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# Definitions of the phenotypic manifestations of sickle cell disease.

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Abstract: Sickle cell disease (SCD) is a pleiotropic genetic disorder of hemoglobin that has profound multi-organ effects. The low prevalence of SCD (~100,000/US) has limited progress in clinical, basic, and translational research. Lack of a large, readily accessible population for clinical studies has contributed to the absence of standard definitions and diagnostic criteria for the numerous complications of SCD and inadequate understanding of SCD pathophysiology. In 2005, the Comprehensive Sickle Cell Centers initiated a project to establish consensus definitions of the most frequently occurring complications. A group of clinicians and scientists with extensive expertise in research and treatment of SCD gathered to identify and categorize the most common complications. From this group, a formal writing team was formed that further reviewed the literature, sought specialist input, and produced definitions in a standard format. This manuscript provides an overview of the process and describes twelve body system categories and the most prevalent or severe complications within these categories. A detailed Appendix provides standardized definitions for all complications identified within each system. This report proposes use of these definitions for studies of SCD complications, so future studies can be comparably robust and treatment efficacy measured. Use of these definitions will support greater accuracy in genotype-phenotype studies, thereby achieving a better understanding of SCD pathophysiology. This should nevertheless be viewed as a dynamic rather than final document; phenotype descriptions should be reevaluated and revised periodically to provide the most current standard definitions as etiologic factors are better understood and new diagnostic options are developed.

## Introduction

Sickle cell disease (SCD) is an inherited disorder due to homozygosity for the sickle  $\beta$ -globin gene mutation at position 6 (glu  $\rightarrow$  val), or double heterozygosity for the sickle gene and another mutation for a different hemoglobin variant or one of numerous  $\beta$ -thalassemia mutations. SCD is a systemic pleiotropic disease that affects nearly all organs during the life of afflicted patients. Specific phenotypic manifestations of the disease are protean in nature and vary considerably in frequency and severity latitudinally among patients and longitudinally in the same patient over time.

The lack of universally accepted nomenclature and diagnostic criteria for the complications of SCD has been confusing to patients, their families, the public, and providers, and has hampered clinical research efforts to collect outcome data and compare research methods and findings. This report defines selected complications of SCD in a uniform manner, drawing on recently published literature and the expertise of a broad variety of active clinicians and investigators. The goals are to provide current consensus definitions of the phenotypic manifestations of SCD and to facilitate research by establishing a common basis for comparison of data.

Therefore, this paper describes the complications that are particularly characteristic of SCD and are due to the sequence of events that result from the pathophysiologic biology of the abnormal sickle red cell. These complications are placed within one of twelve broad categories classified according to basic system/organ involvement and are represented by bold headings. Ten specific complications have been selected for discussion in detail due to their relative frequency and/or potential severity, and are indicated by underlined subheadings within the appropriate category sections. In addition, controversies regarding these complications are discussed. The formal definitions for these complications are included in an accompanying Appendix.

The Appendix, available online at this journal's website, includes all 62 selected complications listed within their respective categories, including those unique to SCD and those that are secondary in nature or due to co-morbidities. The Appendix includes the following for each complication: Definition, Diagnostic Criteria, Severity Index, Classification, and References. The purpose of the Appendix is to provide practitioners and investigators with a concise reference describing the major features of each complication and its associated diagnostic tests and, where applicable, measures of severity.

The description of each complication is evidence-based whenever possible. For some complications, no published evidence or standard was found for the Severity Index and/or the Classification. In some situations, the authors have recommended descriptions based on the vast experience of experts in SCD and have noted the descriptions as such.

## **Methods**

### *Background*

The Statistics and Data Management Center (SDMC) of the National Heart, Lung, and Blood Institute (NHLBI) Comprehensive Sickle Cell Centers (CSCC) Program was charged in 2003 with establishing a database of clinical, quality of life, and outcomes data to support development of multi-center research on SCD. A committee composed of representatives from 5 of the 10 participating clinical centers (C-Data Protocol Committee) assisted the SDMC in developing a protocol for this Collaborative Data Project (C-Data). The SDMC and C-Data Protocol Committee created a detailed case report form (CRF) designed to obtain comprehensive clinical, surgical, hospitalization, and laboratory data from medical record review to focus data collection on those features considered most important and most useful in identifying potential subjects for future trials. However, the lack of standard, universally applied definitions for clinical conditions or phenotypes used in the context of SCD initially threatened to make the collection of uniform data from existing medical records across sites impractical and likely impossible. Therefore, the Committee recommended initiation of a formal effort to establish standardized definitions for use in C-Data prospective data collection, CSCC future studies, and SCD research in general.

In parallel with this effort, an NIH-sponsored conference, "New Directions for Sickle Cell Therapy in the Genome Era", listed as its highest priority the establishment of a SCD network that would include a comprehensive patient database and a biological sample repository to support examination of phenotypic diversity and serve as a resource for future research. As a result, the CSCC Center Directors, with support from the NHLBI, endorsed expansion of the C-Data Project to include the collection, testing, and storage of blood and DNA samples from participants. Based on this decision and the earlier recommendation of the C-Data Protocol Committee, the CSCC Steering Committee approved formation of an ad hoc work group to establish consensus definitions of the phenotypic manifestations of SCD.

### *Preliminary and Work Group Activities*

The work group was composed of 16 clinicians and scientists with extensive expertise in research and treatment of SCD, representing the ten clinical centers and the SDMC, and chaired by Dr. Marilyn Telen of Duke University Medical Center. Dr. Lieff and the SDMC staff established several tools prior to the meeting to facilitate the group's work. A list of complications, based on literature on SCD and complications already included in the C-Data medical history CRF, was compiled by the SDMC and further refined by the C-Data Protocol Committee and the CSCC Program Medical Monitor. A draft format or schema was developed to provide a standardized approach to writing the definitions. Group members were assigned to one of six subgroups based on their expertise. Each subgroup was given a small set of complications and asked to prepare preliminary draft definitions for their complications set, with the goal of having good familiarity with the most recent literature and the real variation in

interpretation and application of a diagnosis for a given complication. Work group members received this information 2 weeks in advance and were asked to provide feedback prior to the meeting.

The 2-day meeting began with a large group discussion of the history, rationale, and goals of the CSCC's priority effort to develop standardized phenotype definitions. Subgroups then received the set of draft definitions for their assigned complications, which had been revised based on member responses submitted previously. The subgroups met separately to rewrite or refine the definitions. Groups were asked to include what most experts accept as a definition of the complication in question, as well as the supporting diagnostic criteria or measurements needed to confirm the diagnosis. If appropriate, levels of certainty for the diagnosis were to be indicated; an MRI for example, may be considered the "gold standard" for determination of a cerebrovascular accident (CVA), whereas a neurological exam is viewed with less certainty.

The large group reconvened to review the subsequent drafts and provide feedback. This process was repeated a second time. At the final group session, some definitions were excluded and a few added, remaining questions for specific complications identified, and plans made to finalize the set of definitions for submission to the Steering Committee for approval.

The C-Data Protocol Committee met to compare the work group's approved draft definitions to the list of complications captured in C-Data at that time, and revised the definitions further. This group modified the CRFs designed to collect prospective clinical data, to accommodate the revised phenotype definitions. The final CRFs were approved in June 2006. Final revisions of definitions continued; they were approved by the Steering Committee in July 2007.

A group of CSCC investigators committed to establishing a final, workable set of phenotype definitions for use within the CSCC program and in the SCD research community formed a writing group to develop a publishable document that would be available to the widest audience possible. This group, led by Dr. Samir Ballas of Thomas Jefferson University, determined the goals and structure of the manuscript, and identified the most appropriate site for publication. The authors decided the best approach was to provide an overview of the process, a description of the 12 body system categories, a description of the most relevant or severe complications within these categories, and to provide the standardized definitions for all complications in an Appendix. A manuscript proposal was submitted to and approved by the CSCC Publications Committee. Professional medical writers and editors were involved in the writing and editing process to ensure the presence of a logical, standard, and consistent style readily accessible and understood by the broad target audience. The writing group worked consistently during the year and a half preceding manuscript submission to successfully accomplish these goals, which offer a potentially important contribution to SCD research.



## **Complications of Sickle Cell Disease**

Major clinical manifestations of SCD include three sets of signs and symptoms: 1) hemolytic anemia and its sequelae as shown in Table 1; 2) pain syndromes and related issues as shown in Table 2; 3) complications affecting major organs and their sequelae as shown in Table 3. Definitions of these complications are described below and/or in the Appendix. Co-morbid conditions associated with SCD will not be defined in this paper, though some of the relatively common co-morbid conditions are defined in the Appendix.

### **Acute Exacerbations of Anemia**

Sickle cell disorders are associated with variable degrees of anemia depending on genotype, with the most severe decrease in hemoglobin level seen in sickle cell anemia (homozygous hemoglobin S) and the least severe decrease in hemoglobin S- $\beta^+$  thalassemia. After the first five years of life, the hemoglobin concentration in an individual patient usually remains constant in the steady state over time. However, clinically significant acute lowering of the hemoglobin concentration below steady state values does occur episodically. These episodes may result from a variety of causes, including hyperhemolysis, acute splenic sequestration, and aplastic crises. Characteristics of these episodes are described in the Appendix and briefly discussed below. It is important to understand the use of diagnostic tests in the differentiation of these causes of exacerbation of anemia, since appropriate treatment is different for each of them.

#### Hyperhemolysis

Although chronic hemolytic anemia is a major feature of sickle cell disorders, a marked drop in hemoglobin with evidence of an increased hemolytic rate is referred to as hyperhemolysis. Hyperhemolysis is ordinarily diagnosed when the exacerbation of anemia occurs in the absence of other identifiable causes of red cell destruction (eg, splenic or hepatic sequestration). It is most often, but not always, accompanied by evidence of increased red blood cell production (increased reticulocytosis). Several sub-phenotypes of hyperhemolysis arising from different pathophysiologic mechanisms may complicate the clinical course of sickle cell disorders. One type is related to acute or delayed hemolytic transfusion reactions, in which hemolysis may occur due to the "innocent bystander mechanism."<sup>1</sup> In the innocent bystander mechanism, both autologous and homologous red cells (RBCs) are destroyed. It is typically, although not uniformly, associated with a paradoxical decrease in reticulocyte count. In hemolytic transfusion reactions, homologous (transfused) RBCs are destroyed, presumably due to interaction with alloantibodies. A positive direct antiglobulin (or Coombs) test is usually but not uniformly present. Recognition of the hyperhemolysis syndrome is especially important, as hemoglobin levels often decrease further with transfusion, even when crossmatch-compatible blood is provided.<sup>1</sup>

Another type of hyperhemolysis in SCD is not related to blood transfusion but is an independent complication of the disease itself, in which autologous RBCs are destroyed at an increased rate in the presence or absence of an acute painful crisis. Isolated episodes of hyperhemolysis in the absence of painful crises are often referred to as hemolytic crises.<sup>ii</sup> Hyperhemolysis may also be drug induced.

It should be noted that a diagnosis of hyperhemolysis in the post-transfusion setting can be made only by calculation of the destruction of transfused and autologous red blood cells using results of serial blood counts, reticulocyte counts, and hemoglobin electrophoresis.

### Acute Splenic Sequestration

Acute splenic sequestration was first recognized in 1945<sup>iii</sup> and is one of the leading causes of death in children with sickle cell anemia.<sup>iv,v,vi</sup> In patients homozygous for hemoglobin S, the lifetime prevalence of acute splenic sequestration has been reported to be between 7% and 30%.<sup>vii,viii</sup> It can occur as early as 8 weeks of age<sup>ix</sup>, though more typically an initial event occurs in the toddler age group. Patients with hemoglobin SC or hemoglobin S/ $\beta$ -thalassemia tend to have a first event later in life, even into adulthood.<sup>x,xi</sup> Although acute splenic sequestration is often associated with an infectious trigger, it may also be unprovoked.<sup>viii,xii</sup>

Acute splenic sequestration is characterized by a tender, rapidly enlarging, and sometimes massive spleen due to the trapping of sickle erythrocytes and other blood constituents and may lead to shock due to loss of effective circulating volume. The hemoglobin concentration decreases from baseline by at least 2 g/dL, usually with evidence of reticulocytosis and often moderate to severe thrombocytopenia. Prompt recognition of acute splenic sequestration is critical to the provision of appropriate and timely therapy of this life-threatening complication.

### Aplastic Crises

Since SCD patients rely on constant overproduction of RBCs to maintain even their baseline low hemoglobin levels, any process that interferes with erythropoiesis can result quickly in severe anemia. Erythropoiesis can be suppressed by almost any infectious or inflammatory process to some degree, but occasionally severe transient red cell aplasia (absolute reticulocyte count <50,000/ul) occurs, leading swiftly to severe anemia. Among infectious causes, parvovirus B19 infection classically causes the most severe reticulocytopenia, often to levels <20,000/ul.<sup>xiii</sup>

### **Cardiac Complications**

Sickle cell disorders are associated with multiple clinically significant cardiac abnormalities, primarily but not exclusively in adults. The anemia of SCD is associated with a chronic high cardiac output state, the physiological sequelae of which are not completely understood. Morphologic and physiologic changes include a thickened interventricular septum, increased left ventricular mass, abnormal left ventricular diastolic filling, and left ventricular diastolic dysfunction,

among others. Electrocardiograms often provide signs of left ventricular hypertrophy and demonstrate nondiagnostic ST and T wave abnormalities, as well as conduction abnormalities. Increased preload and decreased afterload help maintain a normal or high ejection fraction despite these abnormalities, unless and until decompensation occurs. The impact of these cardiac findings is not clearly delineated, but they have been proposed to affect oxygen transport and delivery and may also contribute to the relatively high incidence of sudden death among SCD patients. Cardiac dysfunction also potentially has implications for other end-organ functions.

### **Disturbances of Growth and Development**

Children with sickle cell disorders have significantly decreased height, weight, and body mass index (BMI), as well as delayed sexual maturation, when compared with control subjects.<sup>xiv</sup> Inadequate nutrition, abnormal endocrine function, and, in particular, increased caloric requirements due to elevated energy expenditure may all be etiologic factors. Although definitive evidence is lacking, growth may be enhanced by chronic transfusion, increased caloric intake, or hydroxyurea. In order to evaluate the effects of interventions on growth in persons with sickle cell disorders, comparison with standardized growth charts, such as those from the US National Center for Health Statistics (NCHS), may be utilized, with growth expressed as Z-scores (the number of standard deviations below or above the “normal” mean for age).

### **Gastrointestinal/Hepatobiliary Complications**

Hepatobiliary pathology in sickle cell disorders is common but not always related specifically to the underlying SCD. For example, the definitions presented in the Appendix for cholecystitis, cholelithiasis, pancreatitis, and viral hepatitis are not unique to sickle cell disorders, although their incidence may be more common in this group than in the general population. Hepatic sequestration and intrahepatic cholestasis, however, are virtually unique to sickle cell disorders, and their definitions are of specific interest to hematologists.

#### Acute Hepatic Sequestration / Intrahepatic Cholestasis

Sequestration of red cells and other blood cells may also take place in the liver, either in isolation or in combination with splenic sequestration. Tender, progressive hepatomegaly, accentuated anemia below baseline, reticulocytosis, and hyperbilirubinemia are the usual clinical features of hepatic sequestration and can mimic acute cholecystitis or viral hepatitis, although sequestration usually is accompanied by less pronounced transaminitis and lack of elevation of pancreatic enzymes.<sup>xv,xvi,xvii</sup> Hepatic sequestration is not usually life-threatening, because the liver is not as distensible as the spleen and therefore pooling of red blood cells is rarely significant enough to cause cardiovascular collapse. However, it can lead to decreased liver function and, like splenic sequestration, usually responds to transfusion. Intrahepatic cholestasis (ie, obstruction of bile formation or flow) can

occur in the setting of hepatic sequestration, leading not only to hyperbilirubinemia but also to striking hepatic dysfunction, with marked deterioration of synthetic function. Blood exchange transfusion is often needed for intrahepatic cholestasis.

### **Muscular/Skeletal/Skin Complications**

Dactylitis, avascular necrosis, leg ulcers, osteomyelitis, osteopenia, and osteoporosis are frequent in patients with sickle cell disorders. The clinical features are similar to those in individuals without SCD, but the age at presentation is earlier and the response to interventions, when required, is poor. Musculoskeletal and dermatologic complications are often due to vaso-occlusion, but hemolysis, infection, and chronic co-morbidities can have detrimental consequences if not addressed. Swelling, erythema, and fever can occur from cell death due to hemolysis. Patients with dactylitis, bone infarction, or leg ulcers develop pain at the involved site, but swelling, erythema, and fever may occur, implying the possibility of infection as an underlying or complicating feature. When recurrent leg ulcers and myositis develop, co-morbidities such as diabetes and rheumatologic conditions such as systemic lupus erythematosus should be considered.

### **Neurologic Complications**

The effects of sickle cell disorders on the brain vary with age, may be acute or chronic, may be clinically overt or subtle (“silent”), and may result in significant morbidity and even mortality. The underlying cerebrovascular lesions also vary from extensive, large vessel distribution infarcts to the “silent” infarcts associated with microvascular disease. Central nervous system lesions may be infarctive due to vaso-occlusion, hemorrhage, or both.

#### **Cerebrovascular Accident**

Cerebrovascular accident (CVA) was previously defined by the CSSCD as an acute neurological syndrome secondary to occlusion of an artery or hemorrhage, with resultant ischemia and neurologic signs and symptoms. A small fraction of the strokes in children, but the majority of those in adults, are hemorrhagic, with intraventricular, intracerebral, or subarachnoid bleeding. Like the previous Cooperative Study of Sickle Cell Disease (CSSCD) definitions for cerebrovascular complications, the symptomatic manifestations of stroke rely on physical exam findings but have been modified to include evidence-based practice and imaging techniques to objectively confirm brain lesions and vascular pathology. The availability of diffusion-weighted intensity (DWI) MRI has facilitated the early detection of acute ischemia and provides an objective measure by which to define and classify stroke subtypes. Noninvasive imaging by MRA is now routinely used to document stenosis or obstruction of flow in the large intracranial vessels, as well as abnormal vessel formation, including moyamoya, and correlates well with standard angiography.

The use of transcranial Doppler (TCD) ultrasonography to identify sickle cell patients at increased risk for stroke was introduced in the early 1990s, validated in a series of studies, and demonstrated in the STOP trial (a phase III randomized, prospective, multicenter clinical trial of chronic transfusion versus standard observation) to be remarkably useful in identifying patients at risk for this devastating complication.<sup>xviii</sup> We have adopted the definitions for normal, conditional (borderline), and abnormal TCD velocities used in the STOP studies: time-averaged mean of the maximum velocity in the middle cerebral or distal carotid artery <170, 170-199, and  $\geq 200$  cm/sec, respectively. An important part of the definition is that TCD studies should be performed in patients under steady-state conditions by an experienced technologist.

### Transient Ischemic Attacks

Transient ischemic attacks (TIAs) are relatively infrequent events in persons with sickle cell disorders, but their occurrence indicates an increased risk for overt stroke. Until recently, TIA was defined by neurologic dysfunction caused by focal brain ischemia with symptoms lasting *up to 24 hours*, but recent neurology literature has utilized a period of symptomatology that is typically less than 1 hour.<sup>xix</sup> Resolution of neurologic symptoms and a lack of lesions in the region corresponding to symptoms on neuroimaging are also elements in the current definition of TIA.

### Silent Cerebral Infarcts

Silent cerebral infarcts were initially described in the CSSCD based on brain MRI findings in children with normal neurologic examinations.<sup>xx</sup> Subclinical infarcts detected by MRI are actually not “silent,” since we now know that they are associated with neurocognitive deficits (and an increased risk for overt stroke). An important part of this definition is that these lesions cannot be attributed to an overt neurologic event or finding.

## **Ophthalmologic Complications**

Ophthalmologic complications of sickle cell disorders are relatively common and may occur in any vascular bed of the eye. Sickle cell eye disease may be insidious in nature and may not be detected at its early stages unless an eye exam is performed annually. Annual eye examinations in this population should include an accurate measurement of visual acuity and intraocular pressure, examination of the anterior structures of the eye using a slit lamp biomicroscope, and examination of the posterior structures of the eye, including the retina, through dilated pupils and using fluorescein angiography. In general, diagnostic criteria for SCD patients are the same as for causes of ocular pathology in other populations.

## **Pain Syndromes**

Sickle cell pain is unique in that it occurs as a hallmark feature in a genetic disorder as early as infancy and throughout a lifetime. SCD-associated pain can be acute, subacute, chronic, or episodic. Patients may experience somatic, visceral, neuropathic, or even iatrogenic pain. While pain is most often spontaneous, it is occasionally evoked, but rarely psychogenic. Sickle cell pain syndromes vary in character and intensity depending on the location and severity of tissue damage. Symptom intensity and duration are influenced by a variety of biochemical, neurological, psychosocial, cultural, spiritual, and environmental factors that may be further modified by disease or treatment-related effects. No diagnostic tests are currently available to define the extent, location, or severity of tissue damage from vaso-occlusion. Categorization of pain syndromes thus relies on careful clinical histories and examinations, as well as the clinical context of the pain symptoms. The pain syndromes described reflect the result of the primary disease process and resultant tissue damage (acute sickle cell pain, multi-organ system failure), pain characteristics related to nerve damage or neuronal dysfunction (neuropathic pain), or consequences of treatment (iatrogenic pain syndromes).

### Vaso-occlusive Episodes

Pain from tissue ischemia as a result of vaso-occlusion is the most common complication of SCD.<sup>xxi,xxii,xxiii,xxiv,xxv</sup> Vaso-occlusion may occur in a variety of vascular beds, but those in the deep muscle, periosteum, and bone marrow appear to be most often affected.<sup>xxv</sup> These same tissues are also richly innervated by nociceptors activated by a variety of inflammatory mediators.<sup>xxi,xxvi</sup> Recurrent episodes of acute pain (painful crises) lasting for hours to days (or rarely weeks), begin early in childhood and often become more frequent in adolescents and adults, who additionally may display variable degrees of persistent pain related to chronic bone and joint damage.<sup>xxi,xxii,xxiii,xxvii,xxviii</sup> Neurological changes in response to persistent pain can lead to an enhanced sensitivity to pain, and psychosocial sequelae can increase subsequent suffering.<sup>xxi,xxii,xxiii,xxvi</sup>

As pain symptoms are in part a reflection of disease activity, a better understanding of disease pathogenesis is an important aspect of sickle pain management. Thus the acute painful episode (painful crisis) evolves through four phases: prodromal, initial, established, and resolving.<sup>xxix</sup> Objective laboratory signs do occur during these phases in most patients, provided they are done serially and compared to established steady-state values. Moreover, recent studies have suggested a vaso-occlusive “phenotype” consisting of patients with relatively higher hemoglobin levels who clinically display increased frequency of pain, acute chest syndrome, and avascular necrosis.<sup>xxx</sup>

### **Pulmonary Complications**

Individuals with sickle cell disorders have a unique pathophysiology that puts the microvasculature of the lung at particular risk for complications. Acute chest syndrome is unique to sickle cell syndromes, and physicians must be aware of

the potential for rapid progression that may prove fatal in the child or adult with sickle cell disorders. Pulmonary hypertension is very common in persons with sickle cell disorders and is probably related at least in part to chronic hemolysis and nitric oxide consumption, as it occurs in other hemolytic anemias as well. The diagnostic criteria required to define pulmonary hypertension are distinct for sickle cell disorders. However, chronic obstructive and restrictive pulmonary disease, asthma, obstructive sleep apnea, and pulmonary embolism are not unique to patients with sickle cell disorders and are defined as in unaffected individuals. The hypoxia caused by these conditions affects hemoglobin S polymerization as well as other aspects of sickle red cell biology and may therefore accelerate the microvascular complications of SCD. This pathophysiology requires the caregiver to be cognizant of these potentially deleterious consequences. Recognition of pulmonary embolism is particularly difficult in SCD patients. The recurrent chest or rib pain that is often reported in sickle cell disorders may make recognition and diagnosis of non-sickle pulmonary conditions such as pulmonary embolism difficult. The paragraphs below list features that may be helpful to diagnose these conditions.

### Acute Chest Syndrome

The term acute chest syndrome (ACS) reflects the difficulty in distinguishing pulmonary infection (viral or bacterial pneumonia) from other conditions that may occur in SCD, including inflammatory changes following pulmonary fat embolism or pulmonary infarction by microvascular occlusion or thromboembolism. Bacterial infection is diagnosed by culture of a respiratory pathogen from sputum or blood, but such cultures are negative in the majority of ACS cases. The diagnosis of fat embolism can be established by bronchoalveolar lavage (BAL) with examination for lipid-laden macrophages, but while BAL has a higher bacterial culture yield,<sup>xxxii</sup> it is clinically impractical in most instances. Finally, distinguishing thromboemboli from microvascular occlusion using chest tomography or lung scintigraphy is difficult, as the findings are nearly identical.<sup>xxxiii</sup> Consequently, the historical term ACS cannot be discarded until better diagnostic testing becomes available.

Acute chest syndrome clinically and radiologically resembles bacterial pneumonia. However, the clinical course of ACS in persons with sickle hemoglobinopathies is considerably different from that of pneumonia in hematologically normal individuals. Multiple lobe involvement and recurrent infiltrates are more common in SCD, and the duration of clinical illness and of radiologic clearing of infiltrates may be prolonged to 10 days or longer.<sup>xxxiv,xxxv</sup> Acute pulmonary infiltrates are particularly difficult to classify in sickle cell disorders because of the potential for rapid progression from mild hypoxia to pulmonary failure, acute respiratory distress syndrome (ARDS), and multiorgan failure as a consequence of disseminated microvascular occlusion. Any decline in arterial oxygen saturation increases the fraction of polymerized Hb S with a subsequent deleterious effect on blood flow and pulmonary function.

ACS is associated with considerable morbidity and both acute and delayed mortality. The incidence is highest in children 2 to 4 years of age and, while gradually declining with age, remains common in adults.

### Pulmonary Hypertension

Pulmonary hypertension (pHTN) has been recognized as an increasingly common and deadly complication of sickle cell disorders,<sup>xxxvi,xxxvii,xxxviii</sup> as well as other hemolytic anemias.<sup>xxxix</sup> Approximately 40% of adults with SCD can be identified as having pHTN; similar proportions are seen in pediatric and adolescent patient populations. In contrast to primary pHTN, however, pHTN in SCD tends to exhibit lower pulmonary artery pressures but nevertheless is associated with increased mortality. Adult SCD patients with pHTN have a 6- to 10-fold higher risk of mortality than do SCD patients without pHTN; however, the risk in the pediatric age group is less well defined. In most studies, pHTN in SCD has been defined by the presence of a tricuspid regurgitant jet velocity (TRjet) of  $\geq 2.5$  m/s. Although this criterion has correlated with markedly reduced survival in a number of studies, this diagnostic threshold, though arbitrary, is commonly used and corresponds to a pulmonary arterial (PA) systolic pressure of approximately 30 mmHg. When right heart catheterization is done, pulmonary artery hypertension is considered present when the mean PA pressure is  $\geq 25$  mmHg. In addition, many investigators now feel that SCD patients with pHTN belong to a subset of patients with a “high hemolytic rate” phenotype.<sup>xi</sup> In addition to having lower hemoglobin and higher lactate dehydrogenase (LDH) levels at baseline,<sup>xxxvi,xli</sup> patients with pHTN are now also recognized to have other sequelae of SCD at higher rates than patients without pHTN. Patients with pHTN exhibit a higher prevalence of proteinuria and decreased glomerular filtration rate (GFR),<sup>xxxviii</sup> as well as left ventricular (usually diastolic) dysfunction, leg ulcers, and CNS events.<sup>xli</sup> Finally, we do not fully understand the mechanism and rate of the development of pHTN, especially the hypothesized transition from initially reversible pulmonary arterial vasoconstriction to more fixed and irreversible vasculopathy.

### **Renal/Genitourinary Complications**

Renal complications such as hematuria, proteinuria, pyelonephritis, acute renal failure, and chronic renal insufficiency are more common and occur at earlier ages in persons with sickle cell disorders compared with individuals without SCD. The underlying pathology may be due to the complication of intravascular hemolysis or infarction of tissue beyond a vessel blocked by hemoglobin S red cells. Also, once a condition develops, it may recur or progress more rapidly in SCD patients. Nevertheless, renal complications are defined and managed in a fashion similar to conditions in individuals without SCD. However, the initial hyperfiltration typical in persons with sickle cell disorders results in a lower serum creatinine, so the definition of renal insufficiency is modified accordingly.



## **Splenic Complications**

Splenic pathology in sickle cell disorders is related to the organ's unique interaction with the sickle erythrocyte and subsequent physiologic dysfunction. The relatively hypoxic and acidic splenic environment favors erythrocyte sickling and vaso-occlusion. Intrasplenic vaso-occlusion can be acute, resulting in life-threatening splenic sequestration (see discussion under Acute Exacerbations of Anemia), or chronic, leading to splenic enlargement and hypersplenism with peripheral cytopenias. Vaso-occlusion can lead to an acutely painful infarction of the organ but more commonly results in repeated minor subclinical episodes and gradual loss of splenic phagocytic and immunologic function in early childhood. This functional hyposplenism/asplenia in turn results in increased susceptibility to sepsis, particularly from encapsulated bacteria.

## **Transfusions and Iron Overload**

Patients with SCD receive transfusions for multiple acute and chronic complications during their lifetimes, predisposing them to iron overload and alloimmunization, even when they are not on chronic transfusion regimens. While blood tests such as ferritin and transferrin saturation are helpful in identifying patients with risk for iron-mediated tissue damage, they are unreliable indicators of the degree of tissue hemosiderosis. Liver iron analysis is the most reliable assessment of iron load, but requires a liver biopsy. Other assessments of liver iron, such as SQUID and MRI T2\*, are also reliable and less invasive, but not yet widely accessible. For these reasons, as well as the lack of a carefully performed prevalence study, the degree to which iron overload shortens average life expectancy for patients with SCD is unclear.

Alloimmunization, including the production of multiple alloantibodies, is common after transfusion in SCD. Since most SCD patients in the US are African-American, while most blood donors are Caucasian, efforts to prevent alloimmunization are widely recommended, most often through the provision of C-, E-, K- red cells to SCD patients negative for these antigens. Moreover, there is a relatively high frequency of delayed hemolytic transfusion reactions in SCD. It is important to recognize the unique features such reactions can have in SCD, especially the associated vaso-occlusive symptoms and the phenomenon of hyperhemolysis, discussed above. Autoantibodies and reticulocytopenia may also be found in this setting. Therefore, the clinician must be aware that further transfusion, even of antigen-matched and crossmatch-compatible blood, may result in further exacerbation of anemia and lead to a fatal outcome.

## **Summary**

Provision of clinical care and performance of clinical research in SCD have been hampered not only by the relatively low prevalence of the disease (<100,000 persons in the US) but also by the lack of clear definitions and diagnostic criteria for the myriad complications of SCD and the burgeoning but still inadequate understanding of SCD pathophysiology. This report therefore proposes definitions for the most frequently observed complications of SCD, so that future research studies can be used to validate study results and efficacy of treatment can be measured. We believe that these definitions will facilitate future genotype-phenotype studies that promise to increase understanding of the pathophysiology of SCD complications. It is the hope of those who supported and contributed to this project that this manuscript will be viewed as a dynamic document. A high priority should be given to reevaluation and revision of the phenotype definitions at periodic intervals to ensure the most current and standardized definitions are available, as better etiologic understandings emerge and new diagnostic and treatment options are developed.

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