Sickle Cell Disease

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Case Presentation

A 20-year-old African American woman presents to an adult medical practice for a new patient appointment. She has just recently started classes at the local community college where she is a freshman living in the dorms. In providing her health history, she reports that she has a diagnosis of hemoglobin SS (HbSS) sickle cell disease (SCD). She is single and lives with a roommate.

At the age of 10, she underwent a transcranial Doppler and has since been receiving regular blood transfusions, which she was told would help reduce the risk of having a stroke. Because of the transfusions, she was also prescribed a medication to help minimize the buildup of iron in her blood, although she reports that it tastes bad and she frequently skips doses. Because of how it has helped her in the past, she would like to continue on transfusion therapy. However, she has concerns about how to arrange for this therapy with her specialist who is now located remotely and whether the local blood supply will be a match for her. She has heard about a medicine called hydroxyurea that might be an option for her now. However, she has also heard that she should not get pregnant while taking this medicine. Though she does not currently desire pregnancy, she would like to be in a relationship and to understand the risks associated with hydroxyurea and sexual activity. Moreover, she would like to know what her options are for contraceptive therapy.

She also confirms that at 3 years of age she had to have her spleen removed. As far back as she can remember, she had frequent hospitalizations, up to 5 times a year, and twice she was told that she had a "chest crisis." This pattern continued until she started her transfusions at age 10, and then things seemed to get better, until she started her menses at around age 13. With her menstrual cycles, she has an increase in her pain, and she also has developed pain in both of her hips that she was told was because of her sickle cell disease. Her pain is bad enough that at times she requires doses of opioid pain medications, and about 3–4 times each year she has to go to the hospital for a brief stay to help control her

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symptoms. She has been told to avoid medications such as ibuprofen because it could be bad for her kidneys. Though the adult medical practice is located in a major metropolitan area and she is excited to be attending college, she has expressed anxiety about the move and her medical care.

Case Discussion

This case highlights a combination of complex yet common medical issues that can be present in young adults affected by sickle cell disease (SCD). Though significant advances have been made in strategies to screen for, diagnose, and treat the complications of SCD, resulting in prolongation of life expectancy in affected individuals, these advances have not yet been sufficient to reduce the cumulative burden of acute and chronic complications in the adult population. Several studies have described that both hospitalization and mortality rates increase in individuals with SCD at or after the time of transition from pediatric-oriented to adult-oriented care [1–4], and there is evidence that beneficial therapies are underutilized in this age group [4]. In order to improve clinical outcomes in transition age youth affected by SCD, strategies to overcome these gaps are needed.

A combination of medical, socioeconomic, and provider-related factors combine to pose unique challenges for adolescents and young adults living with sickle cell disease, but the specific contributors to the increased morbidity and mortality in transition age individuals have not yet been fully clarified. In addition to biological worsening of the disease, patient factors such as multiple concurrent life transitions and provider factors such as a lack of familiarity with SCD in adult non-hematology and even specialty care settings are worth considering. As advances in therapy continue to evolve, it is imperative that the adult health care workforce, and in particular the adult primary care workforce, be adequately prepared to anticipate needs and coordinate care for these individuals. This chapter will focus on major themes that highlight the unique needs for young adults with SCD transitioning into adult care.

This case discussion focuses on a young woman who is furthering her education by attending community college for the first time at age 20. Assuming that she has completed her secondary education, it is notable that she is slightly older than the typical college-age freshman. Children diagnosed with SCD are at risk for frequent acute sickle cell crises requiring intensive medical intervention that may begin in infancy. As they age and schooling begins, these episodes can result in missed days of school that accumulate over time. Additionally, progressive vascular changes in the brain can lead to stroke, estimated to affect up to 10 % of children with sickle cell anemia (HbSS or Sβ[beta]^{0}thalassemia), with onset beginning in the first few years of life [5]. Importantly, however, this underlying process may manifest as silent cerebral infarction, with a clinical presentation that may be subtle but that can affect brain function nonetheless. For individuals who have already had or who are at an increased risk of neurological complications, there is a significant risk of new events, progression, and cumulative cognitive and physical impairment unless long-term treatment to address the underlying SCD pathophysiology is undertaken.

Strategies have now been outlined to help not only identify the risk of strokes but also to reduce the risk of first and recurrent strokes, as will be discussed in more detail in a later section of this chapter. This young woman has received evidence-based strategies including screening with transcranial Doppler to identify an increased risk of stroke and then use of transfusion therapy to reduce this risk. Although transfusion therapy is increasingly initiated in children before they actually develop significant neurological complications, and though most individuals are aware of a history of overt stroke, it is not known from this case study if the patient has sustained any silent neurological injury. As such, neuropsychological testing is indicated to provide insight into specific cognitive abilities and potential confounding psychological factors that affect cognition, such as depression. If she has evidence

of cognitive challenges or difficulty adjusting socially given the age difference with her school peers, vocational–educational counseling with specialized educational planning might be helpful. An important challenge in this case is to ensure that the patient can continue to receive transfusion therapy to reduce the risk of further neurologic damage. If resources to continue this locally are unavailable or if she does not want to continue transfusions, then other therapeutic options such as use of hydroxyurea (HU) should be considered. There is no data to support the benefit of using HU together with chronic transfusion therapy, since HU affects only the endogenous red blood cells, which are replaced by transfused red blood cells in an individual receiving chronic transfusion therapy. If transfusion therapy is continued, then the use of medication to reduce iron overload will also need to be addressed, along with the barriers she has identified in medication adherence.

HU therapy in general has been proven to be of significant benefit in individuals with sickle cell anemia (HbSS or Sβ[beta]^{0}thalassemia), reducing pain episodes [6], morbidity and mortality [7, 8]. The National Heart, Lung, and Blood Institute (NHLBI) has recently published guidelines outlining the use of HU therapy for individuals with sickle cell disease [9]. HU therapy is recommended for adults with sickle cell anemia (HbSS disease) who meet any of the following conditions:

- 3 or more acute pain episodes in a year
- pain that is severe enough to impair quality of life or daily functioning
- recurrent severe episodes of acute chest syndrome
- severe anemia

There are no studies to demonstrate whether HU can be safely substituted for transfusion therapy for those individuals who have had a stroke. However, a recent study demonstrated that using HU was as good as transfusion therapy for the prevention of a first stroke in individuals with an abnormal transcranial Doppler, similar to the young woman in this case [10].

There are several practical points when considering HU therapy. It is critical to educate patients who are being considered for HU therapy on the indications for and goals of therapy as well as the need for long-term monitoring for complications of therapy, including low white blood cell (WBC) and platelet counts. Monitoring includes baseline assessment of a complete blood count (CBC) including differential, reticulocyte count, fetal hemoglobin measurement, kidney and liver function assessment, as well as pregnancy testing for women [11], followed by monthly assessments during dose adjustments and every 2–3 month assessments when stable. Dosages may need to be adjusted for renal dysfunction, not uncommon in adults with a history of SCD, and should be titrated to threshold levels of both platelets and neutrophil counts. Therapy can be temporarily held if needed for recovery of abnormally low blood cell parameters, as described in the NHLBI guidelines [11]. A systematic review of adherence of predominately pediatric patients with medications used in the treatment of sickle cell disease, including HU therapy, indicated that HU compliance was much higher in the context of monitoring as a part of a clinical drug trial (74–94 %); adherence in studies that did not include intensive monitoring as part of a clinical trial were much lower (49–85 %) [12]. For young adults, many of whom are on their own for the first time and experiencing other new life changes, adherence may be even more challenging. This may not be the case when treatment is directed at improving symptoms affecting quality of life in the short-term, such as pain. However, among the young adult population, preventing longer term complications of the disease may not seem as compelling of a reason to take medication requiring close monitoring. Despite these challenges, HU therapy can be prescribed and managed in primary care settings, preferably in partnership with an adult hematology specialist. Given the potential risks of HU therapy, collaborative decision-making with SCD patients, especially those of transition age, is critical initially and should be followed by adherence counseling at each office visit. Partnership with pharmacists to assist in this counseling can provide added support.

Another consideration is the impact of HU therapy on reproductive decision-making. Young adults are in a phase of life where entering into intimate relationships and starting families may be high priorities. Men and women are advised against pregnancy when taking HU as it is unclear if there are adverse effects on the fetus. NHLBI guidelines suggest discontinuing HU therapy if women become pregnant or in women who are breastfeeding [9]. The young woman in the case should be counseled about this and other potential risks to her health with pregnancy [12]. Contraceptive options should be offered if she expresses a desire to avoid pregnancy. NHLBI guidelines note that all forms of contraception can be considered, including estrogen-containing contraceptives, as the benefits generally outweigh risks. However, if there is a history of stroke or other thrombosis, this particular form of contraception should be avoided.

If the young woman in this case prefers to continue with transfusion therapy to reduce her risk of stroke, resources to support this therapy should be explored, including collaboration or at least consultation with a sickle cell provider. The NHBLI guidelines provide a consensus protocol for monitoring transfusion therapy, which generally entails transfusion of 1–2 units of packed red blood cells (PRBCs) provided at regular intervals, usually monthly, based on hemoglobin values and intermittent monitoring of HbS levels in the blood. As outlined in the NHLBI guidelines, minor antigen-matched blood is preferred to avoid the development of alloantibodies that could preclude future transfusions. Primary care providers may play a key role in monitoring for evidence of iron overload and for toxicities from iron chelation therapy.

Young adults with chronic conditions often have hesitation at the thought of transferring care from a pediatric specialty setting to primary care, for fear that their primary care provider (PCP) may not be as willing or able to care for them due to a lack of familiarity with the condition. Surveys of providers support there are variable levels of comfort in dealing with sickle cell disease [13]. This may be especially true for individuals with less prevalent and lifelong medical conditions such as SCD, where care is often dependent upon an ongoing relationship with a specialist. Stigmatization related to the pain issues so interwoven with SCD is also a concern. In this case, with the requirement for frequent blood transfusions and a diagnosis of one of the most severe forms of SCD, coordination of care with a hematology specialist is crucial. Likewise, while guidelines now exist for primary care management of HU therapy [9], initiation in most settings still involves coordination with hematology. Over time, coordination may also need to occur with other adult subspecialists as chronic medical conditions arise as described in later sections of this chapter. To capitalize on the gains that have been made in SCD survival, it is prudent for adults with SCD to have a primary care medical home where routine health maintenance and general medical care can be provided and care coordination can occur. Support for accessing primary care and for care coordination within the medical home through community health workers or patient navigators has been helpful in SCD care [14].

Overview of Sickle Cell Disease

Definition and Epidemiology

Though exact numbers are not known, it is estimated that SCD affects anywhere from 70,000 to 140,000 individuals in the United States [11, 14–16]. SCD is a group of blood disorders characterized by the production of hemoglobin S (HbS) due to a point mutation in the hemoglobin β(beta)-globin chain gene. Newborn infants are born producing fetal hemoglobin (HbF), though within 6 months of life this transitions to production of normal adult hemoglobin (HbA). For infants with sickle cell disease, HbS is produced instead of HbA. Individuals with the sickle mutation in both β(beta)-globin genes (HbSS) or those who have 1 gene with the sickle mutation and 1 which does not produce any HbA (HbSβ [beta]^{0}thalassemia) have the most severe forms of the disease—often lumped together and called "sickle cell anemia." [10, 17]. Other individuals

have one β(beta)-globin gene with a sickle mutation and the other with a mutation producing another abnormal hemoglobin (e.g., HbC) or underproducing HbA (i.e., β[beta]$^{+}$thalassemia). The resulting conditions, HbSC and HbS β(beta)$^{+}$thalassemia, are generally milder with less severe anemia. The presence of 1 sickle gene and 1 normal hemoglobin gene results in sickle cell trait, which does not cause any form of sickle cell disease or hematological manifestations. In this discussion, we will focus on SCD. SCD disproportionately affects individuals of African or Mediterranean descent, but is found in Hispanic populations and less commonly among Caucasians as well. Approximately 1 in 2474 live births in the United States are of children diagnosed with SCD (HbSS and HbSC) [2, 18]. It is important to remember, however, that worldwide population shifts and demographic migration patterns can affect local prevalence.

Throughout much of the twentieth century, SCD was considered a disease of childhood, with high infant mortality rates and few children living into adulthood. However, the average life expectancy of individuals with SCD has increased over the last quarter century. A prospective cohort study across multiple US institutions from 1978 to 1988 indicates that the average life expectancy of those diagnosed with sickle cell anemia was 42 years for males and 48 years for females, 25–30 years shorter than African Americans not affected by SCD [17]. For those diagnosed with HbSC disease, the average life expectancy was 60 years for males and 68 years for females. A prospective cohort study of newborns affected by SCD published in 2010 revealed that almost 94 % of children affected by the most severe forms of SCD (HbSS and HbSβ[beta]^{0}) lived to 18 years of age, while almost 99 % of those affected by HbSC and HbSβ(beta)$^{+}$ lived to age 18. The authors note that in this most recent analysis of the cohort, the highest mortality rate now occurs in individuals over the age of 18 years [16]. Cohort data from a 40-year longitudinal study suggest a projected average life expectancy of 53 years for those with HbSS if born after 1975—a 16-year improvement over those born before that date [19], though still significantly shorter than African Americans without SCD.

Pathophysiology and Natural History

The abnormal hemoglobin that is produced in individuals affected by SCD causes reversible deformation of red blood cells ("sickling") due to polymerization of the hemoglobin molecules within the cell after oxygen is released. This phenomenon causes the red blood cells to sustain membrane damage that promotes adhesion to microvascular endothelium, even when unsickled, leading to vasoocclusion, which can in turn lead to disruption or complete blockage of normal blood flow to tissues and organs [2]. Sickled red blood cells are also fragile and may easily hemolyze, severely reducing their lifespan and producing a chronic hemolytic anemia. This ongoing adhesion to vascular endothelium, toxic effects of hemoglobin and iron released from lysed red blood cells, and ischemia created by intermittent vasoocclusion result in a continuous cascade of inflammation, activation of white blood cells, platelets, and endothelial cells through complex biochemical processes, leading to progressive vascular damage. Over time, cumulative vascular and end organ damage can lead to secondary comorbidities and, ultimately, premature death. Relatively abrupt, more extensive vasoocclusion of the microvasculature in a given area can occur episodically, resulting in the characteristic sickle cell "pain crisis" and other acute complications such as acute chest syndrome.

The only known cure for SCD is a bone marrow transplant, though this option is limited by availability of matched donors, and the optimal approach in adults is still under investigation. Advances in diagnosis and therapy have led to an increasing range of options to help prevent complications and reduce morbidity. These advances have also been important factors in

increasing survival rates. Important milestones have included the use of prophylactic penicillin in children to reduce morbidity and mortality from life-threatening infections, the introduction of transcranial Doppler ultrasounds to predict stroke risk, the use of blood transfusion as a therapeutic measure, iron chelation therapy to reduce morbidity from iron overload, and the introduction of oral HU therapy to improve outcomes. The NHLBI published guidelines in 2014 that detail the use of most of these therapies, based on a review of available highest level evidence [11].

Common Clinical Issues for Adults with Sickle Cell Disease

SCD is a lifelong medical condition, the clinical manifestations of which begin shortly after birth as protective levels of fetal hemoglobin decline. Infants and young children present with acute complications of SCD in an episodic fashion. However, as individuals age, these episodic presentations lead to cumulative damage to the organ systems most commonly affected by the vascular pathology of SCD, including the brain, lungs, and kidneys. In addition to treating acute complications such as pain crises and acute chest syndrome, chronic organ system disease must be managed just as it would be for those individuals without SCD. Further, strategies to manage the symptoms of acute episodes of pain may need to be altered or adjusted as a result of accumulated chronic organ damage. Because of the advancing complexity of disease over time, a multidisciplinary team approach and involvement of multiple specialists involved in care decisions becomes increasingly important over time. Notably, the role of the adult primary care provider, particularly as pertains to addressing adult preventive care recommendations, is central to the coordination of this care. This section will review several of the most prevalent issues observed among the adolescent and young adult population of individuals living with SCD.

Chronic Pain

Pain is a hallmark of SCD and a symptom that significantly impacts quality of life. It is among the most recognizable symptoms associated with SCD. While certainly acute pain episodes are a classic presentation, pain is listed intentionally here as a common chronic condition to highlight the variety of pain presentations that can be seen in SCD from childhood into adulthood. Specifically, the pain pattern experienced in infants and children can evolve into a chronic pain syndrome by the time an individual reaches adulthood as cumulative organ damage occurs. Complications such as avascular necrosis, arthritis, chronic skin ulceration, peripheral neuropathy, or organ infarction often result in chronic pain conditions that can underlie acute pain episodes. Both frequency and severity of pain have been associated with mortality [17]. Management plans for pain that were established with pediatric medical providers are at risk of being interrupted during the transition period into young adulthood and may require modification throughout adulthood to optimize pain management.

While HU therapy can reduce the frequency of acute complications and hospitalizations, it is not indicated for the treatment of chronic pain. Patients must often rely on opioid pain medications that are administered in an acute care setting and need help in managing their pain regimens upon discharge to an outpatient setting. Use of opioid analgesics can lead to frustration in both patients and providers, with patients too often labeled as drug seeking and providers concerned about addiction and abuse while challenged by the difficulty of accurate pain assessment [20]. It is necessary to acknowledge both perspectives and the important role of trust in a treatment relationship, as reliance on opioids can erode that trust [21]. While opioid pain medications are commonly used, adjunctive therapies such as nonsteroidal anti-inflammatory therapies, neuropathic pain regimens, and other medications and treatment approaches indicated for chronic pain should also be considered. As

with other chronic pain syndromes, addressing the emotional toll and distress associated with living with a chronic disease are paramount. This often requires a multidisciplinary team.

Approaches utilized in the management of other chronic pain syndromes should be considered in individuals with SCD. In addition to the aforementioned strategies, these include focusing on functional goals, use of pain treatment agreements, provision of care with a medical home approach to avoid multiple prescribers of pain medications, and considering and addressing causes of pain other than SCD. There has been a growing focus in the literature about the role of supporting self-efficacy and self-management [21–23], although very few interventions have been described or tested to clarify their role in treatment. Much can be learned from patients themselves. For example, 1 study highlighted differences in pain management strategies utilized by those with lower hospital use compared to those with higher hospital use [20]. Specifically, helpful patient strategies included increasing knowledge of the disease process, maintaining a stable provider relationship, engaging in a provider–patient relationship that is viewed as a partnership, documenting evidence of symptoms, use of adjunctive modalities such as heat or massage, improving nutrition and hydration, and exercise.

Pulmonary Issues

Acute chest syndrome is a potentially life-threatening event that occurs when acute vasoocclusion occurs in the microvasculature of the lung, with resulting capillary leak and ischemia. Preexisting asthma can worsen outcomes for pulmonary complications, and asthma has been described itself as being a predictor of mortality [2]. Over time, repeated damage to the pulmonary microvasculature can result in pulmonary hypertension (PH), even in the absence of a history of acute chest syndrome. The prevalence of PH in individuals with SCD has been estimated at around 6–11 % [24]. The American Thoracic Society (ATS) has set forth guidelines to help delineate both the diagnostic approach to and management of PH in sickle cell disease, including the requirement of right heart catheterization to make an accurate diagnosis of PH in individuals with SCD [24]. Key points of the published guidelines include assessment of cardiopulmonary status with careful history taking, physical examination, and testing such as echocardiography. An elevated tricuspid regurgitant jet velocity (TRV) on echocardiogram is associated with an increased risk of early mortality, even in the absence of pulmonary hypertension. The ATS guidelines recommend the initiation of HU therapy for individuals with this finding [25], although there is no direct evidence that this intervention reduces mortality. Echocardiography to assess tricuspid regurgitant jet velocity is recommended, with referral to a PH specialist if TRV > 2.5 m/s is detected. For the primary care provider focused on preventive health, it is critical to assess smoking status, treat nicotine dependence, and ensure that appropriate preventive measures are taken to reduce overlapping pulmonary morbidity from non-SCD causes, such as asthma or infection with influenza virus or pneumococcal infection. The Advisory Committee on Immunization Practices (ACIP) regularly updates recommendations for vaccinations for adults without splenic function, which includes individuals with HbSS/Sβ(beta)^{0}thalassemia [25].

Renal Issues

The kidney is a target organ affected by many vascular diseases including SCD. The kidney is highly metabolically active and the local environment of the kidney may predispose this organ system in particular to red cell adhesion, endothelial activation, intermittent ischemia, and reperfusion injury [26], resulting in a cycle of worsening blood flow to the kidney and glomeruli. This can initially result in hyperfiltration of the kidneys and over time lead to glomerulopathies. Proteinuria in the form of albuminuria is commonly the clinical manifestation of chronic SCD kidney damage, and hypertension can also result. In youth under the age of 21 years, the

prevalence of albuminuria has been estimated to be as much as 26 % [26], but in older adults prevalence increases. As with other conditions that cause protein-losing nephropathies, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are recommended when proteinuria is present [26]. Additionally, it is important for hypertension to be appropriately managed, as this can lead to worsening renal function over time. Management principles are similar to the general population with hypertension, though care should be taken to avoid dehydration due to diuretic medications. It is possible the HU therapy may provide renal protective benefits in SCD [26], but data are lacking and further research is needed.

Brain-Related Issues

In the brain, cerebral infarcts may lead not only to clinically symptomatic strokes but small silent infarcts as well. These silent infarcts can lead to progressive cognitive decline and pose educational challenges for children. One of the major therapeutic advances of the last few decades has been the ability to predict risk of strokes in children using transcranial Doppler (TCD) imaging, permitting an opportunity for primary prevention of strokes [27]. It is now recommended that children with sickle cell anemia (HbSS disease) begin screening for stroke using TCD at the age of 2 years and continue annual screening until the age of 16 years [11]. When evidence of abnormally elevated transcranial velocities are found, referral to a specialist for consideration and initiation of red blood cell transfusion therapy should be made [11]. This is largely based on clinical trials that demonstrated significant reductions in stroke risk in individuals receiving regular transfusion therapy compared to no transfusion therapy [27, 28]. For prevention of strokes, chronic red blood cell transfusion therapy, with the goal of reducing the percentage of HbS relative to normal hemoglobin, has become the standard treatment [5]. The introduction of HU therapy, which increases the proportion of fetal hemoglobin in the blood, has been shown to be an alternative strategy to reduce the risk of some SCD complications [6]. The Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) randomized non-inferiority trial evaluated HU as an alternative therapy for recurrent (secondary) stroke prevention. The trial found that while the incidence of recurrent strokes was similar for HU therapy versus chronic transfusion, HU did not confer any advantage in reducing the main complication of chronic RBC transfusion therapy, which is iron overload [29]. However, a primary prevention study comparing continued chronic transfusion therapy to the use of HU for children with an abnormal transcranial Doppler recently demonstrated that HU is non-inferior to chronic transfusion therapy [10]. Thus, HU has now been demonstrated to be an alternative for adults such as our young adult patient who is on transfusion for an abnormal TCD, and it may be an alternative for adults who have a history of overt childhood stroke for whom transfusion therapy may not be possible [11].

Ophthalmologic Complications

The visual manifestations of SCD are varied and depend on the area of the orbital blood supply that is affected. Presentations can range from conjunctival vessel dilation, orbital cellulitis, atrophy or irregularity of the iris, retinal artery occlusion, glaucoma, angioid streaks, and proliferative sickle retinopathy (PSR) [30]. PSR has been well described and characterized [30] and can lead to both vitreous hemorrhage and retinal detachment, which are the primary mechanisms through which visual loss occurs. PSR and other eye diseases associated with SCD can be identified by an eye specialist and treatments are available. Yearly eye exams are recommended.

Immune-Related Concerns

Splenic sequestration of sickled red blood cells results in splenic infarction and functional asplenia within the first 1–2 years of life in children with HbSS/Sβ(beta)^{0}thalassemia, leading to high risk

for overwhelming bacterial infections. Death from bacterial sepsis has traditionally been a major cause of mortality in infants and young children with HbSS/ Sβ(beta)^{0}thalassemia, until the use of prophylactic penicillin in early childhood was demonstrated to markedly reduce life-threatening infections [31]. There are no data supporting the use of this prophylaxis into adulthood, however. In patients with HbSC and HbSβ(beta)$^+$thalassemia, the spleen is often not infarcted early in childhood. These individuals may have an enlarged spleen and may experience episodes of acute splenic sequestration and infarctions. Chronic subclinical repeated insults to the spleen and splenic sequestration can lead to functional asplenia in these patients. Immunization recommendations in adult patients include coverage with pneumococcal vaccinations, both 23-valent and 13-valent vaccines [11]. Additionally, for individuals that have received or are receiving blood transfusion therapy, screening should occur for hepatitis C.

Pregnancy/Genetic Counseling

Knowledge about the type of sickle cell disease is key for both provider and patient. Young men and women should fully understand their own risk of having offspring with SCD or sickle cell trait. Those affected with sickle cell disease will pass on an abnormal hemoglobin gene. This would be a HbS gene if they have HbSS, or it could be a gene for another abnormal hemoglobin-like HbC if they have HbSC disease. If actively planning a family, they should not assume that they are without risk of having offspring affected by SCD if their partner is not having symptoms of SCD, as they may have sickle cell trait or another abnormal hemoglobin trait (e.g., HbC or β[beta]-thalassemia) that could lead to a form of sickle cell disease. Appropriate testing (complete blood count and hemoglobin electrophoresis) of the partner is needed to be able to provide specific genetic counseling. Women with HbSS/Sβ(beta)^{0}thalassemia have higher rates of pregnancy complications and may experience increased episodes of sickle cell pain [32]. These high-risk pregnancies should be comanaged by obstetrical and specialty providers with knowledge of sickle cell disease.

Special Circumstance: Pain Management in the Young Adult

The management of adolescent and young adult patients with chronic pain presents special challenges for primary care providers. Defined as "pain that recurs or persists over a period of at least three months or more," chronic pain is a common problem affecting 15–25 % of adolescents and young adults [33–35]. Chronic pain in adolescents and young adults increases with age, with females reporting more severe pain and reporting it more frequently than males [36]. Common causes include headaches, abdominal pain, limb pain, and back pain [37], with many adolescents reporting pain at multiple sites [34]. Adolescents report that living with chronic pain affects multiple aspects of life, including school, play, and sleep [37–39]. Parents are also affected, with increased rates of mood disorders and stress of parenting among parents of adolescents with chronic pain [40, 41].

In response to increasing advocacy about management of pain, providers are prescribing controlled substances to adolescents and young adults at a rate that has doubled in the last 14 years. A review of more than 2 million visits between 1994 and 2007 found the rate of prescription of controlled substances for adolescents increasing from 6.4 to 11.2 % and for young adults from 8.3 to 16.1 % [42]. This is concerning given that adolescents and young adults are the age group most likely to abuse controlled substances [43–45]. In fact, the nonmedical use of controlled substances has surpassed the use of all illicit substances other than marijuana [43]. One study found an estimated lifetime medical use of opioids among US high school seniors of 17.6 % and lifetime nonmedical use of 12.9 % [46]. Further complicating management, young adults in particular have decreased use of preventive care services, limiting a proactive, comprehensive management approach [47].

Assessment

A structured approach to chronic pain assessment is recommended by the American Pain Society and American Association of Pain Management's clinical guidelines published in 2009 [48]. Standardized pain assessment instruments such as pain intensity self-report scales, including the visual analog scale [49] and the Faces Pain Scale-Revised [50], as well as pain questionnaires such as the Varni/Thompson Pediatric Pain Questionnaire [51], are well-established and recommended for use in the adolescent age group [52]. Despite the recognition of the negative impact of chronic pain on multiple dimensions of life, however, few structured assessments address domains beyond pain such as functional status or social and educational functioning [53]. One such instrument is the Bath Adolescent Pain Questionnaire [54]. Psychological assessment with instruments validated for use in adolescents and young adults, such as the Beck Depression Inventory [55] or the Center for Epidemiologic Studies-Depression Scale [56], is particularly important due to the high rate of comorbid mental health diagnoses in the chronic pain population, especially among those prescribed opioids [57]. Likewise, assessment of risk for opioid abuse —for example, with the Opioid Risk Tool or Brief Risk Assessment [58, 59]—can help identify patients for whom prescription of controlled substances might be particularly hazardous.

Management

A multimodal treatment strategy that addresses the multiple impacts of chronic pain on the lives of adolescents and young adults is needed. Best results are achieved with an interprofessional (IP) approach [60], although access to IP team members is often limited in primary care settings [61]. Collaborative decision-making with patients and families can improve adherence to treatment plans and self-management. In particular, education and support for behavioral changes in lifestyle habits that affect pain—such as sleep, exercise, diet, and stress management—are critical, but may not be provided at home by parents or in the office by providers. Innovative approaches to self-management incorporating technology and tailored to adolescents and young adults may increase effectiveness [62, 63]. Psychological therapies including cognitive behavioral therapy, relaxation training, and biofeedback have also been found effective in adolescents and young adults [64].

Medication use can be guided by the type of pain being experienced, co-morbid conditions, especially mood disorders, and effectiveness of non-pharmacologic therapies. A challenge in medication use in adolescents and young adults is that most evidence is extrapolated from studies on adults. Some uses for common pain syndromes that have been studied in adolescents and young adults include acetaminophen, ibuprofen, and sumatriptan nasal spray for headache [65, 66] and famotidine, pizotifen, and peppermint oil in recurrent abdominal pain [67]. Opioids specifically have little long-term role in the management of chronic nonmalignant pain in adolescents and young adults [68]. Education on medication safety for adolescents and young adults and their families is needed, as adolescents and young adults have decreased awareness of safe use of over-the-counter medications and increased risk of abuse, diversion, and overdose of controlled substances [42]. Invasive treatments such as injections, nerve blocks, and neurostimulators are rarely used in younger age groups relative to adult practice [68].

Conclusion

Chronic pain in adolescents and young adults benefits from a structured approach with use of standardized assessments and a multimodal treatment plan determined in partnership with adolescents and young adults and their support people. An awareness of the abuse potential of controlled substances is warranted to manage pain without increasing risk. Attention to primary prevention (preventing injuries or overuse that could lead to pain problems) and secondary prevention (minimizing progression of acute to chronic pain through effective treatment and follow up) is also in the realm of primary care ("Appendix").

Appendix

Sickle cell disease (SCD) fact sheet	
Definition	Healthy newborn infants are born with fetal hemoglobin (HbF), which transitions to normal adult hemoglobin (HbA) within 6 months of life. **Sickle cell disease (SCD)** is a group of blood disorders characterized by the presence of hemoglobin S (HbS) instead of normal HbA due to a point mutation in the hemoglobin β(beta)-globin chain gene. Disease classification depends upon the specific combinations of abnormal hemoglobin present: • The most severe forms of SCD are HbSS (sickle mutation in both β[beta]-globin genes) and HbSβ(beta)^{0}thalassemia (sickle mutation in one gene and absent production of HbA in the other gene) • These are also referred to as "sickle cell anemia" • Less severe forms of SCD include HbSC (sickle mutation in 1 gene and another mutation causing abnormal hemoglobin in the other gene) and HbSβ(beta)$^+$thalassemia (sickle mutation in 1 gene and underproduction of HbA in the other gene)

Prevalence	SCD disproportionately affects individuals of African or Mediterranean descent, approximately 1 in 2474 live births in US
	  • It can be found, however, in Hispanic and Caucasian populations
	  • Demographic shifts affect local prevalence
	Survival rates into adulthood are increasing

Pathophysiology	Disease manifestations are results of polymerization of abnormal red blood cell (RBC) hemoglobin in low oxygen states
	• Leads to deformation ("sickling") of RBC
	  • Can lead to RBC membrane deformation and vascular wall adhesion even when not sickled
	  • Leads to fragility and decreased RBC lifespan, chronic hemolytic anemia of varying severity
	• Continuous cascade of inflammation, activation of white blood cells, platelets, and endothelial cells through complex biochemical processes affect microvascular blood flow
	  • End organ damage results

Symptoms	**Individuals are at heightened risk for important chronic conditions as they age, including:**
	  • Chronic pain syndromes, acute or chronic pain episodes
	  • Pulmonary hypertension
	  • Chronic renal disease, hypertension, proteinuria
	  • Strokes, silent cerebral infarctions affecting brain function
	  • Proliferative sickle retinopathy, visual loss
	  • Functional asplenia
	  • Iron overload in organs if receiving chronic transfusion therapy

Challenges in transition	The transition from pediatric to adult phase of life is known to be associated with increased SCD complications The use of beneficial therapies to manage SCD complications may also be underutilized in affected adults Many adult health care providers, especially primary care providers, are unfamiliar with the care of those living with SCD. Stigma and lack of trust are key issues when chronic pain is involved
Helpful resources	• Sickle Cell Disease Association of America (resources for patients and family members, may include local chapters in communities throughout the US): http://www.sicklecelldisease.org • Sickle Cell Adult Provider Network (resources for health care providers, includes links to connect with SCD experts): http://www.scapn.net/ohana • National Heart, Lung and Blood Institute Sickle Cell Disease Guidelines (developed by expert panel): http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines

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