Sickle Cell Disease
A Continued Call to Action

Kathryn L. Hassell, MD

One of the challenges facing the U.S. healthcare system is the ability to comprehensively serve those with relatively rare and complex disorders, particularly for those conditions that most impact communities that are historically disadvantaged and underserved. Such a condition is sickle cell disease (SCD), an inherited blood disorder that results in a lifetime of anemia, severe episodes of pain, and childhood onset of acute and chronic organ damage that progresses in adulthood, leading to premature mortality.[1] Affecting an estimated 100,000 Americans,[2] the majority are from African American and Hispanic communities and rely heavily on public insurance and healthcare programs.[3]

Because SCD was first described in the U.S. in 1910, research has elucidated interventions that can significantly improve the course of the disease. Prevention of invasive pneumococcal infection with the use of prophylactic penicillin and vaccination can markedly reduce infant and early childhood mortality,[2,4] which serves as justification for the now-universal newborn screening for sickle cell anemia (SCA) across the U.S. Reduction in the risk of stroke, which may afflict up to 10% of children with SCA, is possible with the institution of transfusion[5] or hydroxyurea therapy[6] after identifying the children most at risk using routine transcranial Doppler screening.[7] Hydroxyurea, an oral agent chemotherapy agent, has been shown to reduce acute pain episodes in infants and adults[8,9] and may extend life expectancy in adults[10]; it is the only U.S. Food and Drug Administration–approved drug for the treatment of SCD. A growing number of new drug therapies are under study,[11] stem cell (bone marrow) transplantation is potentially curative for individuals with a matched donor,[12] and human gene therapy experiments are under way[13].

However, the promise of these and future therapies can only be realized if individuals with SCD have access to a system that is able to provide coordinated care by knowledgeable providers, integrating specialized and routine health care across the life span. An organized system of care, as provided to those living with cystic fibrosis and hemophilia, does not exist for SCD. Mounting evidence[14–16] suggests that therapies of proven benefit, including prophylactic penicillin, transcranial Doppler, and hydroxyurea therapy, are not being utilized.

In recognition of disparities involving SCD, the American Society of Pediatric Hematology and Oncology convened a Sickle Cell Summit in June 2007.[17] The premise and vision of the Summit was as follows:

An adequately funded, coordinated, comprehensive, and integrated national model for care of persons with SCD, involving all stake holders, will lead to improved outcomes for all Americans with the disease; lay the foundation for conducting health services, outcomes, and clinical/translational/basic research; and ultimately improve outcomes of future persons globally with SCD.

With this in mind, participants from major federal funding and healthcare policy agencies, foundations, professional societies, community organizations, patients, and expert clinicians and researchers built consensus around goals and opportunities for bridging the gaps between this vision and the apparent reality, acknowledging that data regarding the status of health care and outcomes for those living with SCD were poorly defined; the number and characteristics of affected individuals have not been definitively determined. Five major goals were identified:

1. speaking with a unified voice to make a clear case statement;
2. access to care from knowledgeable healthcare providers in a patient-centered medical home;
3. population-based surveillance to measure outcomes;
4. basic, clinical, translational, and health services research; and
5. enhanced role of the community.

The papers in this supplement to the *American Journal of Preventive Medicine* highlight some of the progress made since the Summit in these targeted areas through activities sponsored by DHHS agencies, including the Centers for Disease Control and Prevention (CDC), Health Resources and Services Administration, and NIH. A unifying theme of the supplement is the initial assessment of the state of health care for those living with SCD and the uptake

From the Division of Hematology, Colorado Sickle Cell Treatment and Research Center, University of Colorado Denver, Aurora, Colorado

Address correspondence to: Kathryn L. Hassell, MD, Colorado Sickle Cell Treatment and Research Center, 13121 E. 17th Avenue, Anschutz Medical Campus, Box C-222, Room 3211, Bldg L28, Aurora CO 80045 E-mail: kathryn.hassell@ucdenver.edu.

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of management strategies with proven benefit, including vaccination against pneumococcal infection, transcranial Doppler screening, and initiation of hydroxyurea therapy. Data from the Registries and Surveillance System for Hemoglobinopathies program,[18] cosponsored by CDC and NIH, as well as utilization of state-based administrative data sets, can reveal population-based patterns of utilization that may target areas for improvement. At a more granular level, exploration of the impact of care coordination strategies, health information technologies, and use of quality improvement methodologies within specific clinical practices offer guidance to optimization of scalable approaches that lead to an increase in adherence to recommended screening, prevention, and treatment strategies. Successful clinical research requires an understanding of potential barriers to participation. Exploring the role of newborn screening and public health programs, as well as demonstrating the benefits of community health workers, offers the opportunity of supporting individuals and their families beyond the medical facility. In particular, this may represent a key component to comprehensive patient-centered care, especially in culturally and geographically isolated areas of the U.S. as well as in other countries with a much larger disease burden and even more–limited healthcare resources.

The work described in this supplement demonstrates an increasing capacity to better understand the landscape of health care for those living with SCD, informing understanding of the current implementation of interventions and the potential to capture and monitor health outcomes. This represents important progress since the American Society of Pediatric Hematology and Oncology Summit 8 years ago. Even as these papers confirm the continued inconsistent utilization of proven therapies and ongoing struggles with management of acute and chronic complications, mechanisms of improvement are proposed and preliminarily explored. Refinement of these strategies and data are needed to further demonstrate how care coordination strategies, improvement in adherence to guidelines, and implementation of a broader community base of support will translate into improved outcomes. Continued support for this development through DHHS, in collaboration with providers, those living with sickle cell and their communities, and identification of resources within the evolving healthcare system will be necessary to sustain identified successes. And so, the "call to action" made at the American Society of Pediatric Hematology and Oncology Summit remains loud and clear today.

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References

1. Kanter J, Kruse-Jarres R. Management of sickle cell disease from childhood to adulthood. *Blood Rev*. 2013;27(6):279–287. http://dx.doi.org/10.1016/j.blre.2013.09.001.
2. Hassell K. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. 2010;38(4(suppl)):S512–S521. http://dx.doi.org/10.1016/j.amepre.2009.12.022.
3. McCavit TL, Lin H, Zhang S, et al. Hospital volume, hospital teaching status, patient socioeconomic status, and outcomes in patients hospitalized with sickle cell disease. *Am J Hematol*. 2011;86(4):377–380. http://dx.doi.org/10.1002/ajh.21977.
4. Mehta SR, Afenyi-Annan A, Byrns PJ, et al. Opportunities to improve outcomes in sickle cell disease. *Am Fam Physician*. 2006;15(74(2)):303–310.
5. Lee MT, Piomelli S, Granger S, Miller ST, et al. STOP Study Investigators. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood*. 2006;108(3):847–852. http://dx.doi.org/10.1182/blood-2005-10-009506.
6. NIH ends Transcranial Doppler (TCD) with Transfusions Changing to Hydroxyurea (TWitCH) clinical trial due to early results. National Institutes of Health website. www.nih.gov/news/health/nov2014/nhlbi-19.htm. Published 2014. Accessed October 1, 2015.
7. Adams RJ, Brambilla DJ, Granger S, et al. STOP Study. Stroke and conversion to high risk in children screened with transcranial Doppler ultrasound during the STOP study. *Blood*. 2004;103(10):3689–3694. http://dx.doi.org/10.1182/blood-2003-08-2733.
8. Charache S, Barton FB, Moore RD, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *Medicine (Baltimore)*. 1996;75(6):300–326. http://dx.doi.org/10.1097/00005792-199611000-00002.
9. Thornburg CD, Files BA, Luo Z, et al. BABY HUG Investigators. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood*. 2012;120(22):4304–4310. http://dx.doi.org/10.1182/blood-2012-03-419879.
10. Steinberg MH, McCarthy WF, Castro O, et al. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia and MSH Patients' Follow-Up. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: a 17.5 year follow-up. *Am J Hematol*. 2010;85(6):403–408. http://dx.doi.org/10.1002/ajh.21699.
11. Singh P, Ballas S. Emerging drugs for sickle cell anemia. *Expert Opin Emerg Drugs*. 2015;20(1):47–61. http://dx.doi.org/10.1517/14728214.2015.985587.
12. Fitzhugh CD, Abraham AA, Tisdale JF, et al. Hematopoietic stem cell transplantation for patients with sickle cell disease: progress and future directions. *Hematol Oncol Clin North Am*. 2014;28(6):1171–1185. http://dx.doi.org/10.1016/j.hoc.2014.08.014.
13. A Study Evaluating the Safety and Efficacy of the LentiGlobin BB305 Drug Product in Severe Sickle Cell Disease. Clinical Trials.gov website, NIH. www.clinicaltrials.gov/ct2/show/NCT02140554. Updated July 2015. Accessed October 1, 2015.
14. Beverung LM, Brousseau D, Hoffmann RG, et al. Ambulatory quality indicators to prevent infection in sickle cell disease. *Am J Hematol*. 2014;89(3):256–260. http://dx.doi.org/10.1002/ajh.23627.
15. Eckrich MJ, Wang WC, Yang E, et al. Adherence to transcranial Doppler screening guidelines among children with sickle cell disease. *Pediatr Blood Cancer*. 2013;60(2):270–274. http://dx.doi.org/10.1002/pbc.24240.
16. Stettler N, McKiernan CM, Melin CQ, et al. Proportion of adults with sickle cell anemia and pain crises receiving hydroxyurea. *JAMA*. 2015;313(16):1671–1672. http://dx.doi.org/10.1001/jama.2015.3075.
17. Hassell K, Pace B, Wang W, et al. American Society of Pediatric Hematology Oncology. Sickle cell disease summit: from clinical and research disparity to action. *Am J Hematol*. 2009;84(1):39–45. http://dx.doi.org/10.1002/ajh.21315.
18. Hulihan MM, Feuchtbaum L, Jordan L, et al. State-based surveillance for selected hemoglobinopathies. *Genet Med*. 2015;17(2):125–130. http://dx.doi.org/10.1038/gim.2014.81.