

A Biopsychosocial Model for the Management of Patients With Sickle-Cell Disease Transitioning to Adult Medical Care

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ABSTRACT

The lifespan of patients with sickle-cell disease (SCD) continues to increase, and most affected individuals in high-resource countries now live into adulthood. This necessitates a successful transition from pediatric to adult health care. Care for transitioning patients with SCD often falls to primary care providers who may not be fully aware of the many challenges and issues faced by patients and the current management strategies for SCD. In this review, we aim to close the knowledge gap between primary care providers and specialists who treat transitioning patients with SCD. We describe the challenges and issues encountered by these patients, and we propose a biopsychosocial multidisciplinary approach to the management of the identified

issues. Examples of this approach, such as transition-focused integrated care models and quality improvement collaboratives, with the potential to improve health outcomes in adulthood are also described.

Keywords: Adolescent; Pediatric; Sickle-cell disease; Transition to adult care; Young adult

INTRODUCTION

Sickle-cell disease (SCD) refers to a group of genetic disorders caused by an abnormal hemoglobin molecule, sickle hemoglobin, which polymerizes upon deoxygenation. The key pathophysiological features of SCD are chronic hemolytic anemia and vaso-occlusion by abnormal red blood cells, but it is a systemic disease that affects all organs. Over the last few decades, there has been a significant decrease in mortality for children with SCD, resulting in an increased lifespan [1–5] (Fig. 1). In the United States, mortality has significantly decreased by 61% in infants aged <1 year, by 67% in children aged 1–4 years, and by 22–35% in children aged 5–19 years from 1979 to 1998 and 1999 to 2009

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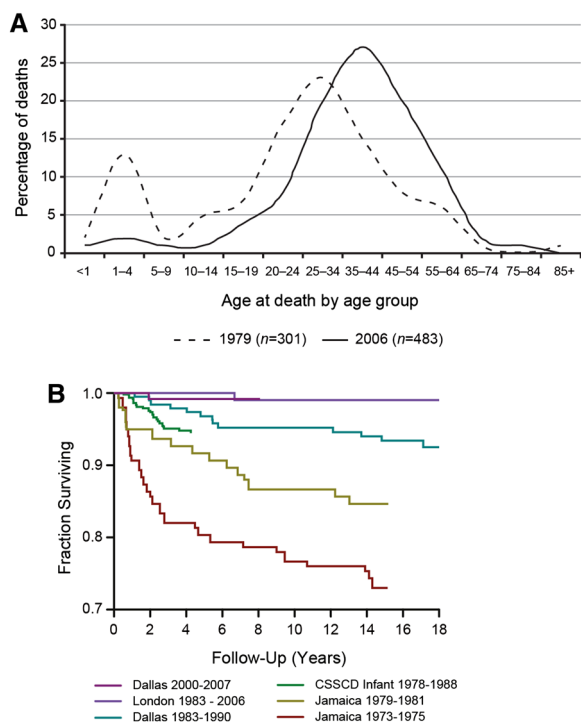


Fig. 1 Improving survival of children with sickle-cell disease. **a** Age at death for individuals with sickle-cell disease in 1979 and 2006 [4]. **b**. Overall survival estimates for children with HbSS and HbS β^0 -thalassemia estimated from large, newborn cohorts in the United States, United Kingdom, and Jamaica [5]. Reprinted from Hassell [4], with permission from Elsevier, and republished with permission of American Society of Hematology from Improved survival of children and adolescents with sickle-cell disease. Quinn et al. [5]; permission conveyed through Copyright Clearance Center, Inc. CSSCD Cooperative Study of Sickle Cell Disease

[1]. Overall, the pediatric SCD mortality rate in the United States has decreased significantly by 3% each year from 1979 to 2005, so most children with SCD now live into adulthood [2, 5]. Contemporary survival data for adults with SCD are lacking, but calculations from the Jamaican SCD cohort suggest a median survival of 53.0 years for men and 58.5 years for women with homozygous SCD (commonly referred to as sickle-cell anemia or HbSS) [6].

Several factors have contributed to this increase in lifespan. Newborn screening, which has been universally implemented in the

United States and the United Kingdom, has allowed early, presymptomatic diagnosis and preventive management [7, 8]. Prophylactic penicillin has been shown to significantly reduce the risk of invasive pneumococcal infection in children with SCD [9]. Effective (protein-conjugate) vaccinations against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* have also decreased fatal infections caused by encapsulated organisms [3, 10]. Hydroxyurea treatment [11, 12] and improvements in general supportive care for acute illnesses have further improved survival for those with SCD [5].

Consequently, the burden of SCD-related mortality in high-resource countries has shifted to young adults, so a successful transition from pediatric to adult care is now critically important [5, 13–16]. Within the first 5 years of transition, there is an increased risk of death [5] probably due to a combination of factors, including different health care utilization patterns and increased likelihood of chronic organ damage from SCD. Furthermore, the care of the transitioned patient with SCD often falls to primary care providers (e.g., internists, family practitioners, and internal medicine/pediatric providers) who may not be as familiar with SCD as are pediatric hematologists [17]. In this review, we describe the challenges and issues for transitioning patients with SCD. Specifically, a biopsychosocial, multidisciplinary approach to the management of these issues is proposed. Examples of this approach, such as transition-focused integrated care models and quality improvement collaboratives, with the potential to improve health outcomes in adulthood are also described.

The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

BIOPSYCHOSOCIAL MODEL FOR TRANSITION OF CARE

The goal of an organized, well-coordinated transition to adult health care should be to assist each young person with SCD in attaining his or her maximum health potential [18]. However, acquiring autonomy and independence while learning to live with SCD is often difficult for young adult patients [13–15]. Thus, a biopsychosocial, multidisciplinary approach to management is recommended. In this approach, health care providers from different disciplines (e.g., medicine, nursing, psychology, and social work) collaborate in a coordinated fashion to address the physical, psychological, and social factors associated with the overall goal of improving health outcomes [19–21]. A multidisciplinary approach to care is widely accepted with the increased understanding of the interplay between the biological, psychosocial, and sociological factors in SCD. These challenges, in addition to differences in the delivery of health care between pediatric and adult systems, support such an approach.

Biological- or Disease-Related Factors

Patients with SCD experience a spectrum of complications, such as acute or chronic pain, chronic hemolytic anemia, and ongoing organ damage [22, 23], including the brain, kidney, spleen, lungs, heart, and eyes. SCD-related organ damage is often chronic and increasingly manifests with age [22]. These cumulative effects and their treatments can result in additional comorbidities such as asthma, avascular necrosis of the long bones, restrictive lung disease, retinopathy, pulmonary hypertension, transfusion-related iron overload, cardiac dysfunction, and renal dysfunction. All

of these complications have important implications for the management of patients transitioning to adult care.

Various SCD-associated signs and symptoms should be assessed and managed in the transitioning young adult [22, 24–31]. Please refer to the guidelines published by the National Heart, Lung, and Blood Institute (NHLBI) for comprehensive details on the management of patients with SCD [24]. Many of these comorbidities require intensive or regular monitoring (e.g., proteinuria and hypertension [29] or yearly ophthalmologic examinations [24]), maintenance of comprehensive and timely medical records (e.g., for blood transfusions, iron overload, and alloimmunization [24]), other specialist care (e.g., for retinopathy [24], nephropathy [29], or chronic pain [24]), patient education, and self-management support (e.g., priapism [24], leg ulcers [22], and prescription refills [14]). Treatment of some conditions can further exacerbate other symptoms (e.g., use of corticosteroids for asthma may contribute to vaso-occlusive events [24]). For these reasons, a multidisciplinary approach is indicated for the management of adolescents with SCD transitioning into adult care.

Focus on Neurological Factors: Stroke and Silent Cerebral Infarct

The progressive nature of SCD and SCD-related cognitive limitations have been identified as factors that significantly complicate the transition process and prevent optimal outcomes for young adults with SCD. Brain injury, a biological issue with direct psychological and sociological ramifications, can affect the success of transition. Patients with SCD are at high risk of overt stroke, which occurs in approximately 11% of

children <20 years of age who have sickle-cell anemia but do not have the benefit of primary stroke prevention programs [32]. Transcranial Doppler ultrasonography (TCD) screening is the standard screening procedure for primary stroke prevention in pediatric patients with sickle-cell anemia [33]. When TCD suggests a high risk of stroke, long-term transfusions or hydroxyurea are indicated [32, 34–36]. Transfusions may need to be continued indefinitely, or may be stopped after some period of time when the risk of stroke is perceived to be lower [24]. Transfusions are costly and carry the risk of iron overload and alloimmunization [24, 34]. Transfusion-related iron overload is managed primarily with chelation therapy (deferasirox, deferoxamine, or deferiprone), and can be limited by partial or automated exchange transfusions [24]. Adherence with chelation therapy is often suboptimal in patients with SCD because of issues associated with the mode of administration (e.g., oral ingestion of chalky substance or subcutaneous injections). A comprehensive program to monitor and treat iron overload and to educate patients is needed [24], but this may be difficult if transitioning patients are mainly using emergency services. For these reasons, chronic transfusion therapy may be stopped after transition to adult medical care. Whether this is the best course of action or simply the most expedient is not clear, especially because the risk of stroke increases during adult life [37].

Treatment with hydroxyurea has been proposed as an alternative to chronic transfusions for primary stroke prevention, and was tested in children in the phase 3, randomized Transfusions Changing to Hydroxyurea (TWiTCH) trial sponsored by the NHLBI (ClinicalTrials.gov number, NCT01425307) [36]. Although not yet published in final, peer-reviewed form, the

results are reported to show that hydroxyurea is not inferior to blood transfusions (using only TCD velocity as the outcome) in children with SCD who are at high risk for stroke by TCD criteria. If the approach of the TWiTCH trial is adopted by the medical community, the number of patients with SCD who are transitioned to adult care with iron overload may decrease as hydroxyurea use increases.

Silent cerebral infarction (SCI) occurs more frequently than overt stroke (37% of patients aged at least 14 years) [38], but the risk of both increases with age [38–40]. Data from the Cooperative Study of Sickle Cell Disease showed that the chances of having a first stroke in patients with sickle-cell anemia were 11% and 24% by the age of 20 and 45 years, respectively [39]. In the same cohort, 24.5% of those with SCI at baseline developed new or more extensive SCI during a mean follow-up period of 5.2 years [41]. Even though evidence for the prevalence of SCI in adults is limited [40, 42], 50% of adult patients with SCD with normal baseline neurologic examination and no history of stroke or transient neurologic events had SCI, and 25% had progressive abnormalities on magnetic resonance imaging (MRI) during a 3.7-year follow-up [43]. Both stroke and SCI are often associated with neurocognitive morbidity [38, 40, 44], and this decline in neurocognitive function may become increasingly apparent in adulthood [40]. Impaired neurocognitive function has also been observed in seemingly neurologically intact individuals and appears to be associated with anemia and age [42].

Results of the phase 3, multicenter, randomized Silent Cerebral Infarct Trial (ClinicalTrials.gov number, NCT00072761) sponsored by the National Institute of Neurologic Disorders and Stroke were published in 2014. This study reiterated that

chronic transfusions, compared with observation, for children with SCI significantly reduced the development of new or progressive silent and overt cerebral infarction and improved quality of life in children with SCI compared with observation alone [45]. If the approach of this trial is adopted by the medical community, the number of patients with SCD who are transitioned to adult care with iron overload may increase. It is not known whether hydroxyurea is equally as effective in reducing the development of SCI.

Decline in neurocognitive function, which appears to be associated with SCI, household income, highest academic attainment of head of household, hemoglobin oxygen saturation, and degree of anemia, can further impact the management of patients transitioning to adult care, both by delaying transition and impeding young people from taking full responsibility for their chronic condition [46]. Assessment of neurocognitive impairment is essential but difficult because it is generally not detected by imaging and other routine diagnostic methods [22], and deficits may be present in seemingly neurologically intact patients. Systematic follow-up of such patients is needed, especially because the rate of strokes in patients with SCD peaks between the ages of 35 and 64 years [37]. Comprehensive screening for stroke in adults with SCD should also evaluate risk factors such as blood pressure [24, 47].

Psychosocial Factors

The transition to adulthood is a critical juncture [48] as young adults navigate rapid social and psychological changes in their journey toward independence [15]. This process is often more difficult in those with SCD. Adolescents with SCD may require support from their families and medical staff to assume increasing

responsibility for the management of their chronic condition [15]. Some adolescents (aged 13–21 years) have expressed concerns about leaving their familiar pediatric health care providers and going to new adult care providers who might not understand their needs [49], as well as having limited information about the transition process and adult health care programs [50]. In addition, young adults may not be capable of effectively advocating for themselves in the adult health care system. As a result, family members may accompany young adults to visits. Providers are encouraged to include family members when appropriate as they may play an essential role in promoting adherence to the treatment plan.

Adolescents with SCD are often poorly prepared for the transition to adult care, even though they acknowledge the importance of this transition. A survey of 70 patients at a pediatric SCD center found high scores of perceived importance of the transition but low scores for transition readiness, particularly in the areas of previous thoughts about transitioning, knowledge of care steps, anticipated difficulty with transitioning, and interest in transitioning [51]. Patients with SCD who had previously transitioned to adult health care reported that they received little preparation and that the transition was based strictly on age rather than readiness or need [52].

Medical complications and comorbidities associated with SCD can exacerbate social, emotional, and behavioral difficulties that may also impede the transition process [53]. For example, successful pain management is essential as patients transition to adulthood, as this will affect their ability to cope with SCD throughout their remaining lifetime [24]. Chronic pain can be difficult to manage due to the complex involvement of sensation,

emotion, cognition, memory, and context. In addition, chronic pain can be physically and psychologically debilitating [24], which can hamper the transitioning process, especially for patients with inadequate support and education. A majority of primary care providers reported being uncomfortable managing chronic pain in transitioning patients with SCD [17]; however, there is a need for continuity of care and good patient/physician communication during the transition phase to provide adequate pain management. Pain assessment requires an understanding of a patient's chronological age, developmental stage, functional status, cognitive ability, and emotional state [24]. Treatment should be tailored to a patient's needs, which necessitates a detailed understanding of the pain experienced [24]. Individuals who experience chronic pain require intense education to understand that the goals of therapy for chronic pain (i.e., to minimize pain, increase pain coping skills, and maintain maximal social and physical functioning) are different than those for acute pain [24].

In addition to the pharmacologic treatment of pain, non-pharmacologic interventions such as physical therapy, cognitive behavioral therapy, or rehabilitation may also be required [24, 54, 55]. Patients may be treated with hydroxyurea to reduce the frequency of pain episodes [24]; however, this modality is underutilized due to a lack of awareness and concerns about toxicity and treatment adherence [56, 57]. Hydroxyurea therapy requires careful monitoring during treatment initiation along with blood counts every 4–8 weeks once a stable, maximally tolerated dose is reached [24]. Treatment adherence to hydroxyurea is often challenging, as it is with any long-term medicine, because patients may

not feel better until several months after initiation. A discussion about barriers and facilitators to adherence in combination with a monitoring plan is recommended [56, 57].

Many factors can impact patient adherence not only to medication, but also to other treatments, referrals to specialists, and clinic attendance [13, 56, 57]. Financial difficulties, skepticism of the health care system, and barriers to access can lead to non-adherence [13, 24]. Adherence may be improved through patient education and intervention, as well as stronger patient/physician relationships and communication [13, 53]. The latter might be achieved through initiatives, such as the pediatric care team introducing patients to physicians responsible for adult care, or through mobile phone or e-mail contact between young adult patients and nurses [13, 58]. Referrals to psychologists and others who specialize in the promotion of treatment adherence may be the best option for some patients [15].

Young adults with mild SCD tend to skip follow-up with specialists, especially if complications are asymptomatic (e.g., nephropathy or retinopathy) [24]. As a result, adults and adolescents in transition tend to rely heavily on emergency care rather than following a developed plan with specific goals [15], as exemplified by the high rates of acute care utilization in young adults with SCD (3.61 per patient per year; 95% confidence interval 3.47–3.75) compared with the general SCD population (2.59 per patient per year; 95% confidence interval 2.53–2.65) [59]. Rehospitalization rates in patients with SCD were also highest among those aged 18–30 years [59]. This poor continuity of care can potentially have a negative impact on health and psychosocial outcomes in young adults with SCD [15].

Sociological Factors

Sociological issues affecting adolescents with SCD transitioning to adult care can include changes in insurance coverage [15], schooling [60], and employment opportunities [61]. Many young adults change or lose the insurance coverage that was in place during their childhood, which can jeopardize their continuity of care [15, 60], and it is estimated that 29% of young adults (18–24 years) with SCD are uninsured [14]. Access to necessary insurance coverage for preventive care and assistance with medication costs is now provided in the United States under the Patient Protection and Affordable Care Act (PPACA) [62]. It will be essential to collect data to determine if this improves access to health insurance for this population.

For many young adults, painful events or hospitalizations may lead to frequent school absences and difficulty in maintaining passing grades [60]. These issues may be further exacerbated by neurocognitive morbidity, such as impairments in selective attention, working memory, and processing speed, all of which have been associated with stroke and SCI in pediatric patients with SCD [40]. Securing or keeping employment can be impeded due to chronic pain, physical disabilities, acute pain episodes, or other complications that can result in hospitalization [60], and rates of unemployment are high for adults living with SCD, although this may be affected by other demographic and psychosocial factors [61]. Among adults with SCD, women are approximately three times more likely to be employed than men [61], and are more likely to be employed if they did not perceive SCD to interfere with maintaining gainful employment; however, those who are more assertive in advocating for sick leave or work

accommodations for their disease may be perceived negatively by employers and coworkers [61]. Limited educational achievement and employment rates, along with the resultant lower income, may thus impact access to health care for some patients and further supports the need for a biopsychosocial, multidisciplinary approach to care.

Differences in Health Care Delivery between Pediatric and Adult Systems

Comprehensive care programs exist for pediatric patients with SCD, but there remains a lack of available, trained providers for adults [15]. Pediatric SCD care centers have established better coordinated support systems compared with adult SCD care centers, which have fewer interdisciplinary services and higher expectations of self-management [15]. Pediatric patients often receive care through a dedicated medical home that has a multidisciplinary SCD clinic to coordinate care with the child's primary care pediatrician, or that is run by a primary care pediatrician who makes referrals to SCD specialists for comprehensive evaluations and management of life-threatening complications [63].

In the United States, the current approach for managing adults with SCD tends to default to primary care providers who do not specialize in the treatment of SCD, making it difficult for transitioning patients to find physicians who are comfortable with and have the resources to manage their condition. These primary providers may instead make referrals to or consult with hematologists as insurance and finances allow [13]. In a national survey conducted in the United States, only 38% of general pediatricians and 51% of general internists thought it would be easy for young

adult patients with a childhood-onset chronic disease to find a general internist who would be willing to oversee their primary health care needs [64]. For both internists and pediatricians, care coordination and effective direct communication between subspecialists are positively associated with higher quality of care during the transition phase, although it may not always be adequate [64].

Management of transitioning patients with SCD contrasts with management of other chronic childhood diseases, such as cystic fibrosis or hemophilia, for which adult patients are more likely to receive disease-specific, center-based, comprehensive, multidisciplinary care in specialized treatment centers [13]. Moreover, patient registries that help monitor outcomes and treatment effectiveness in patients with hemophilia [13] have only recently been established in SCD [65].

The US reimbursement system within adult care may limit the willingness of specialists (e.g., hematologists/oncologists) to see adolescent and adult patients with SCD whose care may be more time intensive, but far less lucrative, than that of cancer patients [13]. This is yet another reason that the primary care of adults with SCD often defaults to general internists [13]. Under the PPACA, adults with SCD are likely to have greater access to primary and specialty care services in the future [62].

BIOPSYCHOSOCIAL, MULTIDISCIPLINARY MODELS FOR TRANSITION OF CARE

Multidisciplinary and biopsychosocially oriented transition programs can provide age-appropriate treatment and continuity of care from pediatric to adult facilities [13–16, 24]. In these programs, the transition occurs within the

larger, holistic context of the life of the young adult (Fig. 2) [15, 66]. The transition plan needs to be flexible enough to accommodate most individual requirements, thereby allowing patients to explore their independence and develop skills in managing their chronic disease [13]. Discussions about transition should occur before transferring care [13, 24], as this allows time for physicians to address patients' and parents' fears or uncertainties and redirect negative feelings about the transition process [16]. Participants can benefit from training in effective communication skills, financial planning, self-advocacy, and life planning [15]. Ideally, the transition team should include pediatric and adult physicians, pediatric and adult nurse practitioners, pediatric and adult social workers, an education coordinator, and a clinical psychologist [13, 15, 24]. A formal meeting initiated by the pediatric care team to introduce the patient and parents to the adult care team

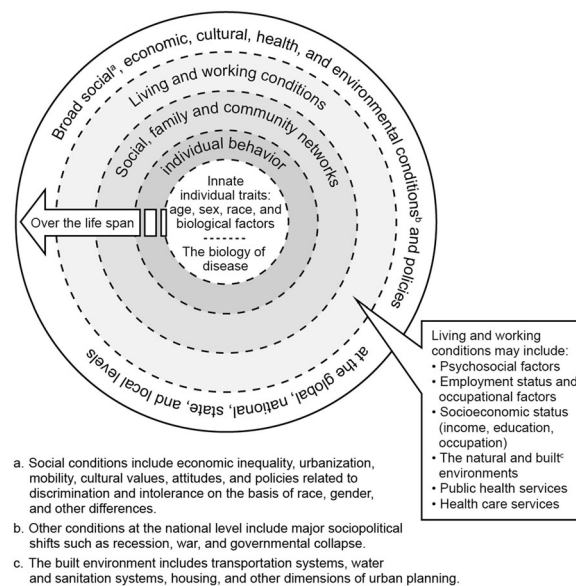


Fig. 2 Institute of Medicine's model of the multiple determinants of health [56]. Reprinted with permission from Centers for Disease Control and Prevention, Liburd and Sniezek [58]

may further enhance the transition process [16, 24]. Developmental age, rather than chronological age, should guide transition as much as possible, as factors such as delayed neurocognitive development may mean that a patient is not ready to transition from pediatric care to adult care at 18 years of age [15, 24].

One example of such a program is Guy's and St. Thomas' Hospital in the United Kingdom, an institution that cares for more than 500 individuals with SCD. Transition of care typically occurs when patients are 16–18 years of age, but timing is flexible and patient focused [58]. The clinic also has biannual transition open days, during which young patients and their families may ask questions about the differences between pediatric and adult care and can learn about the expectations and preparation needs for the transition process [58]. Pediatric nursing and psychological teams can bridge care during the transition period by developing a plan that identifies each patient's unique health, social, educational, and developmental needs.

Another example of this approach is the CHRISTUS Santa Rosa Children's Hospital in San Antonio, Texas, where patients and their families are first introduced to the transition program at a newborn's initial visit or on transfer from another clinic to ensure a continuum of care [67]. At 13 years of age, patient and parent education begins with the provision of a binder that includes skill checklists, appointment and problem-reporting tracking sheets, and additional educational resources. By 18 years of age (or depending on developmental age, usually at an average of 21 years), patients are considered to have transitioned [67]. Evaluation of the efficacy of such transition programs will be essential to identify best practices that can be shared with other providers.

Both the day hospital and chronic care models are exemplars of a biopsychosocial

and multidisciplinary approach that may be especially effective for transitioning young adults with SCD. The day hospital model provides an alternative to inpatient care. In this model, patients with SCD with painful but otherwise uncomplicated vaso-occlusive episodes can obtain care in an outpatient infusion center or SCD-specific day hospital setting where the staff is knowledgeable about the disease [68]. In the chronic care model, a "medical home" or family-centered practice that delivers preventive care, acute illness management, and chronic condition management for pediatric patients and coordinates patient support and transition services could be adopted [14, 69]. A similar, coordinated system of care that allows holistic treatment of patient and family is needed for both adult and adolescent patients with SCD.

Treatment programs for other chronic illnesses (e.g., hemophilia and cystic fibrosis) can guide the development of biopsychosocial and multidisciplinary SCD programs. For example, there are more than 130 hemophilia treatment centers in the United States that not only treat individuals with hemophilia, but also provide continual medical and psychosocial support throughout their lifetimes [70]. These comprehensive, multidisciplinary care programs have resulted in improved health outcomes for young adult patients. In addition, practice models that incorporate patient registries have been effective in helping practitioners monitor key health outcomes and the effectiveness of treatment protocols over time.

Collaboratives, such as the National Initiative for Children's Healthcare Quality project known as WISCH (Working to Improve Sickle Cell Healthcare), are focused on improving quality of care for patients with SCD during their entire lifetime, including

patients who are in the process of transitioning to adult care [19]. Teams consisting of health care providers, patients, hematologists, nurses, and others aim to implement timely acute care management, better coordination of care, better transition from pediatric to adult care, improved screening, counseling, and education for individuals with SCD, and enhanced education for providers on treating, assessing, and monitoring SCD [19]. Recently, the National Institute for Children's Health Quality developed the Curriculum for Transition from Pediatric to Adult Medical Care for Adolescents with SCD, which provides a biopsychosocial framework for the issues to be addressed during the transition period for adolescents and young adults with SCD [19].

CONCLUSIONS

Key issues for patients with SCD who are transitioning to adult care include biological, psychosocial, and sociological factors that require specialist care from multiple disciplines. Therefore, a biopsychosocially oriented, multidisciplinary model should be used to facilitate the successful transition of all pediatric patients with SCD to adult care. This will enable adolescents to fully assume adult roles, actively participate in all aspects of their health care, and take responsibility for the management of their chronic disease. While there are some centers with these types of programs, such programs are still needed at the majority of centers delivering care to young adult patients with SCD. Collaboratives are working toward improving SCD care across patient lifetimes, which may include utilization of a multidisciplinary approach that adapts to the patient needs. Evaluation and

monitoring of the impact and efficacy of biopsychosocial models in comparison to traditional models will provide additional insights into effective methods to improve care during the transition process and health outcomes in young adulthood.

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Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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