Sickle cell disease in the ICU

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Purpose of review
The review focuses on severe acute vaso-occlusive manifestations of sickle cell disease leading adult patients to the ICU.

Recent findings
Careful consideration should be paid to look for pulmonary vascular dysfunction and acute kidney injury, because of their prognostic role during acute vaso-occlusive manifestations. Alloimmunization and delayed haemolytic transfusion reactions are emerging complications that should be thought to be diagnosed, as they may imply a conservative management. The life-threatening complication raises the question about the indications of blood transfusion therapy for acute sickle cell disease complications, no randomized controlled trials being available to assess the role of blood transfusion in the acute setting.

Summary
Acute vaso-occlusive episodes are characterized by an unpredictable course that needs for vigilance for everyone, and justifies ICU or intermediate care unit admission to allow close monitoring, and supportive treatment in a timely fashion.

Keywords
acute chest syndrome, adult, anaemia, ICU, multiple organ failure, sickle cell/complications/therapy

INTRODUCTION

Sickle cell disease (SCD) encompasses a group of inherited haemoglobin disorders caused by a structurally abnormal variant of haemoglobin, known as sickle haemoglobin (HbS). Haemolysis and vaso-occlusive phenomena account for both acute and chronic conditions associated with SCD. These manifestations are related to the polymerization of deoxyHbS within the red blood cells (RBC), which causes a distorted sickle shape of RBC with shortened lifespan, and vaso-occlusion. Besides the polymerization of HbS and cell sickling, both of which are the prime pathophysiological events in SCD, there is a complex network of associated cellular changes inside and outside of the erythrocyte, such as the expression of molecular cell adhesion, the activation of the vascular endothelial cells, the adhesion of sickle erythrocytes and leukocytes to the vascular endothelium [1,2], the ischemia-reperfusion injury [3], and the decreased nitric oxide bioavailability [4].

The most prevalent SCD genotypes include homozygous haemoglobin SS and the compound heterozygous conditions (haemoglobin $S\beta^0$-thalassaemia, $S\beta^+$-thalassaemia, and SC disease). Homozygous disease is estimated to affect annually 300 000 neonates worldwide [5]. Among the last three decades, improved survival of children with SCD has currently enabled more than 90% of children to reach adulthood, and the burden of mortality has dramatically increased to adults in developed countries [6–9]. As a corollary, a growing and aging adult population is expected to increase the need for hospital care [10▪,11], as well as the development of chronic organ damage such as renal insufficiency or pulmonary hypertension [12,13]. The changing face of SCD will also become a challenge for the nonspecialists in care of such patients, and especially in the critical care setting where half of the adult deaths occur [14].

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KEY POINTS

- All SCD patients, including those with a pre-existing mild to moderate disease, are at equal risk of sudden and life-threatening acute vaso-occlusive complications.
- Careful consideration should be paid to search pulmonary vascular dysfunction because of its prevalence and prognostic role during acute chest syndrome.
- Delayed haemolytic transfusion reactions should be considered as a potential diagnosis in all patients with symptoms that appear or worsen within 21 days following a transfusion, and should be managed conservatively.

Although both SCD-related and unrelated events may lead SCD patients to the ICU, this review will focus on the most common acute manifestations of SCD in adults, including not only vaso-occlusive crisis (VOC) and acute chest syndrome (ACS), but also stroke, priapism, sudden deafness, acute anaemia, and in particular splenic sequestration to a lesser extent [15▪,16,17].

SEVERE VASO-OCCLUSIVE MANIFESTATIONS

Recurrent episodes of vaso-occlusion are the hallmark of SCD. Unpredictability and phenotypic variability in both clinical presentation and severity are all remarkable characteristics of these vaso-occlusive events. According to the organ(s) involved, the clinical spectrum of acute vaso-occlusive manifestations may range from simple pain crisis (i.e. painful VOC) to more severe and potentially life-threatening conditions such as ACS or multiple organ failure [14,15▪,16–19].

Acute chest syndrome

The various criteria used for diagnosing ACS [20–22] have been recently unified, defining it as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray [23]. These large definition criteria highlight the old challenge for the physician to determine easily the respective contribution of each mechanism into the genesis of ACS in an individual patient [24]. Indeed, ACS may involve various and nonexclusive mechanisms, namely infection, pulmonary vascular obstruction (fat embolism, pulmonary artery thrombus, and sickling), and regional alveolar hypoventilation induced by bone infarcts [22,25,26].

ACS is the most common cause for ICU admission and death among adult SCD patients [14,15▪,16,17,19]. The overall adult mortality of ACS currently approximates a rate of 1% [10▪,27]. However, the most severe ACS is associated with a higher mortality rate, as high as 25% in the ICU [15▪,16,22,28].

In most patients, ACS will develop during hospitalization, after an initial presentation for an isolated painful VOC [15▪,25,29]. Clinical manifestations may associate variably chest pain, fever, dyspnoea, tachypnea, pulmonary crackles, and cough with golden sputum (Fig. 1) [22,25,30,31]. By definition, a recent abnormal opacitiy of the lung parenchyma (consolidation) is required. Lung imaging is also needed in the management of ACS for diagnosis purposes. Compared to computed tomography (CT), which shows that alveolar consolidation predominating in the lower zones is the most common pattern of ACS (Fig. 1), chest X-ray exhibits an overall good sensitivity [32]. However, discrepancies between abnormal CT and near normal chest X-ray may occur in some patients [32], and raise the question of the best diagnostic tool to use in patients with confirmed or suspected ACS. Furthermore, the non-exceptional (17%) presence of pulmonary artery thrombosis during ACS [26] may support the more frequent use of CT. Because the risk factors and the treatment of pulmonary artery thrombosis during ACS are not well established, further studies are required to target the patients who will benefit from a CT evaluation.

Severe ACS may be complicated by the occurrence of an acute respiratory distress syndrome (ARDS) that is frequently and singularly associated with a pulmonary vascular dysfunction (Fig. 1). Echocardiographic presentations of pulmonary vascular dysfunction include pulmonary hypertension, dilated right ventricle, and acute cor pulmonale in the most severe forms [28,33]. Whereas pulmonary vascular dysfunction is common during ARDS in non-SCD patients and may lead to right ventricle dysfunction with a poor prognosis [33], its prevalence and prognostic role may be even more important during ARDS complicating ACS [15▪,28]. In addition to the many pathophysiologic alterations of lung vasculature observed during all forms of ARDS [34], ACS is specifically associated with alterations that may induce or worsen increases in right ventricular afterload, including worsening anaemia, haemolysis, pulmonary vasoconstriction, fat embolism, and in-situ thrombosis [26,35].

SCD-related multi-organ failure

SCD-related multi-organ failure (SMOF) is a severe and life-threatening event complicating the course

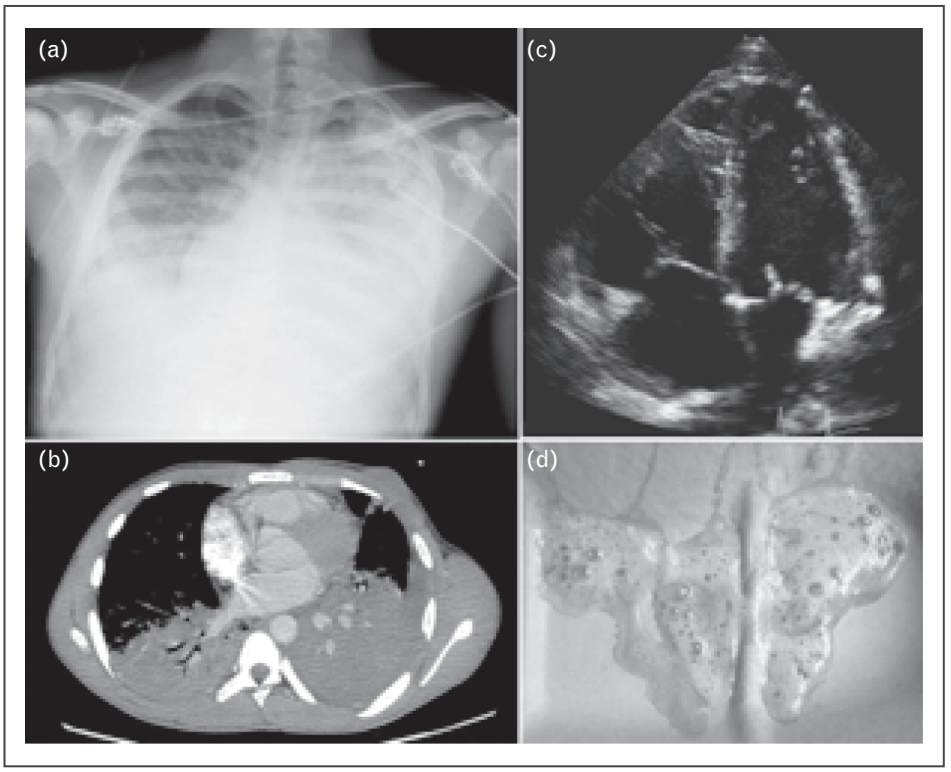

FIGURE 1. Clinical, radiologic, and echocardiographic features of acute chest syndrome alveolar condensation of the lower lobes (a, b), right ventricle enlargement (c) reflecting acute cor pulmonale, and golden sputum (d) in a homozygous sickle cell disease patient with acute chest syndrome. Figure 1d was reproduced with permission from [30].

of an unusually severe painful VOC, and characterized by the sudden onset of organ failures involving the lungs (i.e. severe ACS), liver, and/or kidneys [18,23]. Other features include a rapid fall in haemoglobin level and platelet count [18]. In most cases, the patients exhibit only a mild to moderate baseline SCD without chronic organ failure [14,15▪,18]. Although no haemodynamic impairment was reported in its original description [18], the occurrence of shock is not uncommon and probably accounts for most of the deaths during SMOF [15▪,16,17].The absence of haemodynamic impairment might explain the discrepancy between the low mortality rate reported in the original case series [18] and the fact that SMOF appears to be a major cause of death [14,15▪,16].

A large number of clinical, biological, and autopsy findings highlight many overlaps between SMOF and other non-SCD conditions such as fat embolism and thrombotic microangiopathy syndromes [35–42], especially in patients who worsen despite aggressive and effective transfusion [14,36,37]. Thus, SMOF better meets the definition of a syndrome that we name 'catastrophic sickle cell syndrome'. However, stigmata of fat embolism or thrombotic microangiopathy syndromes are inconstantly associated with SMOF, and vice versa [35,39,43]. It is more likely that each of these mechanisms act in a various combination and whether they play a real pathogenic role or just reflect a severe and diffuse vaso-occlusive phenomenon is unknown.

SEVERITY ASSESSMENT

As mentioned above, SCD manifestations are remarkable for their unpredictability. Thus, all SCD patients, including those with a pre-existing mild to moderate disease, are at equal risk of sudden and life-threatening vaso-occlusive complications [14,15▪,16,18,19]. The finding also concerns compound heterozygous patients, despite their higher survival probability than homozygous patients [19,44–46].

As clinical condition may rapidly deteriorate, signs of aggressiveness of the acute disease should be sought and alert the physician. The markers of severity relate to ACS for the most, and include high lactate dehydrogenase level [47], profound and sustained drop of haemoglobin [15▪], low platelet count [22], high respiratory rate [15▪,22], extensive lobar involvement on lung imaging [22,32],

pulmonary vascular dysfunction [15▪,28], and acute kidney injury [15▪,48].

Careful attention should be paid to look for pulmonary vascular dysfunction and acute kidney injury, for which the diagnosis may be challenging: first, the recognition of pulmonary hypertension and cor pulmonale necessarily involves an echocardiographic exam [15▪,28]; second, because of the high prevalence of glomerular hyperfiltration among SCD patients with SS disease, that is with baseline low or low-normal serum creatinine levels [49], the pattern and rate of change of serum creatinine should be considered rather than the absolute value of creatinine [15▪,48].

ROLE OF THE ICU

Although the reversible nature of severe vaso-occlusive manifestations may undoubtedly justify the admission of these young patients when they are critically ill to the ICU [15▪,18], this is more the timing and the criteria of admission of less severe patients that raise question.

Both the poor outcome associated with a delayed admission to the ICU [16] and the potential rapid deterioration of clinical status [15▪,18] support a strategy of early and large referral to the ICU or at least to the intermediate care unit, even if no organ failure is present. The aforementioned markers of severity might be integrated to the decision [15▪,22,28,32,47,48]. Thus, intermediate care units, by enabling closed monitoring, should be useful to avoid any delayed management in case of clinical deterioration. Furthermore, the management of severe painful VOC that requires high doses of opioid is inconsistent with the ward staffing levels because it may expose patients to opioid overdose, an easily preventable cause of death [15▪,50].

Finally, the association between the volumes of admissions for SCD of a hospital and the outcome, that is the lower the volume of admissions, the higher the mortality rate [51] – may strongly argue for referring SCD patients to centres with SCD expertise, and in the future for the learning spread of the peculiar SCD management among the medical community.

MANAGEMENT

Numerous national guidelines of the management of acute vaso-occlusive manifestations have been updated recently [52,53▪,54▪▪]. Regarding the management of acute SCD complications, a striking point is the relatively weak evidence level on which most of the recommendations are based, underlying the lack and difficulties of performing well designed studies in the critical care setting [29,52,54▪▪]; this contrasts with well proven disease-modifying treatments used in a chronic manner such as hydroxyurea and blood transfusion [55,56]. However, the objective of our review is neither to resume, nor to criticize these guidelines, which represent currently the state of the art reported by SCD experts. The treatment of severe acute vaso-occlusive manifestations is also mainly supportive and sometimes associated with blood transfusion therapy.

Respiratory support

In a large cohort of ACS in adult SCD patients, invasive mechanical ventilation was needed for 4.6% of hospitalizations [10▪]. Invasive mechanical ventilation is associated with a high mortality rate during acute complications of SCD [10▪,15▪,17] that may probably reflect a more severe disease than a deleterious effect per se [10▪,27]. However, and similarly to the management of all ARDS, a protective ventilatory strategy to avoid or limit the deleterious effects of ventilation on the right ventricle is even more critical in SCD patients, because of the high prevalence of pulmonary vascular dysfunction during severe ACS [28]. Such a strategy should target the control of hypercapnia, and the strict limitation of plateau and driving pressures by using low tidal volume, and prone position rather than high positive end-expiratory pressure [33,57].

When applied in the early stage of ACS, including both hypercapnic and hypoxemic adult patients, noninvasive ventilation (NIV) failed to improve outcome [58]. During severe forms of ACS, a rate of approximately 50% NIV failure was observed [15▪], and this rate is similar to that found in non-SCD patients with acute hypoxemic respiratory failure, for whom recent findings have showed the benefit of high-flow oxygen therapy, as compared with NIV [59].

Finally and despite a strong physiologic rationale [4], trials on the use of inhaled NO, as compared with supplemental oxygen, did not demonstrate any improvement in painful VOC [60] or ACS [61▪] courses. A benefit of high doses of inhaled NO was however suggested in the most hypoxemic patients with ACS [61▪].

Red blood cell transfusion therapy

Despite evidence showing that chronic transfusion therapy is effective for the prevention of stroke [56,62] and ACS [63,64], no randomized controlled trials have assessed the role of blood transfusion in acute settings [65]. Indeed, the indications, timing, and doses of RBC transfusion (i.e. the optimal target

of percent HbS) are poorly defined for the treatment of acute complications of SCD, and the transfusion policy is related to clinicians' experience [66] or experts' recommendation [52,53▪,54▪▪].

Early transfusion has beneficial effects on oxygenation [22,67] and duration of resolution of established ACS [68], and may prevent the development of ACS in the patients at risk of ACS during a painful VOC [29,69].

However, the indications for blood transfusion should be strictly defined, because of the occurrence of potential severe complications such as delayed haemolytic transfusion reactions (DHTR). Indeed, RBC transfusions may lead to RBC [70,71] or human leucocyte antigen [72] alloantibodies. Alloimmunization to RBC antigens is the underlying cause of the majority of DHTR. Several risk factors of RBC alloimmunization have been identified: an older age, female sex, high number of transfusions [73], and transfusion in acute setting [74▪,75▪]. DHTR may occur from 24 h to 21 days after a transfusion, and should be considered in all patients with symptoms that appear or worsen within 21 days following a transfusion. Clinical and biological features mimic an acute vaso-occlusive manifestation and include an acute drop in haemoglobin; an accelerated fall in HbA level reflecting the destruction of the donor's RBC; a severe intravascular haemolysis associating marked LDH increase and haemoglobinuria; a relative or absolute reticulocytopenia; and evidence of RBC alloimmunization, also inconstant (new RBC antibodies, positive direct antiglobulin test) [75▪]. The severity of DHTR may range from mild and paucisymptomatic cases to life-threatening cases [15▪,75▪]. These latter are known as the hyperhaemolysis syndrome which exhibits by profound anaemia with a fall of haemoglobin below the pretransfusion level, thereby involving the destruction of both recipient's and donor's RBC [76]. The many similarities with painful VOC lead to frequent unrecognized and misdiagnosed cases of DHTR, exposing to unsuitable and hazardous new transfusion that may exacerbate the phenomenon and be ultimately fatal [75▪]. The management of DHTR mostly aimed to avoid further transfusion, which will be given only in case of life-threatening anaemia. To achieve the goal of this conservative treatment, a closed monitoring is required and erythropoiesis-stimulating agent and intravenous iron might be helpful. Finally, immunomodulatory therapy might be discussed for the most severe cases [75▪,77].

CONCLUSION

The population of adult SCD patients is currently growing and numerous SCD-related complications may lead to the ICU. These deserve to extend the knowledge to non-specialist intensivists, not so much because specific treatments exist – management remains mostly supportive – but because of the *primum non nocere* axiom, well illustrated by complications such as the life-threatening DHTR.

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- ▪ of special interest
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