Chapter 4: Managing Chronic Complications of Sickle Cell Disease

Introduction

Complications may occur early and span the entire life of individuals affected by SCD. Direct SCD complications may include acute or chronic pain syndromes, significant anemia and its sequelae, as well as organ damage and failure. Other coexisting complications may include rheumatoid arthritis and peptic ulcer disease.[147,286] Common acute complications and their sequelae are described in the "Managing Acute Complications of Sickle Cell Disease" chapter in these guidelines. This chapter focuses on the chronic complications of SCD. Chronic complications of SCD can affect almost any organ, and certain acute complications, such as stroke and priapism, often evolve into chronic phases that require special approaches to management.

The phenotypic expression of chronic complications varies considerably among people, in the same person over time, and among the various subtypes of SCD. Because the incidence of chronic complications seems to increase with age, understanding their pathophysiology, precipitating factors, and predictors may help prevent or minimize long-term morbidity.

Just as the presentation and manifestation of chronic complications of SCD may vary, so have their definitions. Recently, a unified definition of each complication of SCD has been published,[287] which may help stimulate further work to better describe and explain each complication. Without universal uniform definitions, the natural history of SCD complications and the effect of therapy will be difficult to determine.

In this chapter, recommendations related to the evaluation and management of the most common chronic complications of SCD are presented. For each complication discussed, information is presented on its frequency, most common presentations, usual evaluation, and treatment.

Methodology

Complete information about the methodology for these guidelines can be found in the "Introduction and Methodology" chapter (pages 1–9). The following information, specific to this chapter, supplements the standard methodology that was conducted for all clinical chapters of these guidelines.

A comprehensive study of several databases was conducted, and all human studies in English published from 1970 to July 2010 that addressed each PICOS question were identified. A total of 549 studies of complications were included.[h] When the literature search found insufficient evidence on a topic (e.g., chronic pain management), these topics were supplemented with recommendations derived from other published guidelines by professional organizations which were based on systematic reviews of broader population groups; these recommendations are labeled "Consensus–Adapted." The key questions for this chapter can be found immediately before the Summary of the Evidence sections for the individual topics.

Sickle cell anemia (SCA) refers to the clinically similar disorders HbSS or HbSβ0-thalassemia. Sickle cell disease (SCD) refers to all disease genotypes, including SCA and compound heterozygous disorders, such as HbSC, HbSD, and HbSβ+-thalassemia. The carrier state for hemoglobin S (HbAS or sickle cell trait) is not a form of SCD.

[h] An updated search was performed to span the time from June 1, 2010 through April 2014. Five additional RCTs were identified, for a total of 549 studies, and a supplemental table reflecting these additions was added to the evidence table document.

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the Management of Sickle Cell Disease Complications evidence table available at http://www.nhlbi.nih.gov/guidelines/scd/index.htm.

Chronic Pain

Background

In SCD, pain is considered chronic if it lasts more than 3 months. People with SCD experience both nociceptive and neuropathic pain. Nociceptive pain is a hallmark of acute pain (see the "Managing Acute Complications of Sickle Cell Disease" chapter). Chronic pain, including that described in people without SCD, is often associated with neuropathic pain. The pathology of the transformation from chronic nociceptive pain to neuropathic pain is not well understood. The Pain in Sickle Cell Epidemiology Study (PiSCES) showed that adults reported chronic SCD pain at home during about 55 percent of the 31,017 days surveyed.[145] Similarly, children reported SCD pain at home on about 9 percent of the 1,515 days surveyed.[288] In the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), at-home analgesics were used for SCD pain on 40 percent of diary days and during 80 percent of 2-week followup periods, with oxycodone and codeine being used most frequently.[289]

The major types of SCD-associated chronic pain include the following:

- Chronic pain often of unclear etiology. This type of chronic sickle cell pain may be an extension of recurrent acute painful episodes. Therefore, early and aggressive intervention in treating acute sickle cell pain may reduce the development of chronic pain.
- Chronic pain in a specific tissue or organ, such as avascular necrosis (AVN) of the hips, or leg ulcers. Chronic SCD pain is usually described as constant and deep, nagging, and achy in nature. It can occur in the chest, back, abdomen, extremities, neck, or head and is difficult to treat.
- Chronic neuropathic pain. This is usually described as burning, numb, tingling, lancinating, shooting, or paroxysmal in nature and is associated with a sensation of pins and needles. Its severity is also enhanced by exposure to either cold or heat. This pain can be secondary to either peripheral or central nerve injury or nerve dysfunction. SCD-related neuropathic pain has two etiologies. The first is tissue damage secondary to occlusion of blood vessels that supply the nerves as can be found in mental nerve neuropathy and spinal cord infarction.[290-292] The second seems to be chronic pain. Persistent chronic pain, the resulting inflammation, and/or pain management seem to lead to neuropathic pain.[286,293-296]
- "Breakthrough" pain is another type of pain often identified by health care professionals who treat patients with SCD. This term literally means the act of breaking through pain relief. Originally used to describe patients with cancer pain who were maintained on a stable dose of analgesics, breakthrough pain was defined as a flair-up of sudden pain unresponsive to usual therapy. Such a flare-up is usually sudden and incidental, and can last from a few seconds to a few hours. There are currently no data that clearly describe or can be used to define breakthrough pain in SCD.[297]

The pathophysiology, management, and goals of treating chronic pain differ from those related to acute pain. Whereas the aim of acute pain treatment is to heal the acute process, the aim of chronic pain management is to restore function and improve the quality of life. With the onset of chronic pain of unknown etiology, there seems to be a process of "rewiring" in the brain, where the threshold for pain perception is lowered so that ambient environmental stimuli that are normally painless or mildly painful induce the perception of severe pain.[298] Chronic pain is often associated with other conditions that enhance its chronicity. These include psychosocial factors such as depression, anxiety, feelings of despair, insomnia, loneliness, helplessness, post-traumatic stress disorder (PTSD), and dependence on pain medications.[23,293,299]

Management of chronic pain in people with SCD is a major challenge for health care professionals. The goals of providing adequate pain relief to improve functionality and quality of life must be balanced by the need to minimize the risk of abuse, misuse, or diversion of opioids—medications which are a mainstay in managing chronic pain in people with SCD. Believing the patient's report of pain is critical to optimizing therapeutic outcomes and achieving adequate pain relief and maintaining or improving functionality and the person's quality of life.[286]

Medications used to treat SCD-related pain should be tailored to the individual. Medications include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, and anticonvulsant medications. Management of all types of chronic pain associated with SCD may be enhanced by adding nonpharmacologic approaches. These may include psychological intervention, occupational therapy, behavioral and cognitive interventions, acupuncture, mild to moderate exercise if tolerable, and aqua therapy.

Key Question

KQ18. In people with SCD and chronic pain, what are the safest and most effective chronic pain management strategies and treatment algorithms (e.g., patient assessment and followup, use of chronic opioids, adjuvant pharmacological therapies, and behavioral therapies)?

Summary of the Evidence

To develop recommendations for the management of chronic pain in SCD, the methodology team conducted a comprehensive systematic review of studies that evaluated the efficacy and harms of different management approaches for chronic pain in SCD. Eight studies (two RCTs and six observational studies) and 13 case reports were eligible for inclusion.[294,296,300-305]

One study explored general chronic sickle cell pain and compared utilization of massage therapy and progressive muscle relaxation to massage therapy alone and found no significant differences between the two approaches.[301] The second study assessed hip pain and demonstrated a statistically significant difference between transcutaneous sodium salicylate iontophoresis and parenteral analgesics, favoring iontophoresis.[300] The observational studies were fairly small and described various sickle cell-related pain presentations and management approaches. The baseline characteristics and outcomes of these studies are described in the evidence table.[24,294,296,300-304,306]

In general, the quality of the available evidence was very low, so the expert panel determined that higher quality evidence with better precision should be derived from studies that evaluated chronic pain management in other settings. Such a body of evidence is larger and includes a wider scope of interventions and comparisons, which could lead to more useful recommendations for practitioners caring for people with SCD who have chronic pain. The panel and the methodology team appraised the quality of the guidelines for the management of chronic pain published by the American Pain Society in collaboration with the American Academy of Pain Medicine.[24] The quality of the guidelines was deemed acceptable, so the panel adapted selected recommendations applicable to people with SCD as shown below in the "Recommendations" section, and these are labeled accordingly.

Recommendations

1. Determine the cause and type of SCD-related chronic pain. This includes chronic pain with objective signs such as avascular necrosis (AVN) and leg ulcers, and chronic pain without objective signs due to neuroplasticity of the peripheral or central nervous system.
   (Consensus–Adapted)
2. Use a combination of the patient's response to treatment—including pain relief, side effects, and functional outcomes—to guide the long-term use of opioids.
   (Consensus–Adapted)
3. Encourage people to use deep tissue/deep pressure massage therapy, muscle relaxation therapy, and self-hypnosis as indicated.
   (Weak Recommendation, Low-Quality Evidence)
4. Use long- and short-acting opioids to manage chronic pain that is not relieved by nonopioids.
   (*Consensus–Adapted*)
5. Assess all people with SCD for chronic pain annually or more often as needed. This assessment should include descriptors of the pain; its severity on a numerical scale; its location; factors that precipitate or relieve it, including biopsychosocial factors; and its effect on the patient's mood, activity, employment, quality of life, and vital signs.
   (Consensus–Adapted)
6. Use a partnership agreement leading to a written, individualized treatment plan (to include risks, benefits, and side effects) with the patient if long-term opioids are indicated. The partnership agreement should list the patient's rights and responsibilities, and the treatment plan should list the type, amount, and route of administration of the opioid in question, including random drug urine testing.
   (Consensus–Adapted)
7. Appoint one physician or other clinician to write the biweekly to monthly prescriptions for long-term opioids. Refills without seeing the patient should be kept to a minimum, and people on chronic opioid therapy must be evaluated in person every 2–3 months.
   (Consensus–Adapted)
8. Document all encounters with a patient, including medical history, physical exam, diagnosis, plan of management, type and amount of opioids prescribed and their side effects, if any, and lab data as needed.
   (Consensus–Adapted)
9. Encourage people receiving opioids to increase their fluid intake, maintain dietary fiber intake per the current dietary fiber recommendations, and to use stool softeners and bowel stimulant laxatives such as senna and/or docusate as needed.
   (Consensus–Adapted)
10. Believe the patient's report of pain and optimize therapeutic outcomes to achieve adequate pain relief and improve the patient's quality of life.
    (Consensus–Adapted)
11. Refer patients for evaluation by a mental health professional such as a psychiatrist, social worker, or addiction specialist as needed.
    (Consensus–Adapted)
12. Assess all people for other types of non-SCD related chronic pain including postoperative pain, pain due to trauma, pain due to therapy, iatrogenic pain, and pain due to comorbid conditions.
    (Consensus–Adapted)

Avascular Necrosis

Background

Avascular necrosis (AVN, also known as aseptic necrosis, osteonecrosis, or ischemic necrosis) is bone death due to compromised blood supply. Necrosis can occur when capillaries are occluded by sickled erythrocytes at distal portions of a bone near a joint where hypoxia is maximal and collateral circulation is inadequate.[307] The hip joint is the most common site of AVN. Involvement of the shoulder and other joints is less common. Risk factors for AVN of the femoral head include SCD genotype, age, frequency of painful episodes, hemoglobin level, and α-gene deletion. The overall prevalence of AVN in SCD is about 10 percent, whereas in people with hemoglobin SS, it is about 50 percent by age 33.[308,309] People with HbSS and concomitant α-thalassemia are at particular risk.[308,309] The SCD genotypes that are associated with relatively mild anemia, such as HbSS-α-thalassemia and HbSβ^0-thalassemia, are at a particularly high risk to develop AVN at a younger age.[308,309]

AVN of the femoral head causes chronic severe pain and disability. The pain is generally worse on walking, relieved by rest, and may be accompanied by a moderate or severe limitation of motion when the patient bears weight on the affected extremity. About 40–80 percent of cases of AVN of the hips are bilateral and, hence, evaluation of patients with AVN should focus on both hips.[310]

The therapeutic approach to AVN depends on the stage of the disease. Ficat[311] proposed a four-stage radiographic classification of AVN of the hip based on plain radiography. MRI was not available at the time. Steinberg et al.[312] expanded the Ficat staging system into six stages using MRI data.[312,313] A report from the Comprehensive Sickle Cell Centers (CSCC) investigators defined an adaptation[287] from the Ficat and Steinberg systems that combines radiography, MRI, and bone scans. The adaptation is provided below in exhibit 8.

Exhibit 8. Stages of Avascular Necrosis

Stage	Radiographic Signs
EARLY: Stage 0. Preclinical	▪ None; marrow necrosis may be present histologically
EARLY: Stage I. Preradiographic	▪ None; abnormal MRI with marrow and bone necrosis
EARLY: Stage II. Before flattening of head or sequestrum formation	▪ Diffuse porosis, sclerosis, or cysts
TRANSITION	▪ Femoral head flattening ▪ Crescent sign
LATE: Stage III. Collapse	▪ Broken contour of head ▪ Sequestrum ▪ Joint space normal
LATE: Stage IV. Osteoarthritis	▪ Flattened contour ▪ Decreased joint space ▪ Collapse of head

Most orthopedists consider core decompression to be most beneficial for Ficat stage I and II of AVN of the hip.[310,314,315]

Key Question

KQ19. In people with SCD and AVN, what are the most effective management strategies to reduce pain and functional disability (e.g., analgesics, physical therapy, surgery, or transfusion therapy)?

Summary of the Evidence

The literature review yielded 1 RCT, 16 observational studies, and 16 case reports describing AVN and treatment outcomes. The overall quality of the evidence was low.

The RCT[316] was a randomized prospective multicenter study of 38 adults (81 percent of enrollees), which evaluated the safety of hip core decompression and compared the results of decompression and physical therapy with those of physical therapy alone for the treatment of osteonecrosis of the femoral head in people with all types of SCD. Results showed that physical therapy alone was as effective as hip core decompression followed by physical therapy in improving hip function. However, the evidence provided by this study is limited due to its small sample size and the high attrition rate.

The 16 observational studies and 16 case reports described AVN of various bones in the context of SCD. These studies included more than 350 people (mostly adults) and most commonly reported on people with SCD with AVN of the femoral head. All studies but one [317] were noncomparative, used hip arthroplasty, and reported a high success rate. A few studies[318,319] reported the use of standard symptomatic therapy with minimal success. In the comparative study,[317] the benefit of the surgical intervention (core decompression) in improving pain and evolution of necrotic lesions was significant relative to conservative management.

The methodological quality of the 16 observational studies was low (mainly observational noncontrolled studies with unclear enrollment criteria). The single comparative study had groups with similar baseline characteristics and outcome ascertainment methods. None of the studies reported adjustment of analyses for confounders.

Recommendations

1. Evaluate all children and adults with SCD and intermittent or chronic hip pain for AVN by history, physical exam, radiography, and MRI as needed.
   (Strong Recommendation, Low-Quality Evidence)
2. Treat AVN with analgesics and consult physical therapy and orthopedics for assessment and followup.
   (Strong Recommendation, High-Quality Evidence)
3. Refer symptomatic patients with advanced stages of AVN to an orthopedic surgeon and SCD specialist for evaluation and possible hip arthroplasty.
   (*Consensus–Panel Expertise*)

Leg Ulcers

Background

Leg ulcers are a common complication of SCD in general and SCA in particular. Leg ulceration was reported in all of the first four people with SCD described in the English literature.[320] Data from the Cooperative Study of Sickle Cell Disease (CSSCD) in the United States[321] found active leg ulcers at entry in 2.5 percent of 2,075

people aged 10 years or older and in none of 1,700 people less than 10 years old. Among those with active leg ulcers, about 22 percent were between the ages of 10 and 20.

Data on leg ulcers from the CSSCD[321] identified five factors which could affect the person's risk. Leg ulcers were more common in males and older people and less common in people with α-gene deletion, high total Hb level, and high levels of HbF.[322,323] Trauma, infection, and severe anemia may predispose people to ulcer formation. Studies showing a positive association between leg ulcers and the severity of hemolysis and priapism are disputed.[324-326] The ulcers occur most frequently on the medial or lateral surfaces of the ankles. Leg ulcers can range from mild and small to large and severe. Severity can be based on depth and duration. Osteomyelitis may complicate chronic leg ulcers, especially deeper ones. A bone scan or MRI and bone biopsy are used to assess this complication. Multidisciplinary teams including wound care specialists have been developed to provide support and consultation in the management of recurrent and recalcitrant leg ulcers.

Key Question

KQ20. In people with SCD and leg ulcers, what are the most effective therapies to accelerate ulcer healing (e.g., topical therapy, surgery, or antibiotics)?

Summary of the Evidence

Five RCTs, three observational studies, and a case series described various approaches to manage leg ulcers in people with SCD and evaluated topical and systemic agents. The methodological quality of the studies was fair, but the studies had small sample size, which led to imprecise estimates of treatment effect and weak inference. The overall quality of the supporting evidence was low to moderate.

The five RCTs included a total of 155 people and had followup periods of 8 weeks to 6 months. Four studies[327-330] compared different topical modalities, including arginylglycylaspartic acid (RGD) peptide; arginine butyrate; DuoDerm; solcoseryl; and an aerosolized preparation of neomycin, bacitracin, and polymyxin B to either standard care or placebo. One study[331] compared oral propionyl-L-carnitine to placebo. Propionyl-L-carnitine was not shown to have any significant differences in healing effect. Of the topical preparations, RGD peptide and the arginine butyrate/standard care combination showed a significant improvement in healing rates. The aerosol solution trial showed significant reduction in ulcer size for ulcers with a positive bacterial swab test. The studies also found severe intolerance to DuoDerm and good tolerance to solcoseryl without any significant differences in healing rates.

The three observational studies[332-334] enrolled more than 70 people and reported no difference in healing between natural honey and eusol dressing (sodium hypochlorite disinfectant); higher healing rate with oral zinc sulphate compared to placebo; and favorable results with hydrocolloid dressing (DuoDerm). The case series[335] reported improved healing after 6 weeks of treatment with subcutaneous heparin and human antithrombin concentrate. The quality of evidence of these observational data is low, thus limiting the ability to make inferences applicable to the general population.

Recommendations
1. Inspect the lower extremities during physical examination for active or healed ulcers, record their number, and measure their depth. ***(Weak Recommendation, Low-Quality Evidence)***
2. Treat leg ulcers in patients with SCD with initial standard therapy (i.e., debridement, wet to dry dressings, and topical agents). **(*Moderate Recommendation, Low-Quality Evidence*)**
3. Evaluate people with chronic recalcitrant deep leg ulcers for osteomyelitis. ***(Moderate Recommendation, Low-Quality Evidence)***
4. Evaluate possible etiologies of leg ulcers to include venous insufficiency and perform wound culture if infection is suspected or if the ulcers deteriorate. ***(Moderate Recommendation, Low-Quality Evidence)***
5. Treat with systemic or local antibiotics if leg ulcer site is suspicious for infection and wound culture is positive and organism susceptible. ***(Moderate Recommendation, Low-Quality Evidence)***
6. Consult or refer to a wound care specialist or multidisciplinary wound team for persistent or recalcitrant leg ulcers. **(*Consensus–Panel Expertise*)**

Pulmonary Hypertension

Background

Pulmonary hypertension (PH) is defined as an elevation of the resting mean pulmonary arterial pressure (≥25 mmHg) as determined by right heart catheterization (RHC).[43] There are several potential etiologies for elevation in mean pulmonary artery pressure in people with SCD. Chronic hemolytic anemias, including SCD, may result in pulmonary vascular changes leading to pulmonary arterial hypertension (PAH), and are placed in Group 1 of the current classification (https://www.nhlbi.nih.gov/health/health-topics/topics/pah/types.html).[44] This type of pulmonary hypertension may occur in up to 10 percent of those with SCA and accounts for 40 to 50 percent of cases of PH.[45,46,336] The second most common type of PH in SCD is pulmonary venous hypertension (PVH), assigned to Group 2 in the current classification, which is associated with an elevated pulmonary capillary wedge pressure of ≥15 mmHg.[43-47] This is often associated with left ventricular diastolic dysfunction.[48] PH also occurs in the setting of chronic lung disease, chronic thromboembolic disease, or can be due to unclear or multiple mechanisms (Groups 3, 4, and 5 of the classification, respectively). Because these circumstances may also be present in individuals with SCD, a thorough evaluation of mechanisms and comorbidities should be undertaken if PH is found.

Initial testing for PH has been done with an echocardiography assessment to estimate pulmonary artery pressure using tricuspid regurgitant jet velocity (TRV),[43,45-47] but diagnosis requires right heart catheterization and direct measurement of the pulmonary arterial pressure and vaso-reactivity of the vessels.[43,45,50,56,337] Transient elevation in TRV has been observed during acute vaso-occlusive episodes in individuals with SCD,[51] which may not reflect baseline values or present chronic PH.

The main symptoms of PH include shortness of breath during routine activity, such as climbing two flights of stairs; fatigue; lethargy; chest pain; palpitations; syncope; peripheral edema; and decreased appetite.[49] Careful history taking is needed to distinguish symptoms related to the anemia of SCD itself from the new onset of symptoms related to the development of PH.

Observational studies show an increase in all-cause mortality for adults with SCA with an elevated TRV by echocardiography,[47,57,61,338] although this association has not been found in children. In children and young adults with relatively normal renal function, only 25–30 percent of those with an elevated TRV may have an elevated pulmonary artery pressure measured by right heart catheterization.[46] Older adults with SCA and a high TRV are more likely to have an elevated pulmonary pressure, although 40 percent of those with a high TRV will have an elevated wedge pressure suggesting left heart disease. A commonly associated finding is renal insufficiency.[47,57,58] The Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy (walk-PHaSST) study was published outside of the range of the evidence review for these guidelines and thus was not included. This study enrolled 33 subjects with SCD and PH defined by an elevated TRV of ≥2.7 m/sec and a 6-minute walk distance (6MWD) of 150–500 meters.[47] RHC was required in the TRV ≥3.0 m/sec group; all subjects were randomized to sildenafil or placebo regardless of findings at RHC. This study was closed early due to an increase in serious adverse events associated with sildenafil use; estimation of results by futility analysis suggested no improvement in 6MWD would be demonstrated if the study continued. These data confirm earlier data that RHC is necessary to confirm the presence of PH and distinguish the mechanism of disease before considering therapy for PH. It is unknown if intervention for SCD (e.g., transfusion or hydroxyurea) would change the all-cause mortality associated with an elevated TRV.

Key Question

KQ21. In people with SCD and PH, what are the most effective therapies to reduce mortality (e.g., transfusion, hydroxyurea, and other pharmacological agents)?

Summary of the Evidence

Two RCTs, seven observational studies, and three case reports examined the management of PAH. No clear therapeutic benefit has been shown for any pharmacotherapy for PAH in people with all types of SCD, and the overall quality of the evidence on therapy was considered very low.

The two RCTs were reported in one paper, and enrolled 26 people, blinded patients and outcome assessors to the intervention assignment, and did not report any baseline imbalances or allocation concealment.[339] Both trials were stopped prematurely due to slow enrollment. The trials compared bosentan to placebo and showed no improvement in the 6MWD or levels of pulmonary hypertension.

The seven observational studies included more than 200 people and evaluated various aspects of PAH. Five studies examined various therapies, and two looked at mortality rates. Increased mortality was reported in all people with SCD[339-343] with true PAH (55 percent vs. 21 percent 10-year mortality respectively in all people with SCD with and without PAH).[61,338] The five small observational studies reported various levels of benefit from five different types of pharmacotherapy, but no consistent definition of PAH was used across these uncontrolled studies, making it difficult to compare results. The five therapies studied were bosentan, sildenafil, L-arginine, L-carnitine, and hydroxyurea. Both bosentan and sildenafil were reported to increase 6MWD.[339,340] L-arginine was reported to improve pulmonary arterial function, although this was a short-term benefit. Although results from a pilot study of sildenafil suggested improved exercise capacity in pulmonary hypertension, the study was stopped early due to safety concerns and the authors cautioned that additional studies on the safety of sildenafil in this patient population were needed.[341] L-carnitine was reported to improve cardiac diastolic function,[342] and hydroxyurea was reported to normalize elevated tricuspid regurgitant velocity (TRV), but this was not sustained long term.[343]

Recommendations
1. If people with SCD have symptoms or signs suggestive of PH, refer them for echocardiography. ***(Strong Recommendation; Moderate-Quality Evidence)***
2. For people with an elevated TRV ≥2.5 m/sec by echocardiography, consult a provider with expertise in pulmonary hypertension to guide further assessment and management, including right heart catheterization, and consideration of PH therapy. **(*Consensus–Panel Expertise*)**

Renal Complications

Background

Chronic kidney disease (CKD) is defined as either having a glomerular filtration rate (GFR) of <60 mL/min/1.73 mL for ≥3 months with or without kidney damage or having evidence of kidney damage for ≥3 months, with or without decreased GFR. Evidence of kidney damage includes pathologic abnormalities or markers of kidney damage (i.e., proteinuria) independent of cause. Kidney disease severity is classified into five stages according to the level of GFR (see exhibit 9 below).[344]

Exhibit 9. Stages of Kidney Disease by GFR Levels

Stage	GFR Parameters
Stage 1	▪ Kidney damage with normal or increased GFR (≥90 mL/min/1.73 m^2)
Stage 2	▪ Kidney damage with mildly decreased GFR (60–89 mL/min/1.73 m^2)
Stage 3	▪ Moderately decreased GFR (30–59 mL/min/1.73 m^2)
Stage 4	▪ Severely decreased GFR (15–29 mL/min/1.73 m^2)
Stage 5	▪ Kidney failure (ESRD); GFR <15 mL/min/1.73 m^2 or on dialysis

Source: Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2005 Jun;67(6):2089–100.[344]

An estimated 23 million Americans have CKD including 4–18 percent of people with SCD.[345] In one study, renal failure was seen in 4.2 percent of people with SCA.[346] In this study, 68 percent of people had proteinuria (defined as any abnormal urinary protein), 40 percent had nephrotic syndrome, and 33 percent had hypertension (HTN) prior to developing renal failure.[346] In another study, Falk et al.[347] evaluated all people with SCD, including both children and adults, followed at the University of North Carolina and Duke University; 26 percent had proteinuria on urine dipstick. Finally, in a study of 300 adults with SCD, the prevalence of any albuminuria in people with SCA was 68 percent, and the prevalence in other genotypes was 32 percent.[348]

Identification of early renal disease in people with SCD is important, as these individuals hypersecrete creatinine through the proximal tubules, thus masking significant renal impairment before the serum creatinine rises.[345] Microalbuminuria is defined as urinary albumin excretion greater than 30 mg albumin per gram urine creatinine in two of three spot urine specimens or 30–299 mg albumin in 24-hour urine collection. Macroalbuminuria (proteinuria) is defined as urinary albumin excretion of 300–3,500 mg albumin in 24-hour urine collection.[344] Microalbuminuria is most often the first manifestation of CKD in SCD. One study showed a prevalence of 16

percent in affected children,[349] and another study showed a prevalence of 32.9 percent in adults with SCD.[350] Spot urine protein/creatinine ratio has not been validated in SCD because creatinine is hyperexcreted.

The most common renal complication in people with SCD is hyposthenuria, or the inability to concentrate the urine, which is progressive with age.[351] This is due to the loss of deep juxtamedullary nephrons. Frequent urination is common in people with SCD and is usually due to hyposthenuria. Because of their hyposthenuria, individuals with SCD are also at higher risk for intravascular volume depletion, as they cannot respond to decreased oral fluid intake by concentrating their urine. In addition, hyposthenuria also causes enuresis, which is prevalent among individuals with SCA, with up to 42 percent of children ages 6 to 8 and 9 percent of adults ages 18 to 20 experiencing this complication.[352]

Renal papillary necrosis, which often causes hematuria, is thought to be due to medullary infarction from obstruction of the vessels supplying the vasa recta. The prevalence of renal papillary necrosis was found to be as high as 23 percent in asymptomatic people with SCA undergoing urography.[353] Proteinuria due to glomerular injury is also common, but both microalbuminuria and macroalbuminuria are typically asymptomatic. Other early manifestations that should lead providers to investigate people for renal disease include HTN and gout. Joint pain due to gout can often be mistaken for vaso-occlusive episode pain. Diagnosis and management of gout in individuals with SCD is the same as in other populations.

There have not been any studies looking at the utility of renal biopsy in individuals with SCD. One study that examined 18 renal biopsy specimens found four histopathologic variants: focal segmental glomerulosclerosis (FSGS) (39 percent), membranoproliferative glomerulonephritis (28 percent), thrombotic microantigopathy glomerulopathy (17 percent), and specific sickle cell disease glomerulopathy (17 percent).[354] The authors of this study note that the long-term outcomes were not different according to the histologic lesions that were identified, with 50 percent of cases having chronic renal failure after a mean followup of 28 months. The decision to perform renal biopsy should be individualized for each patient.

Key Question

KQ22. In people with SCD and CKD, what are the interventions (including pharmacotherapy, dialysis, and renal transplant) that slow the deterioration of renal function, prevent the development of end-stage renal disease, and reduce mortality?

Summary of the Evidence

One RCT, 5 observational studies, and 10 case reports examined the management of several acute and chronic renal complications of SCD. Although numerous SCD-related renal abnormalities have been described in the literature (e.g., hyposthenuria, hematuria, impaired urinary potassium excretion and acidification, tubular and glomerular dysfunction, infection, medullary carcinoma, and acute necrosis and renal failure), most were without effective therapeutic approaches or clear prognosis. The overall quality of the evidence was low.

A double-blind, placebo-controlled randomized trial of 22 normotensive adults with SCA and persistent microalbuminuria found that captopril (25 mg/day) for 6 months significantly reduced albuminuria.[75]

One observational study included more than 300 individuals with SCD and evaluated them for renal dysfunction.[347] Ten people were found to have proteinuria (urinary protein, ≥0.5 g per day) and serum creatinine concentrations of <2.0 mg/dL. They underwent treatment with enalapril for 2 weeks and had a decrease in proteinuria with a mean decrement of 57 percent below baseline. An observational study of 191 patients with SS

with a mean followup of 2.19 years demonstrated that microalbumin excretion normalized in 44 percent of patients treated with hydroxyurea and 56 percent of patients treated with ACEI.[355]

One observational study looked at the prevalence of microalbuminuria in children and found it in 19 of 120 children with SCD.[40]

Two observational studies enrolled 91 people and evaluated the role of renal transplant in end-stage renal disease. The larger study was a retrospective study comparing patient and renal allograft outcomes for individuals with SCD (*n*=82) compared to those without SCD (*n*=22, 565) who were transplanted and compared to those with SCD who did not undergo transplant.[170] The study reported incidence rates of 26 percent and 24 percent for delayed predischarge and acute graft rejection, respectively. There was a trend towards improved survival in the transplant group compared to waitlisted individuals. The second smaller study reported a survival rate of 89 percent in the recipient of the graft, but the study did not have a comparison arm.[171]

Recommendations
1. If microalbuminuria or macroalbuminuria is identified, order a 24-hour urine test for protein. ***(Consensus–Panel Expertise)***
2. Refer people with proteinuria (>300 mg/24 hours) to a nephrologist for further evaluation. **(*Strong Recommendation, Low-Quality Evidence*)**
3. For adults with microalbuminuria without other apparent cause, initiate ACE inhibitor therapy. **(*Moderate Recommendation, Moderate-Quality Evidence*)**
4. For adults with proteinuria without other apparent cause, initiate ACE inhibitor therapy. ***(Moderate Recommendation, Low-Quality Evidence)***
5. For children with microalbuminuria or proteinuria, consult a nephrologist. **(*Consensus–Panel Expertise*)**
6. Consider patients with SCD with modest elevations of serum creatinine (>0.7 mg/dL in children, >1.0 mg/dL in adults) to have renal impairment and refer to a nephrologist for further evaluation. ***(Consensus–Panel Expertise)***
7. Give ACE inhibitor therapy for renal complications when indicated even in the presence of normal blood pressure. ***(Moderate Recommendation, Low-Quality Evidence)***
8. Renal replacement therapy (e.g. hemodialysis, peritoneal dialysis, and renal transplantation) should be used in people with SCD if needed. ***(Strong Recommendation, Low-Quality Evidence)***

Stuttering/Recurrent Priapism

Background

Stuttering priapism is the occurrence of multiple self-limited episodes of unwanted, often painful erections lasting <4 hours.[172] Priapism, including stuttering priapism, is common, affecting 35 percent of boys and men with SCD.[173] Stuttering priapism may lead to a major episode of greater than 4 hours' duration and may adversely affect quality of life and lead to impotence.[172,173] Treatment with chronic hormonal therapy, transfusion therapy, and other treatments may reduce or eliminate these episodes; however, there are no data demonstrating improvement in functional outcomes. Therefore, the decision to treat must be balanced against the side effects of interventions, which can include decreased libido.

Key Question

KQ23. In people with SCD and stuttering priapism, what is the relative efficacy of the available treatments (chronic hormonal therapy, chronic transfusion therapy, alpha-adrenergic agents, PDE-5 esterase inhibitors, and hydroxyurea) on recurrence of priapism and sexual functional outcomes?

Summary of the Evidence

One RCT, 7 observational studies, and 39 case reports described priapism in the setting of SCD. Of these, only two studies evaluated the chronic management of priapism: the RCT and one observational study. Both studies were small, thus making the overall quality of the evidence very low.

The RCT noted cessation of bouts of priapism with stilbestrol during a 2-week cross-over phase[174] in nine men with SCD. The observational study involved 35 participants and examined the effects of finasteride on recurrences of priapism.[175] It reported a decrease in the number of priapic episodes and increased length of time between episodes.

There are no data demonstrating improvement in functional outcomes, so the potential benefits must be balanced against the side effects of interventions, including decreased sexual function. However, even in the absence of RCTs demonstrating long-term benefit, individualized therapy devised in consultation with a urologist may be considered for symptomatic relief.

Recommendations

1. In men and boys with SCD and recurrent or stuttering priapism, offer evaluation and treatment in consultation with a sickle cell disease specialist and a urologist, especially when episodes increase in severity or frequency. ***(Weak Recommendation, Low-Quality Evidence)***

Ophthalmologic Complications

Background

Chronic ophthalmological complications of SCD include proliferative sickle retinopathy (PSR) and vitreous hemorrhage. They occur in up to 50 percent of individuals with SCD, and are found more frequently in persons with HbSC disease and HbSS.[356,357] The presence of PSR is associated with significant visual loss,[83] and its peak prevalence in HbSC disease occurs earlier than in HbSS (i.e., about ages 15 to 24 in men and ages 20 to 39 in women).[358]

Ischemia due to vaso-occlusion of retinal arterioles causes the release of vascular tissue factors that stimulate angiogenesis. The neovascular tissue is predisposed to hemorrhage and vitreoretinal traction forces. Although these preretinal neovascular formations are bright red when viable, they appear white following auto-infarction, when they resemble and are called "sea fans."

PSR is characterized by five stages,[359] beginning with peripheral arterial occlusion and vascular remodeling (Stages I–II), subsequent neovascularization and sea fan formation (Stage III), and ultimately vitreous hemorrhage (Stage IV) and retinal detachment (Stage V) (exhibit 10). All can be detected by using direct and indirect ophthalmoscopy, slit lamp biomicroscopy, and fluorescein angiography.

Exhibit 10. Stages of Proliferative Sickle Retinopathy (PSR)

Stages of PSR	Retinal Characteristics
Stages I–II	▪ Peripheral arterial occlusion and vascular remodeling
Stage III	▪ Neovascularization and sea fan formation
Stage IV	▪ Vitreous hemorrhage
Stage V	▪ Retinal detachment

Stages IV and V appear to be more common in individuals with HbSC disease.

Vitreous hemorrhage is a severe complication of PSR[360] caused by mechanical stress from trauma or by normal vitreous movement on the delicate neovascular formation growing from the retina into the vitreous chamber.

Spontaneous regression of PSR may occur in about 32 percent of all affected eyes, and lack of progression of sea fans may occur in some people.[84] PSR is commonly managed with laser photocoagulation after consultation with an ophthalmologist. Surgical intervention, including vitrectomy to treat severe vitreous hemorrhage, may be indicated in some people.

Key Question

KQ24. In people with SCD and chronic ophthalmic complications (proliferative sickle retinopathy or vitreous hemorrhage), what are the most effective management strategies (surgery, laser therapy, or conservative management) to improve and preserve vision?

Summary of the Evidence

Six studies (three RCTs, three observational) and 28 case reports described sickle cell-related acute or chronic ocular complications. The overall quality of evidence for laser photocoagulation was considered high, while the evidence for surgery in people refractory to medical management was considered low.

The three RCTs included 248 people (with likely overlapping populations, the majority of whom were adults) and assessed PSR and the benefit of laser photocoagulation compared to observation.[86,87,361] One study reported more than a 50 percent decrease in the rates of loss of visual acuity, and another found that laser photocoagulation was helpful in inducing lesion regression but only in people younger than 25 years of age. Two of the RCTs reported a significant decrease in the incidence of vitreous hemorrhage, from 45 percent to 4 percent. None of the trials had any form of masking, allocation concealment, or differences in baseline characteristics of the participants.

The three observational studies included more than 140 people, mostly adults, and assessed the roles of laser photocoagulation and surgery in treating sickle cell-related retinopathies.[362-364] One study found improvement in 83 percent of eyes that received surgery (pars plana vitrectomy) compared to 20 percent spontaneous improvement in the observation arm. One uncontrolled study found lesion regression in 79 percent of treated eyes, with vitreous hemorrhage occurring in only one patient. The last study found benefit from photocoagulation only in "class B" retinopathy (elevated sea fan with hemorrhage). Complications occurred in 13 percent of the untreated people, but not in any treated ones.

Recommendations

1. Refer persons of all ages with PSR to an ophthalmologist for evaluation and possible laser photocoagulation therapy. ***(Strong Recommendation, Moderate-Quality Evidence)***
2. Refer children and adults with vitreoretinal complications of PSR refractory to medical treatment for evaluation and possible vitrectomy. ***(Strong Recommendation, Low-Quality Evidence)***