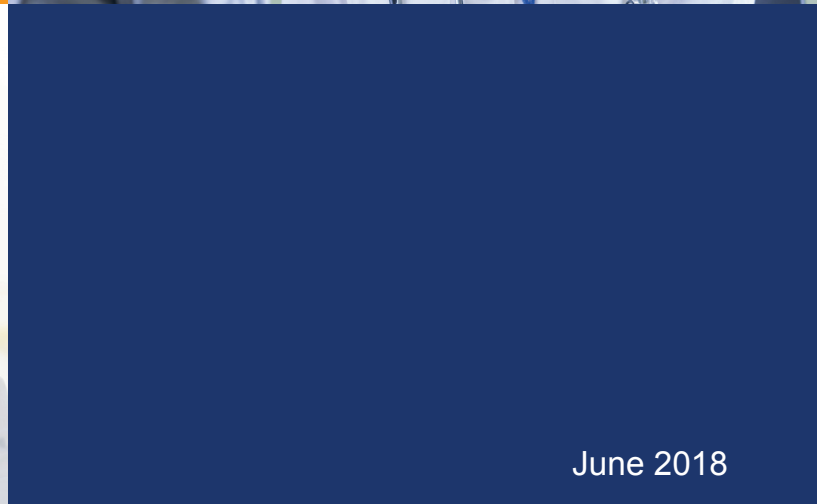




Council For
CHANGE™

Sickle Cell Disease Council For CHANGE

Improving Vaso-occlusive Crisis Management



June 2018

Pfizer Rare Disease supports the mission of the Sickle Cell Disease Council For CHANGE and has provided financial support for their meetings and this report. Pfizer colleagues have contributed to the content in this report in partnership with the members of the Council For CHANGE, but Pfizer does not have editorial control over or responsibility for its final content.



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The Sickle Cell Disease Council For CHANGE was created in 2015 to convene a diverse group of individuals who are committed to improving the education and quality of care for those living with sickle cell disease (SCD) in the United States. Since the formation of the Council, the team has experienced the loss of two wonderful members to SCD, and as a group, would like to honor their contributions to the Council's vision and this report.

This report underscores the imperative for change and provides an overview of the Council, its vision, and the initiatives the Council is undertaking to drive positive change for all who are affected by this disease.

The Council recognizes that we are not alone in our vision and commitment to improving care for individuals with SCD; thus, we welcome the opportunity to collaborate with the many stakeholders, institutions, organizations, and individuals striving to address significant challenges within our community. Collectively leveraging our expertise and unique skill sets will lead to positive change for all individuals with SCD in the United States.

-The Sickle Cell Disease Council For CHANGE

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ABBREVIATIONS

AAPT, Analgesic, Anesthetic, and Addiction Clinical Trial: Translations, Innovations, Opportunities, and Networks—American Pain Society Pain Taxonomy

ACU, acute care unit

APS, American Pain Society

CBCF, Congressional Black Caucus Foundation

CF, cystic fibrosis

CFC, Sickle Cell Disease Council For CHANGE

ECHO, Extension for Community Healthcare Outcomes

ED, emergency department

ESI, Emergency Severity Index

ESL, E-selectin ligand

HB S, sickle hemoglobin

HRSA, Health Resources and Services Administration

IQR, interquartile range

NHLBI, National Heart, Lung, and Blood Institute

NIH, National Institutes of Health

NMA, National Medical Association

NSAID, nonsteroidal anti-inflammatory drug

OPRs, opioid pain relievers

PHRESH, Public Health Research, Epidemiology, and Surveillance for Hemoglobinopathies

PCP, primary care provider

PSGL-1, P-selectin glycoprotein ligand-1

QoL, quality of life

RBC, red blood cell

RuSH, Registry and Surveillance System for Hemoglobinopathies

SCD, sickle cell disease

SCD TDP, Sickle Cell Disease Treatment Demonstration Program

SEER, Surveillance, Epidemiology, and End Results

SS-RBC, hemoglobin S red blood cell

WBC, white blood cell

VOC, vaso-occlusive crisis

VTE, venous thromboembolism

Images included throughout the report are illustrative and do not depict actual patients or medical professionals.

Preface

Many have spoken out about the need for change in the quality of care for individuals with sickle cell disease (SCD). Despite all of the earlier and ongoing research activity, SCD continues to be a major, global public health crisis, and cause of early death and significant disability.

SCD is associated with multiple potentially life- and limb-threatening complications, but vaso-occlusive crisis (VOC*), resulting in acute, excruciating pain, is the most common clinical manifestation of SCD and reason for emergency department (ED) visits.¹ A VOC is defined as pain resulting from tissue ischemia caused by vaso-occlusion, most commonly in the bone(s) and bone marrow.² Although national guidelines have been in place since 1999, acute care remains suboptimal.³ Therefore, there is a critical need to improve care for SCD patients in the United States (Figure 1).

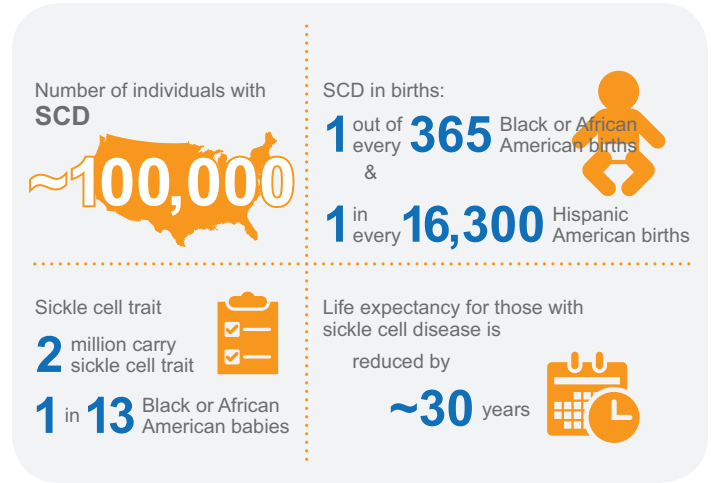
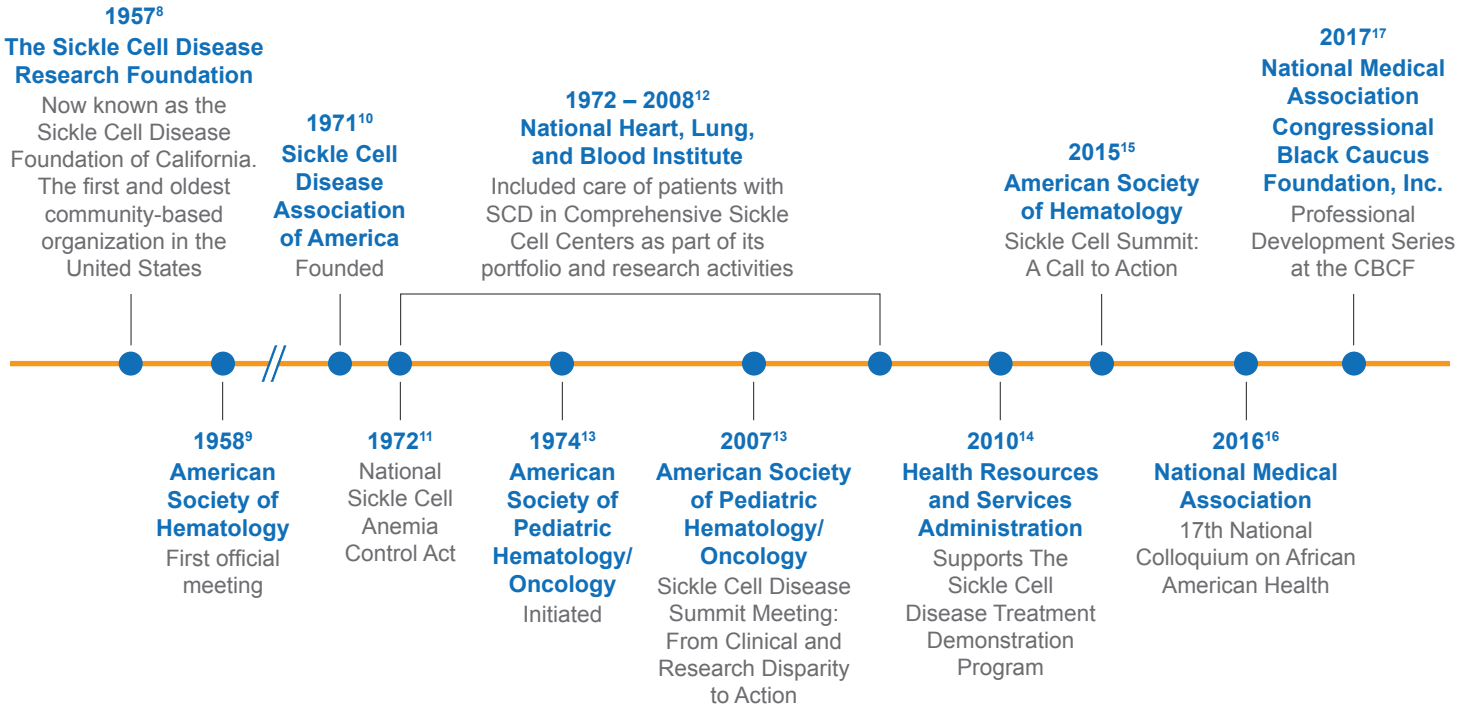


Figure 1: SCD in the United States⁴⁻⁷

Snapshot of SCD Events and Contributing Organizations



*The Council deliberately chose to use vaso-occlusive crisis rather than vaso-occlusive episode based on patient preference.

Areas for Improvement in the Management of VOC in SCD

This level of optimal care requires a comprehensive care network, including primary care providers and hematologists providing specialized SCD care. A myriad of issues prevent most individuals with SCD, particularly adults, from receiving the level of optimal care that they need.¹⁸⁻²⁰

WORKFORCE DISTRIBUTION AND TRAINING FOR SCD CARE VARIES WIDELY

Healthcare providers' knowledge, with respect to caring for individuals with SCD, varies widely based on exposure to such patients, specialty, practice setting, and geographic locale. Exposure of pediatricians and family physicians to SCD during training may be common, because they often shoulder a state-enforced public health responsibility to administer prophylactic penicillin to newborns with SCD to prevent death from infection. Yet, despite this exposure, some primary care clinicians' knowledge of newborn screening management strategies remains poor. Fortunately, the knowledge and confidence to provide appropriate follow-up could be improved with simple educational interventions.²¹ Among adult-oriented physicians, primary care physicians (56%) care for inpatients more than hematologists (21%) and other specialists (22%).²² Although patient care largely resides with pediatricians, family physicians, and general internists, surveys indicate most do not feel comfortable providing care for young adults with SCD.^{23,24} Most community-based adult hematologists/oncologists see fewer than 3 SCD patients per month, and may not prescribe hydroxyurea, the first remittive drug for SCD.²⁵ Moreover, only about a third of community-based hematologists/oncologists use National Institutes of Health (NIH) guidelines to manage patients with SCD. This variability in delivery of care for individuals with SCD likely contributes to the significant rates of morbidity and mortality in this patient population.

INDIVIDUALS WITH SCD OFTEN LIVE IN MEDICALLY UNDERSERVED COMMUNITIES

In the United States, SCD predominantly affects individuals of African or Hispanic descent, many of whom live in areas that are historically underserved medically, including impoverished neighborhoods in urban centers and rural areas.²⁶ Unlike with other genetic disorders, such as cystic fibrosis (CF) and hemophilia, there are too few specialized SCD centers to serve this population, and Comprehensive Sickle Cell Centers experienced in the care of patients with SCD are less widely used because of access issues, likely leading to suboptimal care.¹⁹ For example, researchers in South Carolina found that those with SCD living in rural areas had decreased access to comprehensive SCD care, high rates of acute care utilization, and substantial 30-day readmission rates.²⁷ Currently, treatment models are being tested that disseminate best care practices and enhance the skills of local healthcare providers in settings that lack SCD specialists, such as hub-and-spoke models of care and telementoring through Project ECHO (Extension for Community Healthcare Outcomes).^{28,29}

INSUFFICIENT DATA ARE AVAILABLE ON INDIVIDUALS LIVING WITH SCD

Currently, the best source of data regarding SCD incidence in the United States is from state newborn SCD screening programs.³⁰ The Centers for Disease Control and Prevention has conducted surveillance projects on the SCD population at the state level through the RuSH (Registry and Surveillance System for Hemoglobinopathies)^{31,32} and PHRESH (Public Health Research, Epidemiology, and Surveillance for Hemoglobinopathies)³³ programs, and continues to work with state agencies in Georgia and California as part of the Sickle Cell Data Collection program,^{32,34,35} to analyze healthcare utilization patterns and mortality rates in this population. Other researchers have used state Medicaid or commercial insurance databases to estimate the multistate use of such SCD treatments as hydroxyurea or ED utilization among individuals living with SCD.^{1,36,37} However, no national data sources are available, such as a disease registry for SCD. Disease registries, including the Surveillance, Epidemiology, and End Results (SEER) program, have helped improve the morbidity and mortality of other life-threatening conditions and rare diseases, such as CF or cancer.^{38,39}

FUNDING FOR SCD IS SUBOPTIMAL

Historically, funding for SCD has been provided by federal government programs, such as the National Heart, Lung, and Blood Institute (NHLBI) through the Comprehensive Sickle Cell Centers (8-12 academic centers, 1974-2008), the Health Resources and Services Administration's (HRSA) SCD Newborn Screening Program (1998), and the Sickle Cell Disease Treatment Demonstration Program (SCD TDP, 2006). Other rare diseases, such as CF, have had more support from various sources than SCD.⁴⁰ The Cystic Fibrosis Foundation uses philanthropy dollars to fund CF centers that participate in a national registry, which has been used to conduct randomized controlled trials and other research, contributing to dramatically improved survival and QoL for its population.³⁹ The Hemophilia Foundation supplemented federally funded hemophilia centers through the development of treatments for its population. Encouragingly, interest in funding similar programs and low-cost medications for SCD through the 340B program has increased.⁴¹ The House of Representatives has recently passed the "Sickle Cell Disease Surveillance, Prevention, and Treatment Act of 2018," which will create a national program to collect data on demographics and prevalence of SCD, conduct public health initiatives, identify and evaluate strategies for SCD prevention and treatment, and extend the SCD TDP for 4 more years. Continued advocacy will be needed to ensure this act makes it into law.

Areas for Improvement in the Management of VOC in SCD

OPTIMAL PREVENTION AND TREATMENT OF VOC REMAIN A CHALLENGE

VOCs are the most frequent cause of recurrent morbidity and hospital admissions in those diagnosed with SCD.^{2,18} Individuals of all ages with SCD are at high risk for the development of multisystem acute and chronic conditions that are associated with significant morbidity (**Figure 2**).² Optimal acute care within the first 24 hours of presentation is critical, as this is an especially dangerous time for patients with SCD.⁴² The NIH Expert Panel Guidelines for VOC management suggest rapid initiation of analgesic therapy, typically parenteral opioids, for VOC with severe pain, followed by continuous reassessment of pain and re-administration of analgesic treatment.² Current clinical practice, however, often deviates considerably from these recommendations. Many ED providers are unaware of the guidelines, including the need to triage patients with SCD-related complaints at a high severity level (such as Emergency Severity Index [ESI] level 2), given their risk of severe complications. Lack of knowledge about SCD, especially that many patients have been treated with parenteral opioids previously and need higher doses than the general population, may lead to suboptimal administration of analgesics in the acute care management of VOC, including inadequate dosing and frequency of administration. Finally, EDs are increasingly restricting the use of opioids given the current opioid epidemic. Inadequate acute care experiences leave many adults with SCD reluctant to seek medical attention for subsequent VOCs.

“For the most part, I’ve had such (bad) experiences with pain crises and hospitals, that I try to stay as far away from them as possible.”

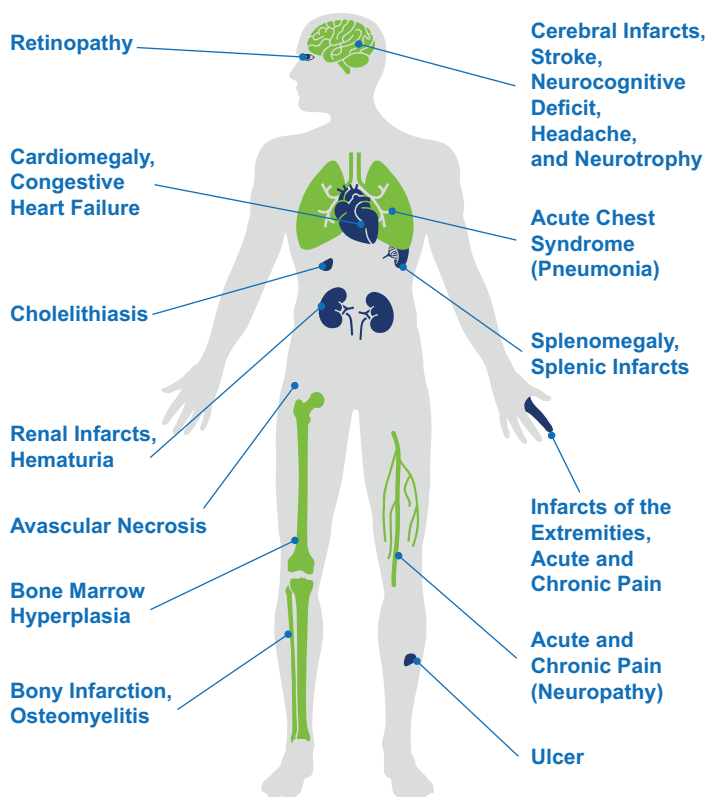
(KS – adult living with SCD)

GAPS IN UNDERSTANDING THE SCIENCE BEHIND SCD AND VOC EXIST

Gaps exist in the community’s (patient, provider, family, research groups) understanding of the complex pathophysiology of SCD and the underlying mechanism of VOC. The old paradigm describes SCD as an inherited disease driven primarily by red blood cell (RBC) sickling, attributing the causes of pain to the occlusion of blood vessels. In contrast to older, simplistic models of SCD, new insights have led to a novel paradigm that reflects a complex disease involving multiple pathways and pathophysiologies, and recognizes that such factors as acute stress, inflammation, cell adhesion, and the microbiome all contribute to SCD.⁴³⁻⁴⁵ This complexity is particularly true for VOC, in which one

or more mechanisms may prevail under different clinical circumstances.^{43,46} Many of the recent updates to the science behind SCD have not been widely communicated to the community. Lack of awareness of the updated model not only hinders the development of targeted therapies and the ability of healthcare providers to deliver cutting-edge care, but it also limits patients’ ability to self-advocate, optimize self-management of their disease, and make informed decisions about their care.

Figure 2: Common Clinical Complications of SCD



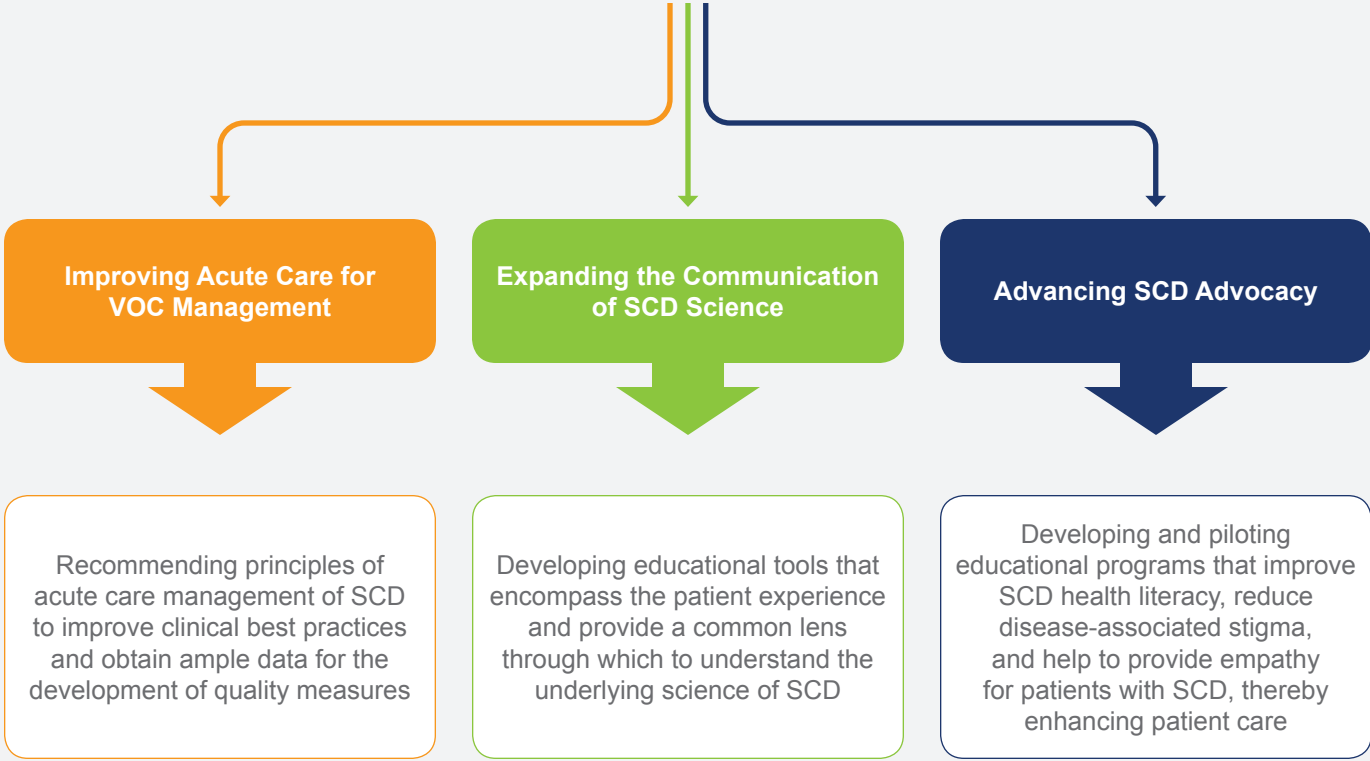
INDIVIDUALS WITH SCD OFTEN EXPERIENCE STIGMA RELATED TO THEIR DISEASE

Those living with SCD remain subject to social stigma related to their disease, and healthcare provider perceptions can contribute to the negative interactions experienced in acute care settings. A review of the literature indicates that very few studies support that SCD patients experience optimal care.⁴⁷ Overall, patients with SCD characterize their negative experiences of hospital care by mistrust, lack of control and involvement in decision making, and neglect.⁴⁸⁻⁵⁰ There is a significant need for patient advocacy that is focused on education to improve clinician attitudes and knowledge about SCD, and to empower the patient as an educator, ultimately translating into improved care.^{50,51}

IMPROVING VOC MANAGEMENT FOR THOSE LIVING WITH SICKLE CELL DISEASE

The Sickle Cell Disease Council For CHANGE (CFC) is a working group of passionate experts and advocates who are dedicated to elevating the quality of patient care for SCD VOC. The CFC aims to optimize acute care for VOC management, educate individuals with SCD and healthcare providers on the science of VOC, and empower advocates to raise awareness of patients' needs.

The CFC Is Organized Into 3 Workstreams* Addressing Unmet Needs



The vision of the CFC is to engage with other multidisciplinary professionals in dialogue and collaborative support of these initiatives, to ultimately contribute to improved healthcare outcomes and overall QoL for those living with SCD.

*At its inception, the CFC organization included a fourth Workstream (Transforming the SCD Care Paradigm), which explored gaps in access to care. This Workstream was recently consolidated into Improving Acute Care for VOC Management to best leverage member expertise in the effort to improve acute care. In consolidation of this Workstream, an Advocacy Workstream member was also transferred to the group to embed the SCD patient perspective.

VOC MANAGEMENT REMAINS SUBOPTIMAL

Ideally, acute VOC management should begin with a thorough and rapid assessment of a patient's pain on presentation. In particular, confirming that a patient is presenting with VOC, and not with a more life-threatening or limb-threatening situation, is critical.^{2,52} Patients with SCD presenting with VOC should be triaged at ESI level 2, similar to patients presenting with chest pain that may be related to acute myocardial infarction or neurological signs that may be related to stroke.⁵³ Additionally, identifying other potential causes of a patient's pain from their past medical history and other risk factors, along with the patient's recent use of analgesics are necessary steps in the evaluation.

“The pain is real. It can be excruciating to the point that you want to give up.”

(SM – adult living with SCD)

In reality, patients with SCD-associated pain tend to wait longer for pain medication than do those with other painful conditions, such as renal colic.⁵⁴ Studies have shown that the median time to initial analgesic administration for adults was 74 minutes (IQR=48–135 minutes)⁵⁵ and for pediatric patients was 63 minutes.⁵⁶ Inaccurate pain assessment may contribute to delays in administration, inadequate pain relief, and the decision for patients to self-manage pain exclusively at home.

In some hospitals, patients have access to specialized acute care units (ACUs). ACUs with focused SCD care and specialists available who have expertise in the management of pain crises have been shown to effectively address pain and limit hospitalizations compared with EDs. A recent study found significant differences between EDs and ACUs in first and hourly opioid dose. The approach taken by ACUs—administering the higher doses of opioids needed to treat acute painful episodes in adults with SCD—was associated with improved pain outcomes and decreased hospitalization rates. Thus, a more aggressive approach by ED clinicians in prescribing larger opioid doses may likewise result in improved outcomes and decreased hospitalizations.⁵⁷ The use of standardized SCD pain treatment plans (either individualized or weight-based) may overcome some of the challenges faced by EDs in providing effective pain management for patients with SCD.⁵⁸ In addition, clinical practice guidelines suggest that inpatient management for adults should include VTE prophylaxis, as SCD patients are at increased risk of thromboembolic events.^{59,60} Also, hospitalized children with SCD 10 years and older should be assessed for risk of VTE, and started on appropriate prophylaxis, as needed.

Discharge planning, transitional care, and follow-up appointments must also be considered when developing treatment plans for patients with SCD. Early post-discharge follow-up with a knowledgeable outpatient provider, including primary care physicians with SCD expertise, has been shown to prevent subsequent hospitalizations and to improve patient care. However, study findings indicate that a minority of patients admitted for VOC are discharged with an outpatient follow-up appointment.⁶¹

STANDARDIZING CLINICAL BEST PRACTICES

The Council believes that a set of SCD standard principles of care can elevate some of these challenges. Principles of care recommended by the CFC are outlined on page 7. The CFC encourages local medical centers to adopt these principles as best practices and to evaluate outcomes associated with their use. It is the position of the CFC that implementation of these best practices can improve such SCD outcomes as morbidity, mortality, the overall patient experience, and cost of care. If the SCD community can generate sufficient data, quality measures can be developed based on the principles of ESI level 2 triage and rapid access to appropriate analgesic care in the ED.

CFC-RECOMMENDED PRINCIPLES OF CARE FOR VOC MANAGEMENT

Recognizing several guidelines exist and the great variability in the levels of evidence that support them, the CFC adopted a philosophy of first outlining overarching principles of care. The Council believed that each principle might be supported by multiple recommendations within multiple guidelines, issued by organizations such as the NHLBI (**Table 2 on page 9**) and American Pain Society (APS).^{2,3} The CFC acknowledges that certain recommendations may not be supported by high-quality evidence and, in some cases, may be consensus-based. The CFC identified highly evidence-based recommendations within various guidelines as candidates for generating measures that could become quality indicators. However, the Council recognized that candidate quality indicators would first have to be tested in the field to assess feasibility and practicality of implementation, ease of use, wide applicability, ease of attribution of specific actions, and demonstration of a relationship between action and outcome. These features are believed to be the standard for quality indicators implemented by many healthcare stakeholders. Only when these criteria have been met can they be recommended for adoption by certifying bodies or payors.⁶²

“The evidence to support many consensus guidelines for SCD care is scant or low-grade. And even when the evidence for best SCD care is high-grade, adoption of recommendations is uneven and slow. Provider, financial, and institutional barriers to guideline adoption are each significant.”

(Dr. WS – SCD specialist)

Assuming this philosophy, the CFC adopted 7 principles of care, which are described in **Table 1**. The Council then determined which of the recommendations contained within the SCD guidelines supported the principles of care the Council had adopted. Further, among these, CFC members debated which recommendations might be candidates for quality indicators and, therefore, should be disseminated for further field testing.

Table 1: Principles for Acute Care Management of SCD

<p>1. Acute presentations of SCD may be life-threatening</p> <ul style="list-style-type: none">• These patients should be cared for as high-acuity patients
<p>2. Rapid assessment upon presentation</p> <ul style="list-style-type: none">• A patient with SCD presenting to the ED should receive a rapid assessment, such as Emergency Severity Index (ESI) level 2• Initial rapid assessment should include documentation of pain severity
<p>3. Confirmation of VOC pain crisis diagnosis</p> <ul style="list-style-type: none">• Identification of potentially life-threatening issues, such as acute chest syndrome and stroke• If other diagnoses are possible, immediate engagement of other specialist(s) is required• Pain crisis is a diagnosis of exclusion• Identify the patient's primary provider early in his or her treatment (in ED, if possible) to check on the existence of a care plan and gain additional guidance on treatment approach
<p>4. Rapid intervention</p> <ul style="list-style-type: none">• Intervention should begin within 60 minutes of arrival• It is also important to ensure a smooth transition, and rapid reassessment and intervention upon transition to a new setting or provider (within 30 minutes)
<p>5. Rapid reassessment</p> <ul style="list-style-type: none">• Reassessment should be performed at least every 30 minutes in the ED and every 1 to 2 hours in the inpatient setting• Analgesics should be titrated until pain control is achieved; confirm pain control by reassessing pain severity (in both the ED and inpatient setting)• It is worse to undertreat the great majority of patients with SCD than to overtreat the small minority of patients
<p>6. Be a patient advocate</p> <ul style="list-style-type: none">• Involve the patient in the care plan• Care should be individualized, using individualized care plans when available• Don't let high-utilizing system abusers define the way the institution approaches acute care for patients with SCD in general
<p>7. Patient should be transitioned to a medical home</p> <ul style="list-style-type: none">• Patient should be transitioned with a plan for follow-up care by accessible PCPs and specialists• Attempt to place/coordinate with a dedicated SCD clinic• Identify nonmedical support systems (eg, social workers) as needed—this step is particularly important for high-utilizing population

Improving Acute Care for VOC Management: Clinical Best Practices

Given that multiple guidelines and expert recommendations exist, in combination with the Council's experience treating SCD patients, the CFC endorses the following principles of care and associated recommendations:

1. Seven overarching principles of care (**Table 1**). Principles 1, 2, and 4 are important for patients, healthcare providers, and institutions alike. If implemented, they are likely to radically shift SCD care, thereby saving lives, improving patient satisfaction, and lowering costs
2. NIH recommendations for the management of SCD that support these principles (**Table 2 on page 9**)
3. Two recommendations, listed in various guidelines, are supported by some evidence, and each should be tested in the field to gather further evidence to determine their suitability for the derivation of quality indicators:
 - a. *Upon presentation to the ED, all patients with SCD should be triaged as ESI level 2.* Acute presentations of SCD may be life-threatening. Therefore, these individuals should be treated as high-acuity patients. Failure to do so might result in higher rates of hospital-related morbidity or mortality, or early readmission after discharge from the ED.
 - b. *Patients with SCD should receive an initial opioid parenteral analgesic within 60 minutes of arrival in the ED.*

Prompt and aggressive analgesic treatment is crucial for the management of acute VOC. Early initiation of opioids has been shown to improve pain outcomes,⁶³ which may lead to earlier discharge from the ED and fewer hospitalizations.⁵⁸ For these reasons, numerous clinical guidelines, including those from the NHLBI (**Table 2 on page 9**), and the APS, recommend that patients receive an initial opioid parenteral analgesic within 60 minutes of arrival or within 30 minutes of triage in the ED. In practice, however, achieving initial opioid analgesic administration within 30 minutes for a VOC is not achieved routinely, with the median time to first analgesic dose usually longer than 1 hour.^{64,65} A practical recommendation, based on the multiple factors leading to delays in opioid administration in the ED, is to have the intervention with analgesic medication for a VOC begin within 60 minutes of ED presentation.

4. Raising awareness, development, and implementation of principles of acute care management of SCD, as well as specific guideline recommendations related to acute care

As a start, the CFC specifically recommend further assessing and testing of the principles recommended above, and perhaps others, through collaboration and partnership with local institutions and organizations. Results may lend themselves to the adoption of new quality indicators for the acute care of patients with SCD. Widespread adoption of these quality indicators may change routine SCD care at both the local and the national level, ultimately raising the standards of excellence in SCD care.




Improving Acute Care for VOC Management: Clinical Best Practices

Table 2: NHLBI Expert Panel Report Recommendations That Relate to SCD VOC Management²

1. Assign ESI triage level 2
2. Administer first parenteral* opioid within 60 minutes of arrival
3. Evaluate pain relief and sedation every 15-30 minutes and re-administer analgesic doses until pain relief is obtained according to patient report a) Maintain or consider escalation of the dose by 25% until pain is controlled b) Use nonpharmacologic approaches such as heat. Manage pain for 6-8 hours. If unable to control pain, consider admission to short-term observation unit or hospital
4. In adults and children with SCD and a VOC associated with mild to moderate pain who report relief with NSAIDs in the absence of contraindications to the use of NSAIDs, continue treatment with NSAIDs
5. To reduce the risk for acute chest syndrome in adults and children hospitalized for a VOC a) Encourage use of incentive spirometry every 2-4 hours while awake b) Encourage ambulation and activity as soon as possible
6. All hospitalized patients treated with opioids are given a stimulant laxative of choice

*Parenteral: administered or occurring elsewhere in the body other than in the mouth or alimentary canal.



If you are involved in current assessments of this nature or have the opportunity to incorporate testing of these principles of acute care within your local institution, please contact the CFC—the Council is eager to hear more about your activities. Current and future evidence will need to be accumulated and inventoried to eventually transform these best practices into quality measures.

Contact Wally R. Smith, MD
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Expanding the Communication of SCD Science: Empowering Improved Care Through Disease Understanding

SCD is caused by a variant of the β -globin gene, sickle hemoglobin (*HB S*). When deoxygenated *HB S* has the capacity to polymerize, polymerization injures the sickle erythrocyte, increases its density, reduces its deformability, increases cell adhesion, and shortens its life span. Polymerization of deoxygenated *HB S* is a pivotal event in the pathogenesis of SCD⁶⁶; however, this process alone does not account for the pathophysiology of SCD.

THE SCIENTIFIC PARADIGM OF SCD PATHOPHYSIOLOGY HAS EVOLVED

The updated paradigm of SCD pathophysiology and underlying mechanisms of VOC proposes adhesive interactions between hemoglobin S red blood cells (SS-RBCs) and vascular endothelium, with SS-RBCs and leukocytes as key components. Mechanisms underlying these interactions have been implicated in the initiation of VOC, as well as endothelial activation by SS-RBCs and other inflammatory mediators, ultimately resulting in activation of the endothelial lining of blood vessels.⁶⁶ Endothelial activation, in turn, attracts white blood cells (WBCs), which then bind to blood vessel cells through a number of adhesion pathways and capture other circulating blood cells either directly or indirectly. Not only does the binding of RBCs and WBCs alter blood flow in the microcirculation, but it also causes complete blockage and ischemia as a result of the obstruction.⁶⁶ A feedback loop is then created, worsening endothelial activation.⁶⁶

“Many view SCD-related pain and organ damage as resulting from a ‘plumbing issue’—with blood vessel blockage occurring solely because of sickled RBCs.

There have been breakthroughs in understanding the mechanism of disease, involving multiple types of blood cells and pathways. It is essential that both providers and patients understand the current view of SCD pathophysiology to effectively communicate and to appreciate the vital role of new treatments that target the disease process.”

(Dr. DM – SCD specialist)

Damaged SS-RBCs and activated endothelial cells can also produce a pro-inflammatory environment that is exacerbated during VOC. Additional triggers of VOC may include stress, increased viscosity of blood, decreased blood flow, hemolysis, or a combination of factors (**Figure 3**), all of which are highly dynamic, and contribute to the multidimensionality of VOC and the variability in patient symptom profiles.

SCD PATHOPHYSIOLOGY INFORMS OPTIMAL MANAGEMENT OF VOC-RELATED PAIN

VOC-related pain is more complex than most conditions associated with pain, with optimal management requiring an understanding of the underlying pathophysiology specific to SCD.⁶⁷ Individuals with SCD can experience aspects of neuropathic as well as nociceptive pain simultaneously, and recurrent episodes of severe pain can lead to augmentation of pain processing and centrally mediated pain.⁴⁶ For this reason, identifying the type of pain, not just the level of pain, is important.

“I pride myself on providing true comprehensive care to my patients with SCD. I have the opportunity to give them a positive outlook on life and hope for the future. I know that they can ‘Live well with sickle cell.’”

(Dr. DM – SCD specialist)

Although SCD is typically accompanied by episodic acute pain, there is an increasing awareness that chronic pain is also a part of the disease process for many older adolescents and adults.⁶⁸ Individuals with SCD can experience a recurrent pattern of acute episodic pain superimposed on chronic pain.⁶⁸ As a result, opioids are often prescribed as part of SCD treatment plans, and regular use of opioids is common because of the frequency of VOCs. The acute and chronic pain should be treated as two separate entities and with different medication regimens. Regular long-term opioid use results in a multifaceted process that likely involves the interplay of multiple regulatory mechanisms at both the opioid level and the level of neural circuits. This process in turn leads to drug tolerance and the need for higher opioid dosages to alleviate a patient's pain. This is why it is critical that there is integration of alternative treatments and the continual reassessment of current medication usage and dose.



Expanding the Communication of SCD Science: Empowering Improved Care Through Disease Understanding

UNDERSTANDING THE SCIENCE OF SCD IS FUNDAMENTAL TO IMPROVING PATIENT CARE

Currently, no official diagnostic criteria exist to classify chronic SCD pain. The Analgesic, Anesthetic, and Addiction Clinical Trial: Translations, Innovations, Opportunities, and Networks—American Pain Society Pain Taxonomy (AAPT) recently proposed a classification system to further standardize pain assessment.⁶⁸ Specifically, the AAPT published a system that differentiates chronic SCD pain. According to the AAPT diagnosis, chronic SCD pain consists of ongoing pain that has been present on most days over the past 6 months, in addition to ≥ 1 of the following signs: (1) focal pain or tenderness upon palpation of the region of reported pain; (2) focal pain upon movement of the region of reported pain; (3) decreased range of motion or weakness in the region of reported pain; (4) evidence of skin ulcer in the region of reported pain; (5) evidence of hepatobiliary or splenic imaging abnormalities (eg, splenic infarct, chronic pancreatitis) consistent with the region of reported pain; and (6) evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain. Differentiation may ultimately lead to improved clinical assessment and management of the complexities of SCD, which is particularly critical because of the relationship between chronic pain and increased morbidity and mortality, especially among adolescents and adults.⁶⁸

Although the research conducted by the AAPT only begins to reflect the complexities of SCD, these findings are a step forward in the development of consistent pain criteria and highlights the need to communicate the SCD paradigm shift. Recognition of updates to the understanding of SCD is fundamental to improving all aspects of patient care, including revised instructions for prescription use and the use of alternative modalities when considering treatment plans. In this way, those living with SCD, healthcare providers, policy makers, and the community can all better assume a holistic approach to SCD patient care. The ultimate goal is to have accessible, individualized, and comprehensive treatment plans for patients that stem from a common understanding of the science behind SCD. An additional goal is to ensure that the necessary steps are taken toward the development and testing of novel therapies for SCD.

“There are HCPs who specialize in hematology and are not only behind in their knowledge of the latest SCD scientific breakthroughs, but also are culturally insensitive and out of touch with the communities they serve.”

(KS – adult living with SCD)

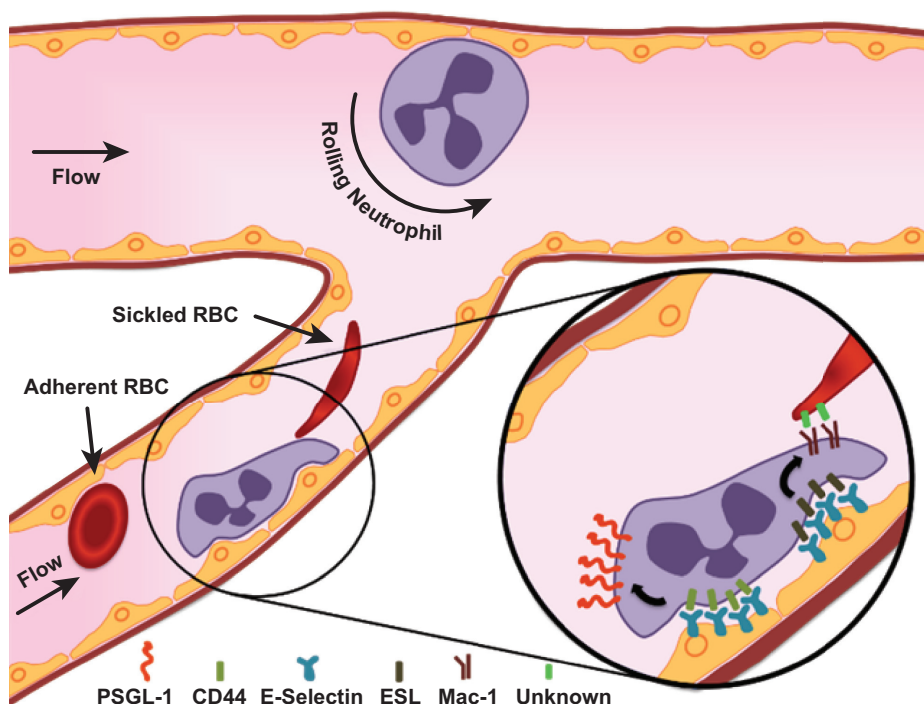


Figure 3: Vaso-occlusive Crisis (VOC) in SCD

SS-RBCs and other inflammatory mediators induce the activation of the endothelium. The damaged and stimulated endothelium is poised to recruit leukocytes. E-selectin on the endothelium is crucial for generating a secondary wave of activating signals, which produces a polarized expression of activated $\alpha M\beta 2$ integrin (Mac-1) at the leading edge of the crawling neutrophil, allowing the capture of circulating discoid and sickle-shaped erythrocytes. These events culminate in VOC in the postcapillary venules.

Expanding the Communication of SCD Science: Empowering Improved Care Through Disease Understanding

EMBEDDED WITHIN THE VISION OF THE CFC IS THE FACILITATION OF A MORE COMPREHENSIVE UNDERSTANDING OF SCD PATHOPHYSIOLOGY AND THE UNDERLYING MECHANISMS OF VOC

Further education of key stakeholders within the SCD community, emphasizing a more comprehensive understanding of SCD pathophysiology, is an important and ongoing challenge. Having a unified understanding and language is vital to best meet the needs of the patient. Thus, the goal of the CFC is to provide educational tools and resources that establish a common lens through which to view and understand SCD and VOC, as well as a common vernacular for discussing the condition. This unification can empower those with SCD to form genuine partnerships with their healthcare providers in the active management of their disease.

The CFC is exploring potential tools across a range of formats that can be developed in the near term (eg, slide modules, pamphlets) and in the longer term (eg, videos, digital apps) that may be particularly useful to those with SCD, their support networks, and advocacy groups. Members of the CFC who represent these ultimate intended users were instrumental in guiding the Council's vision to concentrate on educational tools that will do the following:

- Present the paradigm shift in disease understanding and how the conversation about SCD has changed to reflect not only the acute and chronic models of disease understanding, but also the local and systemic nature of the impact of SCD
- Communicate the pathophysiology and origin of SCD pain in a more comprehensive way, thus better guiding treatment and self-management
- Help individuals with SCD, their caregivers, and healthcare providers to understand and accept the new science of SCD as it relates to the underlying pathophysiology, complications, overall health, and approach to care
- Expand current knowledge in pain, fatigue, and organ damage as they relate to SCD

A proficient and aligned understanding of SCD will encourage healthcare providers to view SCD through the lens of how the science relates to the patient experience, enabling them to approach treatment in a more holistic manner. The opinion of the CFC is that knowledge and comprehension of the underlying science of SCD will empower those living with SCD to better track and manage their symptoms, help them create stronger networks and meaningful connections to lessen social isolation, and encourage them to seek proper care in a much more engaged manner.



The CFC is particularly interested in developing educational tools for the SCD community (ie, patients, medical providers, researchers, families) that are intended to increase understanding and awareness of SCD. Council members have brainstormed several concepts such as slides, brochures, apps, and videos that could be used as vehicles for communicating the novel science of SCD. An example is a real-time interface through which patients would be able to track and better manage their symptoms, as well as receive reinforcement from their support network. The CFC would like to hear from others who are interested in helping advance these ideas.

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Advancing Advocacy for SCD: Removing the Stigma and Increasing Health Literacy to Improve the Patient Care Experience

PERSISTING STIGMA CREATES OBSTACLES FOR THOSE WITH SCD

Extended hospitalization for patients with SCD is often perceived as being due to poor mental health or substance abuse. The reality is that long hospital stays for individuals with SCD are associated with patients remaining medically unstable.⁶⁹ Compounding matters is the opioid drug epidemic in the United States, which has unwittingly and inappropriately rendered those with SCD as targets of suspicion and possibly accused of being drug addicts and/or drug seekers, as well as potential victims of overdose. Although death due to opioid pain relievers (OPRs) is on the rise, as is addiction, it is inappropriate to assume that patients with SCD who take large amounts of opioids are drug addicts. As a result of regular long-term opioid use, patients with SCD often develop tolerance and, therefore, require higher doses of medication

“The last time I was in the ED, I was a bit insulted when the ED physician told me that I could not be in a crisis because my hemoglobin was too high. I am on hydroxyurea, which raises your hemoglobin. That does not mean you will never experience a crisis.”

(SM – adult living with SCD)

to alleviate pain. Without an appropriate context and disease understanding, this consequence can be perceived as drug-seeking behavior, of which patients with SCD are often accused. With acute and chronic pain prevalent among adults with SCD, the need exists to communicate the intricacies of SCD-related pain and how it is managed by healthcare providers, to help overcome the stigma associated with opioid use and misuse.

Additionally, few deaths due to OPRs are observed among the SCD population each year, particularly when compared with the number of deaths due to opioid use observed among non-SCD populations (**Table 3**). Despite this evidence, misconceptions persist among healthcare providers, affecting the timeliness and quality of care.⁷⁰ The relatively high utilization of the ED among adults with SCD may also influence healthcare providers’ perceptions.⁷¹⁻⁷³ The stigma associated with this disease can prevent those with SCD from seeking needed care and can thus result in under-treatment.⁷⁰

“I’ve felt the harsh pain from the common stigma that I am a drug seeker, due to knowing what dosage of IV narcotics usually work for me to get my pain under control.”

(KS – adult living with SCD)

Table 3: Number of Deaths Due to OPRs in Patients Without SCD vs Patients With SCD From 1999 to 2013 in the United States⁷⁴

Year	Non-SCD Patients Who Died Due to OPR	SCD Patients Who Died Due to OPR
1999	4,022	8
2000	4,393	7
2001	5,521	7
2002	7,450	6
2003	8,513	4
2004	9,856	1
2005	10,922	6
2006	13,717	6
2007	14,401	7
2008	14,795	5
2009	15,594	3
2010	16,641	10
2011	16,907	10
2012	16,002	5
2013	16,225	10
Totals	174,959	95



Advancing Advocacy for SCD: Removing the Stigma and Increasing Health Literacy to Improve the Patient Care Experience

Additional common misperceptions and stigmas are often associated with race and socioeconomic status. Attitudes among healthcare providers may be influenced, either explicitly or implicitly, by the socioeconomic status or medical history of patients with SCD,⁷⁵ with providers responding more positively to patients with higher levels of education and less disease severity. In addition, being of African American descent has been shown to contribute to poor care in the ED and the hospital. Moreover, African American adults with SCD also report greater race-based and disease-based discrimination in health-care settings than African Americans without SCD.^{76,77}

INADEQUATE DISEASE UNDERSTANDING AND HEALTH LITERACY LEAD TO NEGATIVE INTERACTIONS

In general, there is a lack of awareness and empathy for the experience of patients with SCD. This may be due to suboptimal disease education during medical training, leaving healthcare providers with an inadequate understanding of SCD and its complications.^{40,78} Despite the core concept of pain treatment—“Believe the patient!”—many healthcare providers do not believe that self-report is the most reliable indicator of the existence and intensity of pain among patients with SCD.⁷² Subpar care and negative interactions with patients can result when healthcare providers lack experience in treating SCD, fail to consider information provided by the patient or patient advocate, or are unfamiliar with a documented acute pain plan.

“I think for me, the most important part of my care is having a healthcare provider who is willing to acknowledge that he or she may lack the knowledge of how to best care for me early on. And even when they don’t possess expertise, be eager to work with me to better understand my needs or consult willingly with a partner who does.”

(JF – adult living with SCD)

Although available guidelines provide recommendations for opioid administration in the management of pain due to VOC in the hospital setting, education about pain management may still be lacking. Most healthcare providers are not familiar with available guidelines or recommendations on opioid use for VOC in patients with SCD or with the treatment approaches suggested by these guidelines.⁷⁹ In fact, medical textbooks may not be up to date or consistent with the latest recommendations. This lack of awareness can translate to inadequate care.

“It is dangerous for the healthcare provider not to listen to or trust his or her patient. I remember thinking during an unnecessary hospitalization, “I just need to make it back home to North Carolina.” And honestly, that was the first time I felt I could have died in the hospital because of the back-and-forth adjustments of my medication dosages by an unknowledgeable hospitalist fighting with the knowledgeable specialist I had called in to correct my regimen and stabilize my condition. How often does this happen?”

(JF – adult living with SCD)

Insufficient health literacy regarding SCD exists among both individuals with SCD and healthcare providers, and can exacerbate the negative care experience for those with SCD.⁵¹ Available materials often exceed recommended reading levels for the average American adult who has completed high school,⁸⁰ and literacy and numeracy demands associated with the use of such materials are likely to exacerbate difficulties in understanding patient education information designed to assist them in managing their SCD. Importantly, healthcare providers must recognize that each patient with SCD may have a different level of understanding of his or her disease.

Furthermore, additional significant challenges include staff and healthcare provider tenure within the ED setting; frequent hospitalist staff turnover, which compounds the issue of health literacy; and, most important, a lack of trust and respect between the patient and the healthcare provider. Creating a strong foundation built on trust and respect between patient and provider needs to be key to all aspects of overall care, regardless of the setting.



Advancing Advocacy for SCD: Removing the Stigma and Increasing Health Literacy to Improve the Patient Care Experience

THE CFC IS UNDERTAKING INITIATIVES TO REDUCE THE STIGMA ASSOCIATED WITH SCD AND TO IMPROVE HEALTH LITERACY

The initiatives of the CFC aim to enhance education, thereby reducing the stigma associated with SCD among healthcare providers and improving health literacy and “self-advocacy” among adults with SCD. By doing so, the goal is to improve SCD patient care, especially in the ED and acute care hospital setting.

Building on previous research that evaluated educational interventions aimed at improving healthcare provider attitudes in SCD care, the CFC is working to create a multimodal educational program that will focus on the following initiatives⁸¹⁻⁸³:

- Providing individuals with SCD materials so they are armed to advocate for themselves during crises
- Introducing patients to healthcare professionals in the ED and other appropriate care settings, so that they can share their lives, careers, and healthcare struggles outside of a pain crisis. Educating healthcare providers to mitigate biases and cultivate positive feelings of connection toward patients with SCD can help improve care
- Reducing gaps in knowledge about the science of SCD, patient needs, debunking stigma, and improving the attitudes of healthcare providers

Additionally, the efforts of the CFC include developing well-designed training and patient-level educational materials that translate the scientific explanation of SCD into patient-friendly language for community-based organizations. The intention is to have organizations share these materials with their members and community, which is a step in the right direction toward empowering individuals with SCD in the self-management and understanding of their disease.

The CFC is seeking to learn more about programs at institutions that have been successful in educating their ED staff and reducing stigmas. The Council wants to hear from institutions interested in developing and fielding an ED educational pilot program.

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Looking Ahead: Bringing Together Those Committed to Educating, Advocating, and Improving Care for Those With SCD

Much work is ahead for the CFC to implement this vision and the initiatives described. The CFC encourages adoption of the recommended principles for acute care management of SCD and testing of outcomes after their implementation by local medical centers and institutions. Data gained from such efforts will be an additional step optimizing acute care management of VOC, supported eventually by the adoption of nationally recognized quality measures.

Additionally, the CFC looks to the entire SCD care community, institutions, and organizations for support in advancing the development of educational tools that will increase understanding of the science of SCD, including digital solutions that help individuals with SCD to better self-manage their disease and leverage support from their care network.

Finally, implementation and pilot testing of an educational program will require partnerships with institutions, physician and nursing organizations, and local advocacy organizations who can help educate others throughout the country. Through the pilot, the CFC hopes to better understand not only whether this educational intervention can sustain improvements in healthcare provider attitudes over time, but also whether attitudinal change will affect sustainable SCD patient care.

The seriousness of this disease, the toll of VOC, and the frequency of deaths from SCD deserve immediate and tireless action.

The CFC hopes this report encourages ongoing efforts and helps to create new opportunities for conversations, collaboration, and involvement as the CFC urgently works to bring these initiatives to fruition. Thus, the Council hopes to create positive change for those affected by SCD and looks forward to keeping the community apprised of its initiatives for CHANGE in the future.



SICKLE CELL DISEASE COUNCIL FOR CHANGE MEMBERS

Improving Acute Care for VOC Management

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Expanding the Communication of SCD Science

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Advancing SCD Advocacy

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**Formerly member of the *Advancing SCD Advocacy* Workstream.

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