

The Challenge of Creating an Evidence-Based Guideline for Sickle Cell Disease

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In this issue of *JAMA*, Yawn and colleagues¹ publish the much-anticipated National Heart, Lung, and Blood Institute (NHLBI) guideline for the management of sickle cell disease (SCD) in the United States. The last SCD guideline sponsored by the NHLBI was published a decade ago. The challenges associated with developing guidelines for individuals with an uncommon disease are unique and formidable because of the reliance on evidence other than clinical trials, in particular expert opinion. Given the importance of evidence-derived guidelines, particularly for management of an uncommon disease, adherence to rigorous methodology is critical for their credibility. The Institute of Medicine (IOM) published guidelines² to address the most important components of any guideline that will allow for primary care clinicians, specialists, and payers to have confidence in its content. For the foreseeable future, the recommendations from the IOM represent the criterion standard by which guidelines should be assessed.



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The SCD guideline¹ has numerous strengths. In reviewing more than 12 000 articles, the NHLBI guideline committee explicitly followed 3 of the key recommendations from the IOM for guideline creation including: (1) performance of a systematic review of the existing evidence; (2) using an explicit and transparent process that minimized distortion, bias, and conflicts of interests; and (3) providing a clear explanation of the logical relationships between alternative care options and health outcomes. Ratings of both the quality of evidence and the strength of recommendations are included.

In addition, the guideline is well organized, with numerous tables that summarize the quality of the evidence and strength of the recommendations in specific areas including: a consensus treatment protocol for the implementation of hydroxyurea therapy and evidence-based summaries for medical management of health maintenance and acute complications. Yawn et al¹ also included a table that highlights the strongest recommendations with the highest-quality evidence. The authors emphasize that the majority of the recommendations are based on moderate or weak evidence and should not be used as quality indicators. An additional strength of the SCD guideline is the provision of a clear roadmap for establishing funding priorities in which the evidence to support recommendations for clinical care is low or moderate.

Despite these many strengths, the creators of the guideline did not follow all of the IOM recommendations. A multidisciplinary panel of experts and representatives from key affected groups were not included and patient preferences were not solicited.

The absence of representation of patients with SCD and their affected family members is an important omission, particularly given the possible differences between the perspectives of the adult with or parent of a child with SCD and the members of the committee. Listening to the perspective of the families and understanding which of these recommendations are important to them and how they may be implemented is critically important. In the new era of patient-centered outcomes research, a rare opportunity was missed in shaping this SCD guideline by not obtaining input from the individuals most affected by the disease.

The guideline did undergo extensive review and revision and ultimately was endorsed by the American Society of Hematology, the American Academy of Pediatrics, and the American Society of Pediatric Hematology/Oncology, representing an attempt to build consensus prior to the release. Notably absent was endorsement from other professional organizations that have expertise in the management of chronic kidney disease, pulmonary hypertension, obstructive lung disease, and stroke, which are the 4 most common comorbidities that occur in individuals with SCD and are associated with earlier death. However, it may be increasingly difficult for guidelines to be endorsed by all relevant societies, particularly when recommendations are based on weak or moderate evidence.

There are a number of clinical areas in which the SCD guideline could have provided additional information. Chronic kidney disease is more common in patients with SCD than in the general population and is associated with earlier death.³ However, the recommendations do not include suggestions for how often to screen and when to screen for kidney disease, only to refer those with proteinuria of greater than 300 mg for 24 hours to a nephrologist. A common clinical problem for children with SCD is asthma. The presence of asthma or asthma symptom (recurrent wheezing), significantly increases the risk of SCD-related morbidity⁴ and mortality.⁵⁻⁷ However, the guideline does not provide any approach to screen and treat asthma or asthma-like symptoms. In SCD, standard therapy for asthma treatment, such as steroids, has short-term SCD-specific⁸ and long-term nondisease consequences.⁹

The management of and screening for pulmonary hypertension or at least elevated tricuspid regurgitant velocity (TRV), a risk factor for earlier death in patients with SCD, was absent from the guideline, along with the absence of the endorsement from the American Thoracic Society (ATS). Most recently, the ATS has published its guideline on screening for and management of pulmonary hypertension.¹⁰ However, the rec-

ommendations, as acknowledged by Yawn and colleagues,¹ are not aligned with the NHLBI guideline for the same comorbidity. Thus, 2 different screening strategies are available for detecting elevated TRV: one in the current NHLBI guideline that is neutral about screening in asymptomatic individuals and another in the ATS guideline that recommends that all individuals regardless of symptoms are screened for elevated TRV. The inconsistency in recommendations is likely to create confusion for both clinicians and patients.

The most common neurological challenge confronting children and adults with sickle cell anemia (SCA) is the presence of silent cerebral infarcts, which occur in 37% of school-aged children.¹¹ Silent cerebral infarcts are not detected with a neurological examination and can only be detected with a magnetic resonance imaging of the brain.¹² In children with SCA, silent cerebral infarcts are a morbid condition, are associated with an average 5-point decline in full-scale IQ,¹³ and increased risk for future strokes.¹⁴ Moreover, the presence of silent cerebral infarcts, coupled with cognitive testing, when appropriate, provide sufficient support for the parents to obtain the federally mandated Individualized Education Program to augment education for their children or facilitate enrollment of adults into vocational rehabilitation programs. Despite these well-established strategies to augment the lives of individuals with acquired brain injuries, the committee decided that there was moderate evidence based on low-quality evidence against screening for silent cerebral infarcts in SCA. At the time of the formation of the guideline, the absence of a medical therapy to mitigate the progression of silent cerebral infarcts does not diminish the opportunity to maximize the cognitive potential of those with silent cerebral infarcts. This is particularly important in this population because most children and

adults with SCD are black and typically have a significantly greater high school dropout rate and unemployment rate compared with nonblacks.

It is unfortunate that no recommendations were provided for hematopoietic stem cell transplant, the only definitive cure for SCD. However, the hope of cure is what the families consistently mention, particularly for adults with severe disease. Notably, a recent study is highlighted in the Discussion section of the guideline report that describes the successful use of nonmyeloablative allogeneic hematopoietic stem cell transplantation in 29 adults,¹⁵ as well successful haplo-identical allogeneic hematopoietic stem cell transplant in 11 adults.¹⁶ Given the chronic nature of this disease, and recent scientific advances, an increasing number of parents and adults will seek a definitive cure for SCD. The medical community, in conjunction with patients, will need guidance to deal with the complex question of when to consider hematopoietic stem cell transplant in the near future.

In summary, Yawn and colleagues¹ have undertaken a monumental effort to produce practical, an evidence-based guideline for SCD. Many aspects of this guideline will help both individuals with the disease and clinicians. As would be expected, when the guideline is based on recommendations from randomized clinical trials, such as penicillin prophylaxis, transcranial Doppler screening, blood transfusion therapy prior to surgery, or hydroxyurea therapy for severe disease, these strong recommendations will be embraced by the SCD community. However, when recommendations are based on consensus panel expertise, practice variation will justifiably continue. Hopefully, the next updated guideline will not take 10 years to be published, and when published will embrace all of the IOM's most recent recommendations for creating clinical practice guidelines.

ARTICLE INFORMATION

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