BHS clinical guidelines on the management of acute complications in sickle cell disease

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SUMMARY

With the increasing prevalence of sickle cell disease patients in Western countries, it is of importance to improve awareness among medical doctors of its complications. To reduce long-term morbidity and mortality, the prompt recognition and treatment of acute complications is important. The existing clinical guideline 'Follow-up and treatment of patients with sickle cell disease hospitalised for Vaso Occlusive Crisis or infection', published in 2012 by the Belgian Haematological Society, was revisited to better suit the practical needs of first-line practitioners.

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INTRODUCTION

Sickle cell anaemia is one of the most prevalent severe monogenic disorders worldwide. The disease is endemic in malarial prone regions, but global migration results in steadily rising numbers in the western world.[1] Because of better treatment (penicillin prophylaxis, pneumococcal vaccination, hydroxyurea, etc.) and follow-up, the average life expectancy of patients increased significantly over the past few decades.[2] For a review on sickle cell disease (SCD) biology, clinical evolution and chronic management, we refer to the 'Management of Sickle Cell Disease, Summary of the 2014 Evidence-Based Report by Expert Panel Members'.[3]

A survey of the Belgian Haematological Society (BHS) in 2014 found 28 departments from 23 hospitals managing patients with sickle cell disease with a large variation in the number of patients in follow-up (less than 10 to more than 40 per department), but patients with an acute complication can present themselves anywhere.[4] This dispersed distribution underlines the need for an easy-to-use management guideline. The existing clinical guideline on 'Follow-up and treatment of patients with sickle cell disease hospitalized for Vaso Occlusive Crisis or infection' as published in 2012 by the BHS was revisited to better suit the practical needs of general practitioners, emergency medical care providers, regional haematologists and paediatricians. The focus is now on the recognition and management of major acute complications in patients with SCD. **The full practical guideline is available via the website of the BHS:** *https://bhs.be/practice/guidelines.*

PRACTICAL GUIDELINE

Some major layout and content changes were carried out to make the guideline more suitable for use by caregivers relatively inexperienced in the management of SCD.

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TABLE 1. Baseline assessment of sickle cell patients presenting with acute complications.

Clinical	Technical
Vital signs • T°, Blood pressure, heart rate, respiratory rate	Laboratory • Full blood count including reticulocytes • Electrolytes, urea, creatinine, LDH, AST, ALT, bilirubin • Extended RBC phenotyping (if not previously performed) • blood and urine cultures in case of fever
Pain scoring • Use age-appropriate pain scoring system	
Fever • Age-appropriate definition: • 38°C if <2 y • >38.5°C if >2 y	Chest pain or respiratory distress: • Chest X ray • Nose/throat aspiration • Avoid acute X-ray evaluation of painful limbs. • Evaluate osteomyelitis or avascular necrosis of hip or shoulder by MRI or ultrasound if symptoms persist
Pallor (sign of anaemia) • Hard to evaluate: look at palms and soles • Ask for parent evaluation	
Pulse oximetry • Underestimation in anaemic patient • Abnormal if <96%	
Spleen and liver size • Compare with baseline evaluation (if available)	
Weight	
Any recent events or transfusions? • Beware of delayed severe haemolysis	

LDH: lactate dehydrogenase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, RBC: red blood cell.

Foremost, the layout was altered so the essence of diagnostic actions and acute management in acute complications fits on a single page. By using a tabular layout and a two tone (red and black) colour scheme, we hope to improve the readability and applicability of the guideline. We did also extend the content of the document to include specific clinical guidelines regarding transfusion management, use of antibiotics and discharge conditions for patients with acute complications. The most prevalent and relevant acute SCD complications are aplastic crisis, Vaso-occlusive crisis (VOC), acute chest syndrome (ACS), splenic and hepatic sequestration, intrahepatic cholestasis, sepsis, osteomyelitis, avascular necrosis of the bone, acute stroke, transient ischemic attacks, acute renal failure, priapism and bystander haemolysis or delayed haemolysis after recent transfusion. For a comprehensive description of their diagnostic criteria, we refer to 'definitions of the phenotypic manifestations of sickle cell disease'.[5] A summarised list of them and the caveats in management are added to the clinical protocol to improve awareness. The content of the guideline was updated with respect to the outcome of the 2014 international consensus conference on the management of SCD patients.[3]

Baseline assessment is of utmost importance to recognise acute complications that require swift management. Clear baseline assessment recommendations were missing from the previous guideline version. In *Table 1*, we provide an easy overview of the clinical and technical investigations necessary at baseline. This limited set of investigations should enable primary health care providers to diagnose specific complications of SCD and to promptly decide on appropriate treatment. We would like to stress the importance of anamnestic information: current medication, previous and recent acute events and time of last transfusion are important in diagnosing acute severe complications (e.g., late haemolytic reaction causing severe anaemia). When history taking is difficult (language barrier, patient condition, child presenting without relatives, etc.) or for detailed patient information, the treating (paediatric) haematologist should be contacted. In the technical

TABLE 2. Acute management of sickle cell patients presenting with acute complications.

Immediate	Points of attention
Analgesia • Consider strong opioids fast (see pain management) • Re-evaluate every 30 minutes	Avoid transfusion whenever possible (see transfusion instructions) • Transfuse only in (agreement with) experienced centre • Be aware of urgent (exchange) transfusion indications • Beware of delayed severe haemolytic reaction
Fluid management • Hyperhydrate, IV or PO at 2.5 l/m² (max 3 L/day) • Preferably oral (consider nasogastric tube) No hyperhydration in case of acute chest syndrome (see specific management)	Hospitalise or transfer patient to expert centre • Unless patient meets strict criteria (See discharge criteria)
Fever -> antibiotics • ASAP after microbial sampling • choice of antibiotics (see antibiotics instructions) • 3rd generation cephalosporin (cefotaxim/ceftriaxone) • associate macrolide in case of respiratory symptoms (clarithromycin or azythromycin)	
Desaturation < 96% -> oxygen	
Beware of specific clinical conditions (see management guidelines)	

IV: intravenous, PO: per oral.

assessment, reticulocytosis is an often overlooked but essential parameter in the differential diagnosis of acute complications. On the other hand, we would advise to limit the technical investigations to explore common complaints like limb pain in sickle cell patients. Criteria for the diagnosis of specific medical conditions encountered in SCD, and their specific treatment modalities, are available as a supplemental table in the practical guideline.

Acute management differs greatly depending on the presenting signs or diagnosis. In contrast to the 2012 protocol, our recommendations differ with regard to fluid management, transfusion and antibiotic treatment depending on the underlying condition. *Table 2* highlights general aspects of acute management and possible pitfalls. Additionally, the protocol provides more detailed tables discussing pain management, antibiotic guidelines, transfusion instructions and nursing instructions during hospitalisation. In general, it is important to remember that treatment of patients with acute complications of SCD is best done in an experienced setting; referral to a specialised centre is therefore desirable in any but the lightest SCD crisis.

Analgesia is addressed, although we refrain from a detailed pain management discussion. Local hospital practices differ significantly among expert centres in Belgium without clear proven superiority of one over the other. In general, we feel there is strong evidence that beside the use of non-steroidal anti-inflammatory drugs and paracetamol, rapid initiation (<30 min) of parenteral opioids is key in treating SCD painful crises (e.g., VOC, ACS).[3,6,7] Frequent reassessment and dose titration are key. Availability of an opioid antagonist, correct patient monitoring and incentive spirometry (the practice of breathing into a spirometer providing visual motivational clues encouraging sustained maximal inspiration) can help avoid evolution to ACS.[3,8] Tailoring pain relief (consider patient-controlled anaesthesia), the quick instigation of N_2O (laughing gas) and non-pharmacological support can help manage pain.[3,6,7] An isolated painful crisis is not an indication for transfusion.[3,9]

Aggressive fluid management aiming at a reduction of the sickling process is part of the management of acute complications of SCD. This holds true for VOC, priapism and in the initial management of a stroke, were fluid is given as adjunct treatment. In splenic or hepatic sequestration, hypovolemia should be corrected in anticipation of transfusion.[3] Hydration rate should be adjusted to fluid balance and clinical status.[10] This is especially true for ACS, where we advise against a

hyperhydration management because of the risk to provoke pulmonary oedema and respiratory decline. In this specific situation, the administration of diuretics should be considered. *Treatment of infection* consists of rapid initiation of a third-generation cephalosporin in case of fever or suspected ACS because of the functional asplenism in SCD patients.[3] Although vaccination and prophylactic use of oral penicillin in young SCD patients have reduced the incidence of infection-related deaths, aggressive treatment remains important. Such as initiation of macrolides in case of respiratory symptoms because of frequent involvement of atypical pathogens (mycoplasma, chlamydia).[1,2,10] We also advise to consider specific seasonal viral infections as a cause of SCD complications and to treat them appropriately (e.g., Tamiflu® in case of influenza virus). *Transfusion management* guidelines where introduced. Strong recommendations for simple or exchange transfusions exist in specific conditions, but we draw attention to overuse in acute management. As transfusion is associated with complications including hyperviscosity, (hyper)haemolysis and iron overload, it should be restricted to patients who will benefit from it.[3,11] Delayed transfusion reactions and haemolysis could occur up to three weeks after transfusion, underlining the importance of adequate follow-up. Repeated transfusions can result in allo-immunisation and can complicate future allogeneic stem cell transplantation, which is required in the clinical management of some patients.

Discharge conditions were adapted to include emergency department discharge conditions (see online guideline). We stress the importance of patient education, involvement and adequate follow-up. Late complications (delayed haemolysis, ongoing VOC, development of ACS, etc.) can be avoided by ensuring follow-up. Each medical contact in the context of an acute complication is an opportunity to ensure adequate long-term follow-up: at least one outpatient visit with the treating (paediatric) haematologist should be planned annually.

CONCLUSION

Acute complications of SCD require prompt recognition and specialised treatment. The 2012 guideline issued by the BHS was revisited to better suit the needs of first-line medical practitioners. Our current guideline outlines baseline assessment, acute management and management of specific medical conditions concerning acute complications of sickle cell disease. The practical guideline is available via the website of the BHS: *https://bhs.be/practice/guidelines*.

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