of ACS is made, as these conditions may require additional treatment (1B).
- ACS can be a severe, life-threatening condition. Early recognition to prevent progression to acute respiratory failure is vital (1B).
- Patients should be monitored for severity predictors, including worsening hypoxia, increasing respiratory rate, decreasing platelet count, decreasing haemoglobin concentration, multi-lobar involvement on chest radiographs, and neurological complications (1B).
- Patients should be treated aggressively, irrespective of their sickle cell phenotype (1C).
- Essential investigations for the diagnosis and management of ACS are plain chest X-ray, full blood count, reticulocyte count, C-reactive protein, Erythrocyte Sedimentation Rate (ESR), basic biochemistry tests (creatinine and liver function), blood group, and crossmatch. Others include blood cultures, sputum for microscopy, and culture as needed (1B).
- Arterial blood gas analysis should be performed in cases of ACS with worsening hypoxia (2C).
- If there is a high clinical suspicion of pulmonary embolism (PE) (2B), a computerised tomography pulmonary angiogram (CTPA) is recommended.
- All hospitals should have a treatment pathway for ACS, which should include a referral pathway to the intensive care unit (1B).
- According to the PAN pain treatment guideline (1B), all patients with ACS

should receive prompt and adequate pain relief (1B).

- Incentive spirometry has proven beneficial in preventing ACS in patients with chest or rib pain (1A) and should also be recommended in all patients with ACS (2C). In low-resource settings, inflatable latex balloons may be considered in the absence of a spirometer (consensus opinion).
- Prescribed antibiotics should also cover atypical organisms, even if blood and sputum cultures are negative. Antiviral agents should be used if there is a clinical suspicion of a viral infection (1B).
- The PAN guideline suggests that all children with SCD from malaria-endemic areas should be commenced on effective antimalarial medications in line with the current national guidelines on the treatment of malaria (1C).
- Simple blood transfusion (top-up) is recommended early in the hypoxic patient, but an exchange transfusion is suggested if there is evidence of deterioration despite the initial simple transfusion (1B).
- Blood for transfusion should be sickle-negative and fully matched for Rh (C, D and E type) and Kell, where feasible. A history of previous red cell antibodies should be sought, and appropriate antigen-negative blood should be given (1A).
- The intensive care unit team should be consulted early for respiratory support (2C).
- Bronchodilators should be used if there is a history of asthma or evidence of acute bronchospasm. (1B).
- All patients should be offered penicillin V prophylaxis, pneumococcal polysaccharide vaccination, pneumococcal conjugate vaccine and appropriate seasonal vaccinations (1A/2B).
- Hydroxyurea is recommended for prevention of recurrent ACS (1A).
- Chronic blood transfusion is recommended for the prevention of recurrent ACS if hydroxyurea therapy is not effective (2B).
- Stem cell transplantation should be considered for the prevention of recurrent ACS if hydroxyurea therapy is not effective (2B).

Introduction and background

ACS is defined as a new pulmonary infiltrate, irrespective of the aetiology on a chest x-ray, in a child with SCD characterised by fever and/or respiratory symptoms. [1-3] It is a severe form of acute lung injury unique to SCD, but in some cases, ACS may appear similar to bacterial pneumonia in a patient without SCD.[2] The presence of hypoxia may not be needed for a diagnosis, but in clinical practice, hypoxia is a useful predictor of severity and outcome.[1] ACS is a major cause of hospitalisation and a potentially life-threatening complication that is associated with a high risk of sickle cell-related morbidity and mortality.[3] Patients with SCD may present to the hospital acutely unwell with ACS, or it may develop during a hospital admission following a painful crisis or post-operatively. Hence, a high index of suspicion is required. The affected children commonly have respiratory symptoms such as cough, breathlessness, chest pain, especially in older children, wheezing, and hypoxaemia with or without fever. The cause of ACS is multifactorial and sometimes unidentified, but most are due to infection, infarction, and fat embolism.[3]

Scope and purpose

The purpose of this guideline is to provide evidence-based recommendations for accurate and timely diagnosis, management, and early

recovery of paediatric patients with SCD and ACS.

Target audience

The guideline was developed primarily for medical practitioners who manage children with SCD in secondary and tertiary health facilities. However, other health team members who care for children with SCD will find it extremely useful in their practice. This document will also help policymakers develop management plans for children with SCD.

Target population

Nigerian children with SCD up to the age of 18 years are the target population to which this guideline will be applied.

Guideline Writing Methodology

This guideline development group (GDG) was formed from a subcommittee set up by the Paediatric Association of Nigeria to develop guidelines on common haematological diseases in children in Nigeria. This subcommittee then co-opted more paediatricians and other healthcare professionals, especially those involved in the care of the child with SCD. The names of members of this GDG as well as caregivers, representatives of persons with SCD and persons with SCD, are listed at the end of this document. Parents and caregivers made inputs to represent patients' perspectives of care. The aim was to develop a suitable guideline for managing ACS in children with SCD in Nigeria and similar low-income settings.

The physician members of the GDG were trained over several weeks by Cochrane Nigeria on guideline development. Subsequently, the ACS GDG adopted a guideline rather than develop one *de novo*. The ACS GDG then conducted a systematic search of the literature to identify the most recent international guidelines on ACS for adaptation. Several guidelines from developed and developing countries were scrutinised and scored using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool.[4] The British Haematology Society guideline was chosen based on their scores.[2] This guideline also involved adapting the recommendations of other evidence-based clinical practice guidelines per the process described in the ADAPTE Framework.[5] Inputs from stakeholders like parents and parent groups were also considered in developing this guideline. The GDG produced the adapted draft guideline and sent it for external review. Corrections were incorporated, and further actions were taken. The strength of evidence and applicability to the Nigeria setting was considered for some of the recommendations for adaptation.

Strength of recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh the harm and burden. Grade 1 recommendations can be applied uniformly to most patients. This is to be regarded as 'recommended'.

Weak (Grade 2): Where the magnitude of benefit or not is less certain, a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. This is to be regarded as 'suggested'.

Quality of evidence and definitions

The quality of evidence is graded as high (A), moderate (B) or low (C).

Grade A *(High):* Further research is very unlikely to change confidence in the estimate of effect. Current evidence is derived from randomised clinical trials without important limitations.

Grade B *(Moderate):* Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence is derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision, wide confidence intervals or methodological flaws, e.g., lack of blinding,

large losses to follow-up, failure to adhere to intention to treat analysis) or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).
***Grade C** (Low):* Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence is derived from observational studies, case series or just opinion.

Epidemiology

The incidence of ACS is highest among patients with the homozygous (HbSS) phenotype and is more common in children than adults.[3] ACS is a major cause of hospitalisation second only to vaso-occlusive crisis. It is potentially a life-threatening complication.[3]

Pathophysiology/aetiology

ACS is a unique pulmonary illness in patients with SCD. It refers to a spectrum of diseases ranging from a mild pneumonic illness to acute respiratory distress syndrome and multi-organ failure.[1] The lung injury is initiated by three major mechanisms: pulmonary infection, bone marrow and/or fat embolisation, and direct pulmonary microvascular infarction due to the sequestration of sickled erythrocytes in pulmonary blood vessels.[1] There is ventilation-perfusion mismatch and hypoxaemia due to lung injury that further leads to increased deoxygenation and polymerisation of haemoglobin S.

Infectious agents were isolated in 38% of ACS cases where detailed investigations **(**blood culture, nasopharyngeal sampling for viral culture, sputum culture and serum samples for antibody response and bronchoscopy**)** were done.[1] Infection is a more common cause of ACS in children than adults and shows seasonal variations. In children less than ten years, viral agents such as respiratory syncytial virus (RSV) are the most common organisms**. I**n comparison, *Mycoplasma pneumoniae* is the most common bacterial organism (12% of those under five years and 14% of 5-9.9 years.[6] *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae* and other respiratory viruses are also implicated in ACS.[1,6,7] The prevalence of viruses and atypical bacteria as common causes of infection suggests that the clinician must carefully consider the choice of antimicrobial agents for adequate atypical bacteria coverage. The clinical course of ACS is significantly different from that of infectious pneumonia in children without sickle cell, probably because of the damaged microvasculature of the lungs in individuals with SCD.[8] Malaria infection is a known cause of significant morbidity in SCD, but its exact role in the aetiopathogenesis of ACS remains ill-defined.

Fat embolism: During a painful crisis, vaso-occlusion within the bones leads to bone marrow necrosis and the release of fat emboli. These enter the bloodstream and lodge in the pulmonary vasculature, causing acute hypoxia. Evidence of fat emboli has been shown in autopsy studies, and fat-laden macrophages have also been found in bronchoalveolar fluid and induced sputum.[9]

Microvascular pulmonary infarction: This occurs following hypoventilation, which leads to pulmonary atelectasis, hypoxia, and pulmonary intravascular sickling.[10] Microvascular pulmonary infarction must be distinguished from pulmonary embolism, which can present with chest pain and tachypnoea without a new infiltrate on chest X-ray. Whilst patients with SCD have a hypercoagulable state and are at an increased risk of pulmonary embolism, the clinical picture is usually distinct from ACS.

Predisposing or risk factors:[11-14]

- Young age (less than ten years with the highest incidence in the 2-4 years age range).

- Low steady state foetal haemoglobin (HbF) level.
- Low haemoglobin concentration.
- Higher steady-state White Blood Count (WBC) count.
- Severe SCD phenotypes (SS, Sβ°-thalassaemia).
- Vaso-occlusive crisis (VOC) of the spine, ribs, and abdomen.
- More than three severe VOCs in the preceding year.
- Post-operative atelectasis (e.g., following abdominal surgery).
- Pre-existing asthma.
- Hypoventilation.
- Opiate overdose.
- Fluid overload.
- Exposure to tobacco smoke.

Recommendations on the aetiology of ACS

ACS has a multifactorial aetiology, including infections, infarction, and pulmonary fat embolism. Infections are common and should be considered in treatment algorithms. Fluid overload, opiate narcosis and hypoventilation may also cause or trigger ACS.

Health questions

Question 1

In children with sickle cell disease (SCD) in a resource-poor setting, can the treatment of ACS be commenced in the absence of a chest X-ray (CXR)?

Recommendation

Yes, treatment can commence based on the strength of the appropriate symptoms and signs of ACS.[15] A chest radiography should be obtained, if available, on admission or soon after, with a repeat chest radiography, if possible, for comparison. It has been shown that a chest radiograph underestimates pulmonary involvement,[16] and that infiltrates can appear a few days after initial clinical presentation.[1,17]

Summary of the evidence:

This recommendation is based mainly on the fact that most patients in low-resource settings may not have access to radiological services immediately at presentation.[18] ACS should be suspected in a child with SCD with sudden onset of lower respiratory tract disease signs and symptoms such as cough, breathlessness, hypoxaemia (SpO_2 ≤94% in room air) on pulse oximetry or a fall in SpO_2 greater than or equal to 3% of baseline steady-state values. Others include fever, tachypnoea, tachycardia, chest pain, wheezing and crackles, especially in older children.[1,2] A chest radiograph is indicated in hypoxic SCD patients but must not delay the institution of urgent clinical management.[2,18] Clinical signs often precede the chest X-ray findings, and initial chest X-ray findings may be normal even in the presence of significant respiratory distress.[3,17] Clinicians should maintain a high index of suspicion in patients with suggestive signs and symptoms, especially if the child is hypoxic. [18] Close monitoring should be undertaken, and therapy should be initiated to prevent the child from going into respiratory failure.

Question 2

Should simple blood transfusion be used over exchange blood transfusions for patients with ACS?

Recommendation:

Blood transfusion has a role in the management of children with ACS.[1,19-21] It produces rapid and dramatic improvements in clinical, radiological and oxygenation parameters. The decision to perform either simple blood transfusion or exchange blood transfusion (EBT) is determined by the clinical condition of the child and the progression of ACS.[2,21,22]

Summary of the evidence:

The role of blood transfusion in the management of ACS has yet to be formally investigated in randomised controlled trials. Still, there is observational and case-control evidence for its efficacy in ACS, and it can be lifesaving in severe cases.[19] Blood transfusion

can produce rapid and dramatic improvements in clinical, radiological and oxygenation parameters.[1,17,20] Both simple ('top up') and exchange transfusion increase oxygenation to similar extents.[1,21] Exchange blood transfusion may have additional benefits by reducing the number of circulating sickle cells, thereby preventing their further participation in vaso-occlusive events and consequently reducing the harmful effects of haemolysis without an unacceptable increase in blood viscosity.[22]

Not all patients with ACS will require a blood transfusion, and deciding to transfuse may be difficult, so a senior decision-maker should be involved. Patients may deteriorate rapidly, so the need for transfusion should be frequently reassessed, and samples should be taken early for blood grouping and antibody screening. A simple ('top-up') transfusion should be considered in patients with a SpO_2<95% in room air but may also be needed at less severe degrees of hypoxaemia, depending on the child's history and clinical features or if the child's oxygen requirements are increasing. An exchange transfusion is indicated for children who show features of severe disease, in those who deteriorate despite an initial simple transfusion or in those with a higher haemoglobin concentration (>90 g/l).[2,23]

In general, it is better to initiate transfusion early as acute respiratory failure can develop rapidly. Early simple transfusion, aiming for a final haemoglobin concentration of 100–110 g/l, is often effective at preventing progression.[20] Exchange transfusion may be a manual or automated procedure. It can be safely performed in children with ACS; a study described the use of exchange transfusion in 53 ACS episodes (44 patients) without any complications.[22]

Question 3

Should children with SCD in malaria-endemic regions who present with ACS and fever (temperature ≥ 38.5°C) be given antimalarial medications concomitantly with antibiotics?

Recommendation:

All children with SCD from malaria-endemic areas should be commenced on antimalarial medications in line with the current national guidelines on the treatment of malaria: that is, investigate using a rapid diagnostic test strip and treat based on the result.[24]

Summary of the evidence:

There is no documented evidence that malaria causes or triggers ACS in children with SCD. However, malaria (which is endemic in Nigeria) has some pulmonary manifestations that could mimic ACS.[25,26] Also, as a comorbid infection, malaria can worsen the prognosis of ACS in affected children. Therefore, malaria testing should be part of the investigations carried out in children with SCD and ACS; hence, the concomitant administration of antimalarial medications (if blood film or rapid diagnosis test is positive for malaria parasite) with antibiotics. Further research will be needed to determine the role of malaria in ACS.

Clinical features of ACS

The clinical features of ACS may not be evident at the time of admission, but the clinical state of affected children may deteriorate rapidly. ACS may develop during admission for another indication, such as a painful vaso-occlusive crisis, which can occur within 24 to 72 hours after the onset of severe pain.[3] In addition, ACS can develop post-operatively, especially following abdominal surgery and in patients who did not receive a pre-operative blood transfusion.[2] Often, the clinical diagnosis is sought when a child is found to be hypoxic. Close observation is mandatory for rapid deterioration, with regular monitoring of vital signs and at least a daily chest examination.

Symptoms and signs

The clinical features vary depending on age; fever, cough and wheezing are usually more prominent in young children. Clinical signs often precede chest X-ray findings. The most

common respiratory symptoms of ACS are cough, chest pain and shortness of breath.[1,17] Other features of ACS are:[1,2,17]

- Hypoxia – ACS should be suspected in any unwell child with SCD who is hypoxic: suggested as oxygen saturation (SpO2) ≤94% (in room air) on pulse oximetry or a fall in SpO2 of 3% or more from the baseline steady-state values. Hypoxia may precede clinical signs and chest X-ray abnormalities. Oxygen desaturation may not always correlate with the degree of hypoxia and can be influenced by other factors (such as chronic anaemia, pulmonary hypertension, and chronic sickle lung disease). Thus, arterial blood gas (ABG) measurement may be needed to confirm hypoxia.
- Fever
- Tachypnoea
- Intercostal recession, nasal flaring, and other signs of increased work of breathing.
- Wheeze
- Tachycardia
- Chest signs, including dullness to percussion, reduced air entry, crepitations, bronchial breath sounds, rhonchi, and pleural rubs

Challenges in the diagnosis of ACS

Although ACS is often precipitated by an infection, treating ACS as a purely infective episode may lead to the progression of the disease and rapid clinical deterioration.

Other considerations when making a diagnosis of ACS should include:

- Pulmonary embolism (PE) may present with chest pain, dyspnoea, and hypoxia and may complicate ACS or vice versa.[9] If there is a high clinical suspicion of PE (sudden onset of unilateral pleuritic pain that is not typical of sickle cell disease pain), treatment should be instituted for both conditions pending a Computer Tomography Pulmonary Angiogram (CTPA).
- Fluid overload – overzealous fluid replacement during ACS may lead to pulmonary vascular congestion and oedema, especially in patients with decreased cardiac function. Close attention should be paid to fluid balance. Acute deterioration in a child after a blood transfusion should prompt consideration of this complication or transfusion-related acute lung injury (TRALI).[2]
- Opiate narcosis - this may trigger or worsen ACS. Careful attention should be paid to respiratory rate, sedation, and pain score to avoid untoward effects of opiates, as opiate narcosis is associated with a falling respiratory rate.[13] Dose modification or discontinuation may be necessary, and naloxone may be required if there is evidence of opiate toxicity.[13]
- Alveolar hypoventilation due to pain may contribute to the development of ACS. Restrictive ventilatory defects may ensue as a result of ongoing chest pain, particularly in the context of children with chronic sickle lung disease. Effective analgesia is necessary to prevent hypoxia and hypercapnia that can lead to alveolar hypoventilation.

Recommendations on clinical features of ACS

The diagnosis of ACS could be made at presentation or in children already on admission receiving treatment for acute painful episodes. Hence, for children with SCD on admission, a high index of suspicion is needed in making the diagnosis of ACS, particularly in children who have respiratory symptoms and signs (especially if hypoxic), even in the presence of a normal chest X-ray (1C).

Pulmonary embolism, fluid overload, opiate narcosis and hypoventilation may cause or trigger ACS. It should be considered when a diagnosis of ACS is made as they may require additional treatment, as indicated above (1B).

Summary of the evidence (clinical features)
As discussed above

Course and outcome

ACS has a variable severity from mild illness to a severe life-threatening condition with similar death rates per event in the homozygous (HbSS) and heterozygous (HbSC) states.[17] Aside from variation in age-dependent clinical presentation, the degree of severity is also influenced by age. Although ACS is more common in children (21 events per 100 person-years in children vs 8.7 events per 100 person-years in adults), it tends to follow a milder course with infection frequently implicated in the aetiology. In contrast, ACS in adults tends to be a more severe illness marked by severe hypoxia, a higher requirement for transfusion and a higher risk of mortality. It can be considered a form of acute lung injury that can progress from acute respiratory distress syndrome, albeit infrequently, to acute multi-organ failure. All patients should be treated aggressively, irrespective of their sickle genotype and age.

The predictors of ACS severity can be clinical, laboratory or radiological. [2,27]

Clinical: Worsening hypoxia, increasing respiratory rate and neurological complications (altered mental status, seizures, and strokes) or petechial rash may suggest fat embolism.

Laboratory: Decreasing platelets count and haemoglobin concentration.

Radiological: Multi-lobar involvement on chest X-ray.

Children usually have shorter hospital stays than adults (5 d vs. 10 d in adults). Recurrence is a feature of ACS, and some patients have multiple episodes, with previous episodes increasing the likelihood of further similar events.

Recommendations on course and outcome of ACS

ACS can present as a mild disease or a severe life-threatening condition. Those with mild symptoms can, however, develop severe symptoms such as progression to acute respiratory failure. Evidence of worsening ACS includes worsening hypoxia, increasing respiratory rate, decreasing haemoglobin concentration, decreasing platelet count, multi-lobar involvement on chest X-ray and neurological complications (1B).

Patients should be treated aggressively irrespective of their sickle phenotype (1C).

Summary of the evidence

All patients, especially those with chest signs and symptoms, can progress rapidly during ACS to acute hypoxic respiratory failure and therefore, regular SpO2 monitoring is essential. Predictors of acute respiratory failure include extensive lobar involvement and a history of cardiac disease.[1]

Other morbidities are of paramount consideration in ACS. For example, neurological manifestations, such as altered mental status, seizures, and strokes, may be associated with ACS. Patients with neurological symptoms more often progress to acute respiratory failure and have a significantly higher mortality compared to those without neurological features.[1] A recent history of ACS is a risk factor for overt stroke, silent stroke, and posterior reversible encephalopathy syndrome in children.[28,29]

An acute drop in haemoglobin concentration with an associated increase in markers of haemolysis before the onset of ACS is common. Reduction from steady state haemoglobin concentration of 70g/l has been documented, and it is related to the severity of illness.[17] Similarly, some studies reported a decline in platelet count to predict ACS.[30,31]

ACS remains a leading cause of premature mortality in SCD. In a national survey in the

United Kingdom, ACS was the third most common cause of death reported in adults.[28] It is a recognised risk factor for early death in HbSS patients above the age of 20 years.[29] Respiratory failure is the most common cause of death. Other causes of death in these patients included pulmonary haemorrhage, cor pulmonale, overwhelming sepsis and cerebrovascular events.

Mortality rates in ACS will be dependent in part on the appropriateness of medical management. Even with good medical treatment, overall mortality rates of up to 3% are reported, with the overall death rate in adults being four times higher than in children.[1,17]

Monitoring and investigations

The diagnosis of ACS is typically straightforward when a high level of clinical suspicion is combined with the usual clinical features. In this scenario, the appearance of a new infiltrate on a plain chest X-ray in a child with SCD with recent onset hypoxia, tachypnoea, chest signs, fever and chest pain is diagnostic.[1] However, the diagnosis can be difficult because (i) clinical features may be few,[32] (ii) hypoxia may be challenging to determine on clinical examination unless severe, [16] and (iii) the radiological signs often lag behind the physical signs.[32,33]

Monitoring: The following should be measured and recorded four-hourly or more frequently depending on the patient's clinical condition.

- Temperature, pulse rate, blood pressure, respiratory rate, level of consciousness.
- Oxygen saturation (SpO_2 in room air) initially, but once diagnosis is established, subsequent monitoring will continue while on oxygen therapy.
- Pain score.

Other parameters to be monitored include:

- Hypertension (defined by age/sex/height centile charts) should be treated.
- Clinical examinations should be performed daily but more frequently if there is a clinical concern.
- FBC, reticulocyte count and serum electrolytes should be repeated daily until the patient improves.

Investigations: Clinical suspicion is very important for early diagnosis. Aside from chest radiography, the following investigations are essential and should be performed on all patients with suspected ACS: [29].

- Full blood count, reticulocyte count, C-reactive proteins.
- Basic biochemistry (Serum Electrolytes, Urea, Creatinine, and liver function tests).
- Group & antibody screen/crossmatch and save blood.
- Blood culture.
- Sputum culture if cough is productive.
- Pulse oximetry (both in room air and on oxygen).
- Rapid diagnostic test and blood film for malaria parasites.
- Arterial blood gas (ABG) analysis if SpO_2 <94%
- High-performance liquid chromatography (HPLC) for haemoglobin S and F quantification (if available).
- Computer Tomography Pulmonary Angiogram (CTPA) - if pulmonary embolism is suspected.

Recommendations on monitoring and investigations.

Essential investigations for diagnosing and managing ACS include a plain chest X-ray, full blood count, basic biochemistry tests (creatinine and liver function) and blood group and screen (or crossmatch). Blood film for malaria parasites should be done for all patients

with ACS. Blood cultures should also be performed if clinically indicated.

Summary of the evidence (monitoring and investigations)
As discussed above

Treatment of ACS

The goal of treatment is to break the vicious cycle of deoxygenation, sickling of the RBC, ischaemic and hypoxic injury to the lungs to reduce the risk of mortality. The key to success is early recognition of ACS followed by prompt and effective treatment that minimises irreversible lung damage and its associated long-term sequelae. All three causes (infection, infarction and embolism) are assumed to be present, and treatment is given accordingly. The goals are best achieved by providing early haematological, acute medical care and critical care support, as clinical deterioration may occur rapidly and unexpectedly.

Recommendations on general treatment of ACS

- ACS may present as a medical emergency. Children with SCD and ACS are often very ill and require close monitoring and management to ensure optimal delivery of care.
- All children with ACS should be admitted and monitored closely for deterioration and prompt referral to the intensive care unit if need be.
- Pulse rate, systemic blood pressure, respiratory rate and SpO_2 should be monitored four-hourly or more frequently depending on the patient's condition. SpO_2 should be monitored in room air initially, but once the diagnosis is established, monitoring of SpO_2 can continue whilst on oxygen therapy.
- Serial chest radiography is indicated in ACS, especially in deteriorating patients.
- Daily blood counts, serum electrolytes and urea, and liver function tests must be performed until a trend towards normalisation of abnormal values is observed.

Summary of the evidence
All children with ACS will require admission for appropriate treatment strategies, and monitoring of clinical status.[27,34] Evidence for supportive care, hydration, pain control and maintenance of adequate ventilation and oxygenation delineate the effectiveness of these interventions.[15,34] There are no RCTs comparing the use of various antibiotics in ACS. However, due to the difficulty in separating the features of ACS from infective processes in the lungs and documented evidence of the presence of atypical microorganisms isolated in these patients, antibiotics are prescribed to manage ACS in all cases.[6,7,35]

Close monitoring of clinical status and oxygenation is critical in managing all patients with ACS.[36,37] Evidence for the other specific treatments, vis-a-vis supplemental oxygen, hydration, and incentive spirometry, is mainly from observational studies.[16,38-40] Evidence for the use of analgesia round the clock in ACS, in the form of NSAIDs and opioids in patients with severe pain, is derived from RCT and observational studies.[3,41-43]
Evidence from observational studies shows that transfusion, either as a simple transfusion or exchange transfusion, improves the outcome of ACS. Clinical trials on the effect of simple versus exchange transfusion are inconclusive due to a lack of consistent studies demonstrating the impact of simple and exchange transfusions in ACS.[1,3,17,18,23] Evidence from observational studies also supports using bronchodilators in children with airway hyper-reactivity and asthma, irrespective of wheezing.[44] The use of steroids showed controversial evidence. A randomised controlled trial found that dexamethasone compared to placebo, decreased the mean

hospital stay (from 80 to 47 hours), the need for transfusions (from 47 per cent to 9 per cent), the number of administered opioid doses (from a mean of 20 to a mean of 2.5), and clinical deterioration (defined as an increase in oxygen requirements and respiratory rate).[45] However, this short-term benefit was not demonstrated to persist when examined by larger observational studies with longer follow-up periods. The largest of these observational studies was conducted among over 3,000 participants (more than 5,000 admissions).[46] The study demonstrated a significant increase in the duration of hospitalisation in people who received corticosteroids as part of their ACS management. Other observational studies have linked the use of steroids to the incidence of haemorrhagic stroke, rebound pain and other adverse effects; therefore, routine use of steroids in ACS is not advocated. [3,47,48] The effectiveness of other supportive care, such as nitric oxide, antimalaria medications and antiviral agents, has not been tested in any RCT as such evidence is based on expert opinion.

Specific treatment steps in ACS

a. Admit for in-patient care.
b. Give supplemental oxygen to maintain oxygen saturation at ≥ 95%.
c. Analgesia- there must be adequate control of pain: use morphine or NSAID as indicated. Adequate analgesia of the spine, ribs and abdomen must be achieved promptly to prevent hypoventilation, hypoxia, and atelectasis. Care should be taken with opiate analgesics, as over-sedation can precipitate or worsen ACS.
d. Correct dehydration, if present, to prevent increased sickling. Cautiously maintain optimal hydration (to prevent lung oedema). Intravenous crystalloid infusion should be given until the patient can drink adequate fluid. Fluid requirements should be individualised and be guided by the patient's fluid balance and cardiopulmonary status. In case of fluid overload, give intravenous frusemide cautiously.
e. Blood transfusion facilitates oxygen delivery to the tissues and helps to abort the progression of ACS. It can be a simple top-up or exchange blood transfusion (EBT). A simple top-up transfusion is easier to perform and recommended for all cases of ACS with haemoglobin < 90 g/dl (15 ml/kg of sedimented cells or 10 ml/kg of packed cells). EBT is for those with Hb ≥90 g/dl or patients with progression of ACS despite a simple top-up transfusion (as indicated above).
f. Broad-spectrum antimicrobials, preferably macrolides (clarithromycin or erythromycin – 40 mg/kg/day in four divided doses for 7 to 10 days, azithromycin 10 mg/kg/dose daily for five days) for mycoplasma and chlamydia; third-generation cephalosporins (intravenous ceftriaxone 75 mg/kg/dose or cefotaxime 50-75 mg/kg/dose twice daily for 7 to 10 days).
g. Use nebulised bronchodilators to improve oxygen delivery to the lungs, especially when there is a history of asthma or clinical evidence of acute bronchospasm. Inhaled or nebulised bronchodilators such as salbutamol (children < 5 years - 2.5 mg; > 5 years - 5 mg given over 10-20 mins. This may be repeated twice in one hour). Subsequent doses will depend on the patient's response and can be provided hourly to four-hourly.
h. Incentive spirometry is offered to all children at ten breaths every two hours to prevent atelectasis from hypoventilation. Without a spirometer, children can be encouraged to blow inflatable latex balloons about ten puffs every two hours.
i. Antiviral agents should be used if there is clinical suspicion of a viral infection.

j. Antimalarial medications are administered according to the national guidelines on the treatment of malaria.
k. Use anticoagulation therapy if marrow fat or thromboembolism is suspected.
l. A short-term course of corticosteroids may benefit children with ACS, especially those with asthma or acute bronchospasm (intravenous dexamethasone for 48 hours is suggested).
m. Acute neurological symptoms should be carefully monitored as they may herald the onset of a stroke, which is a common sequela of ACS.
n. Fever should be controlled with paracetamol in the absence of significant bone pain.

Supportive treatment

1. Chest physiotherapy.
2. Continuous positive airway pressure (CPAP) may be useful for patients with poor respiratory efforts or rising oxygen needs.
3. Use of nitric oxide.
4. Encourage ambulation as soon as the pain subsides.
5. Monitor for progression of ACS as indicated above and anticipate the transfer of the patient to ICU.

Recommendations for specific treatments

- All children with ACS should be given prompt and adequate pain relief according to the PAN acute pain management guideline.
- Although incentive spirometry has proven beneficial in preventing ACS in patients with chest or rib pain and should also be considered in all patients with ACS, the use of inflatable latex balloons can be a good alternative in the absence of a spirometer.
- Antibiotics, including those for atypical organisms, should be used even if blood and sputum cultures are negative. Antimalarial medications should be administered if blood film for malaria parasite or rapid diagnostic test for malaria is positive.
- Simple blood transfusion (top-up) should be considered early in the hypoxic patient, but an exchange transfusion is necessary if there are severe clinical features or evidence of progression despite the initial simple transfusion. Fresh blood that is sickle-negative is preferred.
- Bronchodilators should be used if there are clinical features suggestive of asthma or evidence of acute bronchospasm.
- The critical care team should be consulted early for respiratory support (2C).

Summary of the evidence (treatment of ACS)
As discussed above

Differential Diagnoses

- Acute severe asthma
- Pulmonary embolism from DVT (older children)
- Severe vaso-occlusive crisis
- Opiate toxicity
- Fluid overload

Complications

- ACS may lead to scarring, pulmonary fibrosis, and chronic sickle lung disease. Previous episodes of ACS are associated with worse lung functions.
- Restrictive lung disease.
- Obstructive lung disease.
- Pulmonary hypertension.
- Respiratory failure
- Neurologic events, e.g., stroke, altered mental status and seizures.

Prevention

- Prompt treatment of VOC that involves the chest, ribs, vertebra, and abdomen to prevent progression to ACS.
- Vigilance for symptoms of ACS in all hospitalised SCA patients.
- Hydroxyurea (HU) therapy.
- Antibiotics prophylaxis (for example, penicillin V) and routine immunisations, including pneumococcal vaccines.

Recommendations on chronic complications and prevention of ACS

- Children with ACS should be offered penicillin V prophylaxis (optional), pneumococcal conjugate vaccine, and appropriate seasonal vaccinations.
- Hydroxyurea should be offered to prevent the recurrence of ACS.
- Chronic blood transfusion should be considered if hydroxyurea therapy is not effective.

Summary of the evidence

Recurrent episodes of ACS can result in complications such as restrictive and /or obstructive lung diseases, chronic sickle lung disease and pulmonary fibrosis.[44,49] There are no known RCTs highlighting the effectiveness of various preventive measures for ACS. However, observational studies show that penicillin V prophylaxis, pneumococcal conjugate vaccination and other seasonal viral vaccinations, hydroxyurea, and routine use of incentive spirometry at ten puffs every two hours (while awake) during episodes of acute vaso-occlusive crisis and post-surgical state, have proven to be effective in preventing ACS.[39,50-52] In cases where hydroxyurea is ineffective in preventing recurrent ACS, chronic blood transfusion should be considered.[1,17,19-22]

Follow-up care

This is to prevent recurrence and monitor for long-term complications of ACS through the following:

- Prevention of infections (appropriate childhood immunisation including pneumococcal vaccines and use of oral penicillin V)
- Patients who survived ACS should have a pulmonary function test (PFT) performed to evaluate the risk of restrictive and obstructive pulmonary disease every two to three years.
- Episodes of bronchospasm should be detected early and promptly treated with a bronchodilator.
- Pulmonary hypertension (a known sequela of ACS) should be promptly detected and appropriately treated.
- Hydroxyurea should be used to reduce the risk of RBC sickling and frequency of ACS.
- Short-term (less than six months) or long-term (greater than six months) transfusion therapy should be performed if hydroxyurea fails.
- For multiple ACS, haematopoietic stem cell transplantation is recommended.

Prognosis

- Early ACS increases the odds of more frequent ACS throughout childhood.
- About 10% of the children with ACS will progress to respiratory failure with a high mortality rate.
- Children who survive may develop scarring, pulmonary fibrosis, and chronic sickle lung disease.
- The overall mortality rate is 3%, though four times higher in adults than in children.
- Repeated episodes of ACS are associated with chronic sickle lung disease.

Strength of supporting evidence and information for the recommendations

The group used the guideline development method recommended by the Institute of Medicine and the Guidelines International Network (GIN) and also utilised the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations.[53-55]

Strong recommendation (Grade 1) is made when there is confidence that the benefits do or do not outweigh the harm and burden of applying the recommendation. Grade 1 recommendations can be applied uniformly to most patients. These recommendations are regarded as 'recommend'.

Weak recommendation (Grade 2): Where the magnitude of benefit or not of a recommendation is less certain, a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. These recommendations are regarded as 'suggest'.

Quality of evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). This is put in context by considering the certainty of knowledge and whether further research could change what we know or our certainty.

(i) High evidence: Evidence is derived from RCTs without important limitations. Also, further research is very unlikely to change confidence in the estimate of effect.

(ii) Moderate evidence: Current evidence is derived from RCTs with important limitations such as inconsistent results, imprecision or methodological flaws, e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis) and/ or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient). Further research may well have an important impact on confidence in the estimate of effect and may change the estimate.

(iii) Low evidence: The current evidence is from observational studies, case series, or expert opinion. Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

External review and consultation process: The draft guideline was reviewed by expert paediatric haematologists who were not members of the GDG. After careful consideration, their input and corrections were reviewed and incorporated into the guideline.

Plan for scheduled review and update

This guideline will be reviewed and updated within five years of completion of the final draft.

Authorship roles: The panel members were involved in literature reviews, reviews and grading of evidence, drafting of the guidelines, and revision of the draft for sound intellectual content, and they all approved the final version of the guideline draft.
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