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WHAT'S NEW IN INTENSIVE CARE

Ten tips for managing critically ill patients with sickle cell disease

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Sickle cell disease (SCD), one of the most common monogenic disorders in the world, is caused by a mutation of hemoglobin (typically β6Glu > Val). When deoxygenated, sickle hemoglobin tends to polymerize within the red blood cells, causing their deformation and rigidity (sickling), with hemolysis and vascular obstruction leading to vaso-occlusive pain crisis. Vaso-occlusive crisis will be experienced by nearly all individuals with SCD during their lifetime. There is a complex network of associated cellular changes (e.g., cell adhesion, endothelial activation, ischemia–reperfusion, and hemolysis-driven scavenging of nitric oxide), leading to a multisystem vascular disease involving progressive chronic organ damage and acute complications that may require intensive care unit admission (Fig. 1). We herein review some tips to manage critically ill patients with SCD.

SCD patients are at high risk of complications when admitted to the intensive care unit, especially those with a sustained drop of hemoglobin, acute respiratory distress, and kidney injury at admission [1]. Acute chest syndrome (ACS) accounts for 70 % of intensive care unit admissions and is the major cause of death in adults with SCD [1]. Lung ultrasound may be preferred to chest radiograph for bedside detection of typical lower lobe consolidations during adult ACS [2]. Vaso-occlusive crisis is the main trigger of ACS, along with surgery, pregnancy, and environmental factors [3]. ACS is a lung injury syndrome with a complex pathophysiology comprising bone necrosis-driven fat emboli (with positive Oil-Red-O staining of macrophages in pulmonary samples), in situ pulmonary artery thrombosis (mandating therapeutic anticoagulation in patients with positive computed tomography) [4], and infection (antibiotic treatment is often empiric to cover both pyogenic and atypical bacteria, the latter being the main responsible pathogens along with viruses) [5]. The characteristic plasma-like golden color of pulmonary secretions during ACS may suggest an intense exudative process rather than the presence of bilirubin [6]. Acute pulmonary hypertension is frequent during vaso-occlusive crisis and ACS, and is associated with a higher risk of death [7]. Risk of ACS can be reduced by the early use of incentive spirometry during hospital admissions for vaso-occlusive crisis or by preoperative blood transfusion [8]. Vaso-occlusive crisis and ACS management are mainly supportive. Avoidance of desaturation (<95 %), hypothermia, acidosis, dehydration, and hyperviscosity contributes to red blood cell homeostasis and may blunt sickling [9]. Multimodal analgesia including parenteral opioid-based patient-controlled analgesia should be readily initiated. Despite a faster improvement of gas exchange, noninvasive ventilation did not shorten intensive care unit stay during ACS [10]. Inhaled nitric oxide at high doses (80 ppm, to consider scavenging by hemolysis products) did not improve ACS outcome, but a post hoc analysis suggested its efficacy in the subgroup with acute respiratory distress syndrome [11]. Acute respiratory distress syndrome due to ACS is characterized by a major pulmonary vascular involvement (pulmonary vascular dysfunction and acute cor pulmonale are found in 100 and 80 % of patients, respectively) [12]. Close monitoring (e.g., echocardiography) and a "right ventricle protective approach" with correction of risk factors for cor pulmonale (especially high driving pressure, severe hypoxemia, and hypercapnia) are essential; prone positioning may help alleviate RV afterload [13]. Future trials should test the usefulness of

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intravenous pulmonary vasodilators, extracorporeal carbon dioxide removal, or membrane oxygenation in this setting.

Red blood cell transfusion, either simple or by exchange, is an established treatment option for prevention of chronic organ damage, preoperative care, and acute complications of SCD (e.g., severe ACS with hypoxemia or respiratory distress, acute stroke, prolonged priapism, acute liver injury, severe sepsis, multiple organ failure) [9]. Blood transfusion is generally aimed at increasing total hemoglobin (without exceeding the patient's basal value or 10 g/dL to avoid hyperviscosity) and/or decreasing hemoglobin S (targeting <30 % in the most severe cases). Transfused SCD patients have a particularly increased rate of alloimmunization (reaching 50 %), probably because of racial differences in red blood cell antigens from Caucasian donors. Delayed hemolytic transfusion reaction is a potentially life-threatening complication which is often suspected when a patient with SCD presents several days after a blood transfusion with development or intensification of symptoms suggestive of a vaso-occlusive crisis, hemolysis, reticulocytopenia, and more severe anemia than was present before blood transfusion [14]. A diagnostic nomogram depicting changes in hemoglobin A relative to early post-transfusion values accurately identifies patients with delayed hemolytic transfusion reaction (available at http://www.reamondor.aphp.fr/nomogram-2/). The benefit/risk of transfusions should be carefully evaluated in patients with alloimmunization. In case of delayed hemolytic transfusion reaction, further blood transfusion should be withheld to avoid fatal intravascular hemolysis. More studies are needed to define the optimal immunomodulating treatment for delayed hemolytic transfusion reaction (e.g., steroids, intravenous immunoglobulin, rituximab, or eculizumab).

Other causes of worsening anemia in acutely ill SCD patients should be considered on the basis of the presence of reticulocytosis, which is usually (1) marked in case of vaso-occlusive crisis or ACS-driven accelerated hemolysis, malaria, bleeding, acute splenic, or hepatic sequestration; (2) impaired in case of vitamin B9, B12 or iron deficiency, hydroxyurea toxicity, parvovirus B19 infection (aplastic crisis), or generalized bone marrow necrosis. The last case is easily diagnosed with bone

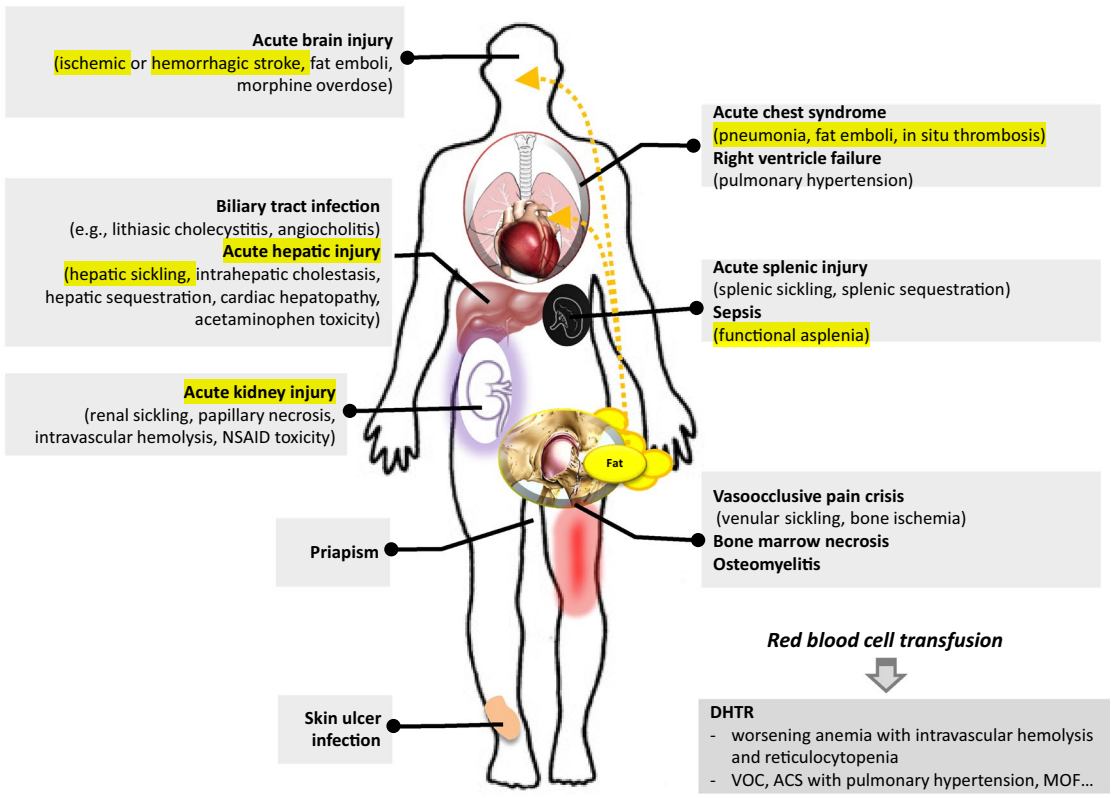

Fig. 1 Main contributors to acute organ failure in critically ill sickle cell disease patients. Acute decompensation of various chronic organ damages (which are beyond the scope of the present paper) may also participate. *VOC* vaso-occlusive crisis, *ACS* acute chest syndrome, *NSAID* nonsteroidal anti-inflammatory drugs, *DHTR* delayed hemolytic transfusion reaction, *MOF* multiple organ failure

marrow aspiration (demonstrating extensive destruction of hematopoietic tissue) and may lead to systemic fat embolism with lung and brain involvement. Acute osteomyelitis should be suspected in case of persisting local signs of vaso-occlusive crisis. Because of reduced or absent splenic function, SCD patients have an increased risk of severe bacterial infection (especially from encapsulated bacteria); it is therefore imperative to promptly identify and treat all suspected bacterial infections. The higher glomerular filtration rate observed in SCD patients may alter therapeutic antibiotic concentrations.

Acute organ failures are usually multifactorial in SCD patients (Fig. 1). Although usually limited to bone, vaso-occlusive crisis may also encompass sickling within specific organs like the liver and kidney. Acute pulmonary hypertension may induce cardiac hepatopathy and renal congestion [15]. Systemic fat embolism and intravascular hemolysis are also frequent contributors to multiple organ failure.

In conclusion, SCD patients admitted to intensive care unit are prone to multiple organ failure as a result of a multisystem vascular disease particularly affecting the lung.

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