PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Management of Children With Sickle Cell Disease: A Comprehensive Review of the Literature

Patricia L. Kavanagh, Philippa G. Sprinz, Samuel R. Vinci, Howard Bauchner and C. Jason Wang

Pediatrics 2011;128;e1552; originally published online November 28, 2011;
DOI: 10.1542/peds.2010-3686

Management of Children With Sickle Cell Disease: A Comprehensive Review of the Literature

WHAT'S KNOWN ON THIS SUBJECT: Sickle cell disease (SCD) is a multisystem disease with hemolytic and infectious complications that contribute to high morbidity and mortality rates in children. However, a comprehensive review of the literature for the prevention and management of pediatric SCD-related complications is lacking.

WHAT THIS STUDY ADDS: This article presents a comprehensive review of the literature for the care provided to children with SCD. The results will enable practitioners and researchers to identify areas with the strongest evidence for clinical practice and those that need additional research.

abstract

OBJECTIVE: Sickle cell disease (SCD) affects 70 000 to 100 000 people in the United States, and 2000 infants are born with the disease each year. The purpose of this study was to review the quality of the literature for preventive interventions and treatment of complications for children with SCD to facilitate the use of evidence-based medicine in clinical practice and identify areas in need of additional research.

METHODS: We searched the Ovid Medline database and the Cochrane Library for articles published between January 1995 and April 2010 for English-language abstracts on 28 topics thought to be important for the care of children with SCD. We also added pertinent references cited by studies identified in our search. Each abstract was reviewed independently by 2 authors. Data from articles retrieved for full review were abstracted by using a common form.

RESULTS: There were 3188 abstracts screened, and 321 articles underwent full review. Twenty-six articles (<1% of abstracts initially screened), which consisted of 25 randomized controlled trials and 1 meta-analysis, were rated as having level I evidence. Eighteen of the 28 topics selected for this review did not have level I evidence studies published. The management and prevention of pain episodes accounted for more than one-third of the level I studies.

CONCLUSIONS: Although significant strides have been made in the care of children with SCD in the past 2 decades, more research needs to be performed, especially for acute events associated with SCD, to ensure that the health and well-being of children with SCD continues to improve. *Pediatrics* 2011;128:e1552–e1574

AUTHORS: Patricia L. Kavanagh, MD,[a] Philippa G. Sprinz, MD, MSc,[a] Samuel R. Vinci, BS,[a] Howard Bauchner, MD,[b] and C. Jason Wang, MD, PhD[c]

[a]Department of Pediatrics, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts; [b]Journal of the American Medical Association, Chicago, IL; and [c]Department of Pediatrics, Center for Policy, Outcomes, and Prevention, Stanford University School of Medicine, Stanford, CA

KEY WORDS

sickle cell disease, systematic reviews, child and adolescent, evidence-based medicine

ABBREVIATIONS

SCD—sickle cell disease
RCT— randomized controlled trial
ACS—acute chest syndrome

Dr Kavanagh was responsible for performing the electronic literature searches, review of abstracts and articles, data entry and analysis, and drafting the manuscript; Dr Sprinz served as the hematologist on the team and participated in the review of abstracts and articles and write-up; Mr Vinci assisted in the literature review, data entry, and write-up; Dr Bauchner contributed significantly to the data analysis and write-up; and Dr Wang oversaw the entire project, including the study design, review of abstracts and articles, data analysis, and write-up.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-3686

doi:10.1542/peds.2010-3686

Accepted for publication Aug 16, 2011

Address correspondence to Patricia L. Kavanagh, MD, Division of General Pediatrics, Boston University School of Medicine/Boston Medical Center, 88 E Newton St, Vose Hall, 3rd Floor, Boston, MA 02118. E-mail: patricia.kavanagh@bmc.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Sickle cell disease (SCD) is one of the most common genetic disorders in the United States and affects ~70 000 to 100 000 children and adults, predominantly of African and Hispanic descent.[1] SCD is a multisystem disease characterized by vascular injury caused by vaso-occlusion and hemolytic and infectious complications that contribute to high morbidity and mortality rates in this population.[2,3] Many severe complications of SCD occur in childhood, including sepsis, stroke, acute chest syndrome, and painful episodes that require hospitalization.[2,4]

Universal newborn screening and advances in routine care, including penicillin prophylaxis[5] and immunization against serious bacterial infections,[6,7] have significantly decreased mortality in young children with SCD.[8,9] In addition, transcranial Doppler screening has been shown to identify children at higher risk of first-time stroke that can be treated prophylactically with chronic transfusion therapy.[10,11] However, research studies are lacking in key areas for children with SCD, including studies of disease-modifying treatments. For example, the Multicenter Study of Hydroxyurea was published in 1995 and a significant decrease was shown in painful episodes and acute chest syndrome in adults,[12] and a single-center study revealed decreased mortality with long-term use.[13] However, only 1 small randomized controlled trial (RCT) has been published on the use of hydroxyurea in children to date.[14]

The purpose of this study was to review the quality of the literature for preventive interventions and treatment of complications for children with SCD to facilitate the use of evidence-based medicine in clinical practice and identify areas in need of additional research. In this study we have focused on level I evidence, because it typically helps define the standards of medical care, including for pediatric SCD.

TABLE 1 Evidence Level of Articles Selected for Full Review

	Level I	Level II	Level III	Total
Acute events, *n*				
ACS	2	3	8	13
Aplastic crisis	0	1	1	2
Fever/sepsis	0	2	7	9
Osteomyelitis	0	1	7	8
Pain episodes	10	6	14	30
Priapism	0	0	8	8
Splenic sequestration	0	2	6	8
Stroke	0	8	13	21
Chronic conditions, *n*				
Asthma	0	4	3	7
Avascular necrosis	0	2	5	7
Gall bladder disease	0	1	7	8
Hepatic dysfunction	0	0	2	2
Leg ulcers	1	0	1	2
Nephropathy	0	2	5	7
Pulmonary hypertension	0	7	4	11
Retinopathy	0	2	0	2
Silent infarcts/neuropsychological testing	0	9	8	17
Routine health care maintenance and disease-modifying treatments, *n*				
Cardiac care	0	1	1	2
Comprehensive care	1	0	7	8
Folate supplementation	0	1	3	4
Genetic counseling/newborn screening	0	0	3	3
Growth	1	3	6	10
Prevention of pneumococcal infections[a]	4	4	7	15
Pulmonary function testing	2	0	8	10
Transcranial Doppler screening	2	7	17	26
Transfusion[b]	2	17	14	33
Hematopoietic stem cell transplant	0	7	3	10
Hydroxyurea	1	21	16	38
Total, *n* (%)	26 (8)	111 (35)	184 (57)	321 (100)

US Preventive Services Task Force ratings.[17] Level I indicates RCTs; level II, well-designed controlled trials without randomization, cohort or case-control analytic studies, or multiple time series with or without intervention, and dramatic results from uncontrolled experiments; level III, opinions of respected authorities based on clinical experience, descriptive studies, or case reports, reports of expert committees.

[a] Includes pneumococcal immunizations and penicillin prophylaxis.

[b] Includes perioperative transfusions, chronic transfusions, and iron overload.

METHODS

Evidence Acquisition

We identified topics important to the care of children with SCD by using guidelines,[2,15] review articles,[3,16] and clinical expertise. In addition, we specifically searched for screening, diagnostic, and treatment interventions used in routine SCD care to ensure their inclusion in this study. The 28 topics identified are listed in Table 1. Individual topics were organized into 3 categories: (1) acute events; (2) chronic conditions; and (3) routine health care maintenance and disease-modifying treatments for SCD. Acute SCD-related events were defined as those that require urgent or emergent care. Chronic conditions included (1) SCD-specific complications that typically do not require immediate attention and persist for ≥ 3 months (eg, avascular necrosis) and (2) chronic illnesses prevalent in the pediatric SCD population (eg, asthma). Finally, routine health care maintenance and disease-modifying treatments were defined as the comprehensive care needed for children with SCD. We searched for these topics in Ovid Medline for the time period of Janu-

ary 1995 through April 2010 and the Cochrane Library.

For each topic, we used several key words to identify relevant articles. We also added the term "sickle cell" to ensure that all of the articles captured for a topic were related to SCD and its specific genotypes (eg, sickle cell anemia, hemoglobin SC disease). We limited each search to "children 0–18 years" and "human" (Appendix 1). In addition to abstracts identified electronically, we performed an ad hoc search of bibliographies of articles selected for this review.

Study Selection

Each abstract was independently reviewed by 2 authors (Drs Kavanagh, Wang, and Sprinz). Abstracts were selected for full-article review if they pertained to the key topics identified, used experimental (eg, RCT) or quasi-experimental (eg, cohort studies with comparison groups) research methods, and enrolled children in the study. If the research methods were unclear in the abstract, the article was reviewed in detail. Studies were excluded if they enrolled adults only, were in vitro or animal studies, gene or genome-wide association studies, non–English-language abstracts or articles, commentaries or editorials, or case reports. We also excluded longitudinal cohort studies that presented outcomes aggregated over 1 or more decades without description of the care processes. Although these studies could provide important information on the historical natural history of SCD, they might not reflect outcomes that could be achieved under current standards of care.

Data Extraction

Articles selected from the review of abstracts were retrieved for full article evaluation. Data were abstracted by each reviewer using a common form.

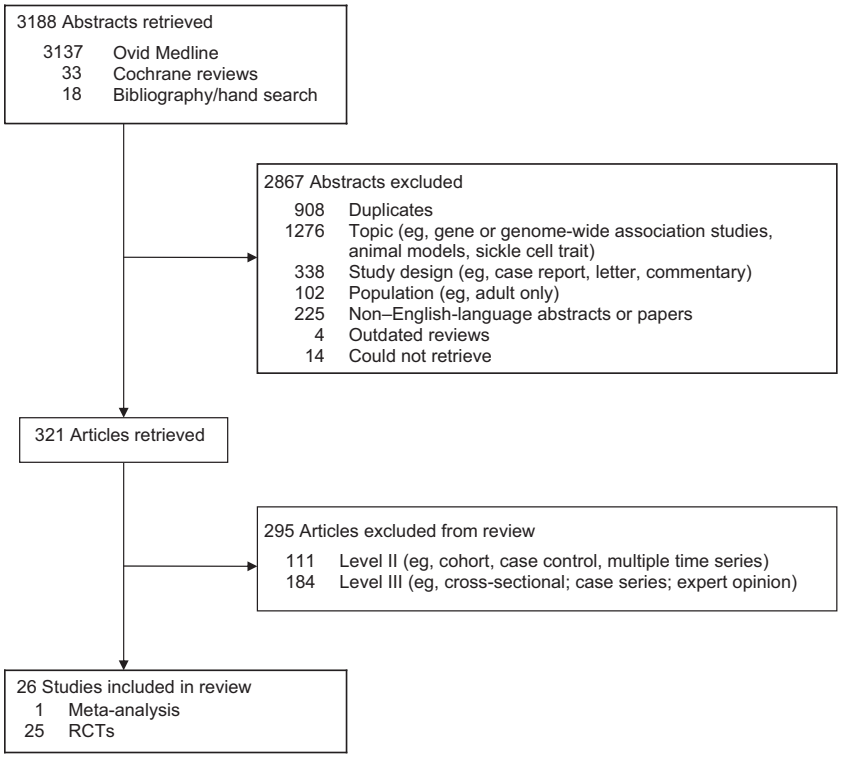

FIGURE 1
Flow diagram of identification of articles for full review.

The abstraction form included fields for the number of participants, population of interest, intervention(s) studied, and study design. Differences in coding were reconciled by the pair of reviewers (Drs Kavanagh, Wang, and Sprinz) in consultation with the third reviewer as needed. All references and abstracted data were maintained in Microsoft Excel 2003 (Redmond, WA).

Quality of the Literature

The hierarchy of research design was assigned following the US Preventive Services Task Force ratings.[17] RCTs and meta-analyses were categorized as level I evidence. Level II evidence included well designed controlled trials without randomization, cohort and case-control studies, multiple time series analyses, and results from uncontrolled experiments. Level III evidence was defined as studies reflecting the opinions of respected authorities on the basis of clinical experience, descriptive studies or case reports, and reports of expert committees.

RESULTS

We identified 3188 abstracts for screening (Fig 1). Of these, 2867 abstracts were eliminated because of duplicate references, topic, study design, population, non–English-language abstract or article, outdated reviews or unable to be retrieved. There were 321 (10% of abstracts screened) articles selected for full review (Appendix 2), of which 26 were rated as level I evidence (Table 1). We identified 25 RCTs and 1 meta-analysis from which we extracted summary data. Eighteen of the 28 topics selected for this literature review did not have level I evidence published during this 15-year period. Of the 321 articles selected for full review, 111 and 184 articles were categorized as level II and level III evidence, respectively (Table 1).

TABLE 2 Acute Events and Chronic Conditions in Children With SCD

Source	*N*	Age Range, y	Population	Intervention	Design
Acute events					
ACS					
Styles et al[18] (2007)	15	10–20	SCD	Single red blood cell transfusion vs standard care	RCT
Bernini et al[19] (1998)	43	1–21	SCD	Dexamethasone vs placebo	RCT
Pain episodes					
Treatment of pain episodes					
Qari et al[20] (2007)[a]	253	Not given[a]	HbSS	Tinzaparin vs placebo plus morphine intravenous	RCT
Weiner et al[21] (2003)	20	10–21	SCD	Inhaled nitric oxide vs placebo	RCT
Orringer et al[22] (2001)[a]	255	9–53	SCD	Poloxamer 188 vs placebo	RCT
Eke et al[27] (2000)	58	3–14	HbSS	Piroxicam vs aspirin	RCT
Hardwick et al[24] (1999)	41	5–18	SCD	Ketorolac vs placebo plus morphine intravenous	RCT
Adams-Graves et al[23] (1997)[a]	50	15–55	SCD	Poloxamer 188 vs placebo	RCT
Jacobson et al[25] (1997)	50	5–17	SCD	Sustained-release oral morphine vs morphine continuous intravenous infusion	RCT
Prevention of pain episodes					
Lemanek et al[28] (2009)	34	Not given[b]	SCD	Massage administered by caregivers vs standard care	RCT
Alvim et al[29] (2005)	73	5–20	SCD	Piracetam vs placebo	RCT
Wambebe et al[30] (2001)	82	Not given[c]	SCD	Niprisan vs placebo	RCT
Chronic conditions					
Leg ulcers					
Serjeant et al[31] (1997)[a]	15	17–40	HbSS	Propionyl-L-carnitine vs placebo	RCT

SCD indicates that all sickle genotypes were eligible for the study; HbSS, sickle cell anemia.
[a] Mean: 22.8 ± 4.5 y (tinzaparin group) and 21.6 ± 3.8 y (placebo group).
[b] Mean: 9.97 ± 2.47 y (massage group) and 11.55 ± 1.00 y (attention-control group).
[c] A majority were adolescents (81.9%); only 3.6% were older than 30 y.

Acute Events

Twelve RCTs were identified for 2 topics: acute chest syndrome (ACS) and pain episodes (Table 2). We did not find any level I evidence for the acute management of aplastic anemia, fever/sepsis, osteomyelitis, priapism, splenic sequestration, or stroke in children with SCD for the 15-year period reviewed.

Two RCTs have been performed for ACS. In a pilot RCT, elevated serum phospholipase A2 seemed to identify those at risk of ACS, which could be prevented by a single blood transfusion.[18] In addition, treatment with dexamethasone limited the severity of ACS in children, although it was associated with rehospitalization for severe pain within 72 hours of discharge.[19]

The treatment and prevention of SCD-related pain accounted for nearly 40% of the level I studies identified. Ten RCTs were identified for the management of SCD-related pain in children; 7 examined treatment regimens and 3 studied pain prophylaxis. Tinzaparin decreased the number of severe pain days and hospital days but was associated with minor bleeding events in 1.5% of patients.[20] In a pilot RCT it was found that nitric oxide was also a potentially useful as a treatment for acute pain.[21] However, poloxamer 188 had little[22] to no[23] effect on the duration of pain in intent-to-treat analyses, and ketorolac[24] proved ineffective as an adjunct to opioid treatment for severe pain requiring hospitalization. Sustained-release oral morphine proved as effective as the parenteral formulation in the inpatient setting[25]; however, it was associated with an increased incidence of ACS in posthoc analyses.[26] In resource-poor settings, the nonsteroid anti-inflammatory drug piroxicam was superior to aspirin for SCD-related pain.[27] For pain prophylaxis, massage therapy was shown to decrease average pain scores among children with SCD, but increased anxiety among the parents administering it and had no effect on health care use.[28] Piracetam was not found effective in a Brazilian RCT[29]; however, the Nigerian herbal remedy Niprisan did decrease the number of severe pain episodes.[30]

Chronic Conditions

For SCD-related leg ulcers, a pilot RCT compared oral propionyl-L-carnitine to placebo in adolescents and adults, but showed no benefit as an adjunct to usual care (Table 2).[31] Level I evidence was not available for the management or prevention of asthma, avascular necrosis, gall bladder disease, hepatic dysfunction, nephropathy, pulmonary hypertension, retinopathy, and silent infarcts/neuropsychological testing.

Routine Health Care Maintenance and Disease-Modifying Treatments

Our review found 1 meta-analysis and 12 RCTs for 7 of the 11 topics included in this category (Table 3). However, no level I evidence was identified for cardiac care, folate supplementation, genetic counseling, or hematopoietic stem cell transplant.

TABLE 3 Routine Health Care Maintenance and Disease-Modifying Treatment Options for Children With SCD

Source	*N*	Age Range	Population	Intervention	Design
Comprehensive care					
Chernoff et al[32] (2002)[a]	136	7–11 y	HbSS	Community-based, family support intervention vs standard care	RCT
Growth					
Zemel et al[33] (2002)	42	4–10 y	HbSS	Elemental zinc vs placebo	RCT
Prevention of pneumococcal infections					
Immunizations					
Vernacchio et al[34] (1998)	23	4–30 y	SCD	2 doses PCV-7 plus 23V pneumococcal PSV vs 23V pneumococcal PSV	RCT
Penicillin prophylaxis					
Hirst et al[5,35,36,62] (2009)	457	<16 y	HbSS, HbSβ^0	Prophylactic antibiotics to prevent pneumococcal infection	Meta-analysis
Berkovitch et al[37] (1998)	45	9–84 mo	HbSS	Slide show, weekly telephone calls, and a calendar vs standard care	RCT
Falletta et al[36] (1995)	218	5.1 y	HbSS, HbSβ^0	Penicillin vs placebo in children with SCD older than 5 y	RCT
Pulmonary function testing					
Hsu et al[39] (2005)	20	5.6–13.4 y	SCD	Positive expiratory pressure device vs incentive spirometry	RCT
Bellet et al[38] (1995)	38	8–21 y	SCD	Incentive spirometry vs standard care	RCT
Transcranial Doppler screening					
Adams et al[10] (2005)	80	2–16 y	HbSS, HbSβ^0	Chronic transfusion vs standard care	RCT
Adams et al[11] (1998)	130	2–16 y	HbSS, HbSβ^0	Chronic transfusion vs standard care	RCT
Transfusion					
Iron chelation					
Vichinsky et al[41] (2007)[a]	195	3–54 y	SCD	Deferasirox vs deferoxamine	RCT
Perioperative transfusion					
Vichinsky et al[40] (1995)[a]	604	Not given[a]	HbSS	Aggressive transfusion to decrease HbS to <30% vs simple transfusion	RCT
Disease-modifying treatment					
Hydroxyurea					
Ferster et al[14] (1996)[a]	22	2–22 y	HbSS	Hydroxyurea vs placebo	RCT

23V, 23-valent; PSV, polysaccharide vaccine; SCD, all sickle genotypes were eligible for the study; HbSS, sickle cell anemia; HbSβ^0, hemoglobin sickle-β^0 thalassemia.
[a] Age from Table 1; 0 to 20 y or older at time of enrollment.

Comprehensive care for children with SCD includes family support and monitoring of growth.[2] A RCT that randomly assigned patients and their families to receive community support had a positive effect on the adjustment of children with serious conditions, including SCD, compared with those who received standard care.[32] For growth, zinc supplementation for 1 year was proven beneficial in children with SCD.[33]

Protection against *Streptococcus pneumoniae* through immunizations and penicillin prophylaxis has been studied extensively among children with SCD over the past 15 years. Immunization against *S pneumoniae* using the 7-valent conjugate vaccine resulted in higher immunoglobulin G antibody concentrations than using the 23-valent polysaccharide vaccine alone.[34] A recent meta-analysis found that penicillin prophylaxis significantly reduced the risk of pneumococcal infection in children younger than 5 with sickle cell anemia.[35] Current guidelines recommend stopping prophylaxis at 5 years of age for children without a history of invasive pneumococcal disease or splenectomy because continuing prophylaxis provided no additional benefit.[35,36] Adherence with penicillin prophylaxis, nevertheless, remains an issue. Interventions to increase adherence through education, telephone calls, and use of a calendar were not more effective than education alone.[37]

Optimizing pulmonary function during pain episodes and use of transcranial Doppler screening, transfusions, and iron chelation have been shown to be effective preventive or treatment strategies for SCD-related complications in children. Incentive spirometry has also been shown to prevent ACS during acute pain episodes in the chest or back.[38] In a pilot study, no difference was seen between the use of a positive expiratory pressure device (which requires less coordination to use) and incentive spirometry in preventing pulmonary complications during pain episodes.[39] Two studies provided level I evidence for chronic transfusion regimens to decrease the rate of first-time stroke in children with HbSS disease and HbSβ^0 thalassemia identified as high risk by transcranial Doppler screening.[10,11] Prophylactic transfusions are used to prevent perioperative SCD-related complications before

elective surgery. A large, multicenter RCT revealed that a conservative transfusion regimen designed to increase the hemoglobin level to 10 g/dL was as effective as an aggressive transfusion program that reduced the percentage HbS to <30%, for several elective surgical procedures.[40,42–44] Finally, management of transfusion-related iron overload with oral deferasirox was shown to be comparable to deferoxamine.[41]

Hydroxyurea is currently used to treat individuals with severe manifestations of SCD. Only 1 small RCT has been published on its use in children with SCD to date, which showed a significant reduction in the number of hospitalizations and length of stay.[14] Results from the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) study[45] and Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG),[46–49] in which the efficacy of hydroxyurea was examined in secondary stroke prevention and prevention of end-organ damage in infants with SCD, respectively, were not published at the time of this review. However, it is suggested in preliminary data from Infant HUGS that hydroxyurea use decreased the frequency of pain episodes and ACS in young children.[46] In addition, RCTs have not been conducted on different conditioning regimens or other aspects of management of hematopoietic stem cell transplantation in this population.

DISCUSSION

To our knowledge, this is the first comprehensive review of the literature for the care provided to children with SCD. On the basis of the results of this study, <1% of studies for children with SCD published from January 1995 to April 2010 represent level I evidence. In addition, >60% (18 of 28) of the topics selected for this review did not have any RCTs or meta-analyses supporting treatment or prevention strategies for pediatric SCD. These findings are consistent with our review of the Cochrane Library of Systematic Reviews, in which it was concluded that in 14 of the 29 reviews on pediatric SCD-related topics no high-quality studies currently exist. The lack of RCTs performed in children with SCD is not unique to this population. Although we did not search the adult SCD literature to make a direct comparison, it was found in previous reports on other topics that significantly fewer high-quality studies have been published for children compared with adults in the both the generalist[50] and specialist[51] journals.

The area most in need of additional investigation is acute events associated with SCD because many are associated with significant morbidity and mortality. We did not find any high-quality studies for 75% of the acute events listed, including the management of splenic sequestration and treatment of overt strokes. In addition, the level I evidence found for SCD-related pain focused primarily on the management of severe pain requiring emergency department or inpatient care. However, most pain episodes are managed at home,[52] and no high-quality studies have been conducted in this setting to date.[53]

In only 3 of the 26 studies included in this review was the effect of SCD measured on a child's academic achievement, parental stress level, or the quality of life of either the child or their parents.[28,29,32] However, many SCD-related complications, particularly pain episodes, might last for days or weeks after the health care encounter.[2,54] These outcomes are important measures to capture for children, especially those with chronic illness such as SCD, because their disease can negatively impact both their educational attainment and their family life.[55–57]

In this review we focused on RCTs and meta-analyses conducted on children with SCD. However, there are circumstances when conducting a RCT might not be feasible. For example, it is impractical to use a RCT to study conditioning regimens for hematopoietic stem cell transplant at present because only a small number of children with severe SCD-related complications currently undergo this procedure. Research methodologies such as comparative effectiveness research and long-term observation studies can provide valuable information for these interventions.

There are several potential limitations to this study. First, we might have missed some studies by using our defined search strategies, including studies that enrolled both children and adults. However, we believe that our use of a broad approach using a combination of electronic search terms and hand-searches of bibliographies minimized the omission of important studies. In addition, more than one-third of studies selected for full review (90/321 articles) included both pediatric and adult subjects. Second, we limited our review to the English-language literature, which possibly eliminated important studies conducted abroad. However, by reviewing the bibliography of the articles reviewed for this study and those cited in National Institutes of Health guidelines for the management of SCD,[2] we believe that we captured the important articles on this subject. Third, we used Ovid Medline to conduct our searches, which largely focuses on the medical literature produced in North America. Therefore, we might have missed European and other international studies that would have been identified had another database been used. However, we captured a large number of European, South

American, and African studies in this review, whose bibliographies were used to supplement our electronic searches. Fourth, we conducted our literature searches using a list of predefined topics for pediatric SCD. Although we might have missed high-quality studies in areas not considered in this review, we believe this effort had an appropriately broad scope to comment on the evidence for the care currently provided to children with SCD. Finally, we limited our study to the 15-year period that ended April 2010 to focus on the recent advances in pediatric SCD. Although studies done before 1995 contributed significantly to the knowledge base, a review of the 15-year period (1980–1994) before our study revealed 7 RCTs had been conducted during this time.[5,58–63] Except for folate supplementation, these studies informed subsequent trials which are included in this report, which have helped define the current standard of care for children with SCD.

CONCLUSIONS

Providing appropriate care for children with SCD might help prevent or ameliorate many of the complications associated with this disease, and allow them to have a healthier, more productive adulthood. There are many important areas of care in pediatric SCD that lack RCTs. This finding highlights the dual difficulties of performing research on a rare disease[64] in a pediatric population.[65] Several important trials are currently under way, including the use of hydroxyurea in children with abnormal transcranial Doppler screenings to prevent additional damage to the cerebral vessels and the use of chronic transfusions to prevent silent infarcts in children with SCD.[47,66] However, more work is needed to ensure that the health and well-being of children with SCD continues to improve.

ACKNOWLEDGMENTS

This work was supported in part by an unrestricted research grant from Novartis Pharmaceuticals Corp (to Dr Wang) that guaranteed researchers full scientific independence for this work.

We thank Barry Zuckerman, MD, for support of this project and Naomi Ilaire for contributions to data entry and article retrieval.

REFERENCES

1. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. 2010; 38(suppl 4):S512–S521
2. National Heart Lung and Blood Institute. *The Management of Sickle Cell Disease*. Bethesda, MD: National Institutes of Health; 2002. NIH publication No. 02-2117
3. Steinberg MH. Management of sickle cell disease. *N Engl J Med*. 1999;340(13): 1021–1030
4. Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative study of sickle cell disease. *Blood*. 1995; 86(2):776–783
5. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: a randomized trial. *N Engl J Med*. 1986;314(25):1593–1599
6. Adamkiewicz TV, Silk BJ, Howgate J, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. *Pediatrics*. 2008;121(3):562–569
7. Adamkiewicz TV, Sarnaik S, Buchanan GR, et al. Invasive pneumococcal infections in children with sickle cell disease in the era of penicillin prophylaxis, antibiotic resistance, and 23-valent pneumococcal polysaccharide vaccination. *J Pediatr*. 2003;143(4): 438–444
8. Yanni E, Grosse SD, Yang Q, et al. Trends in pediatric sickle cell disease-related mortality in the United States, 1983–2002. *J Pediatr*. 2009;154(4):541–545
9. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. *Blood*. 2010;115(17):3447–3452
10. Adams RJ, Brambilla D, Optimizing Primary Stroke Prevention in Sickle Cell Anemia Trial I. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med*. 2005;353(26): 2769–2778
11. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial doppler ultrasonography. *N Engl J Med*. 1998;339(1):5–11
12. 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
13. Voskaridou E, Christoulas D, Bilalis A, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). *Blood*. 2010;115(12):2354–2363
14. Ferster A, Vermylen C, Cornu G, et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. *Blood*. 1996;88(6):1960–1964
15. Section on Hematology/Oncology and Committee on Genetics. Health supervision for children with sickle cell disease. *Pediatrics*. 2002;109(3):526–535
16. Dick MC. Standards for the management of sickle cell disease in children. *Arch Dis Child Ed Pract*. 2008;93(6):169–176
17. US Preventive Services Task Force. *Procedure Manual*. Rockville, MD: Agency for Healthcare Research and Quality; 2008. Publication No. 08-05118–EF. Available at: www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual4.htm. Accessed July 5, 2010
18. Styles LA, Abboud M, Larkin S, Lo M, Kuypers FA. Transfusion prevents acute chest syndrome predicted by elevated secretory phospholipase a2. *Br J Haematol*. 2007; 136(2):343–344
19. Bernini JC, Rogers ZR, Sandler ES, Reisch JS, Quinn CT, Buchanan GR. Beneficial effect of intravenous dexamethasone in children with mild to moderately severe acute chest syndrome complicating sickle cell disease. *Blood*. 1998;92(9):3082–3089
20. Qari MH, Aljaouni SK, Alardawi MS, et al. Reduction of painful vaso-occlusive crisis of sickle cell anaemia by tinzaparin in a double-blind randomized trial. *Thromb Haemost*. 2007;98(2):392–396
21. Weiner DL, Hibberd PL, Betit P, Cooper AB, Botelho CA, Brugnara C. Preliminary assessment of inhaled nitric oxide for acute vaso-

occlusive crisis in pediatric patients with sickle cell disease [published correction appears in *JAMA*. 2004;292(8):925]. *JAMA*. 2003;289(9):1136–1142

22. Orringer EP, Casella JF, Ataga KI, et al. Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA*. 2001; 286(17):2099–2106
23. Adams-Graves P, Kedar A, Koshy M, et al. Rheothrx (poloxamer 188) injection for the acute painful episode of sickle cell disease: a pilot study. *Blood*. 1997;90(5):2041–2046
24. Hardwick WE, Jr, Givens TG, Monroe KW, King WD, Lawley D. Effect of ketorolac in pediatric sickle cell vaso-occlusive pain crisis. *Pediatr Emerg Care*. 1999;15(3):179–182
25. Jacobson SJ, Kopecky EA, Joshi P, Babul N. Randomised trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet*. 1997;350(9088):1358–1361
26. Kopecky EA, Jacobson S, Joshi P, Koren G. Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. *Clin Pharmacol Ther*. 2004;75(3): 140–146
27. Eke FU, Obamyonyi A, Eke NN, Oyewo EA. An open comparative study of dispersible piroxicam versus soluble acetylsalicylic acid for the treatment of osteoarticular painful attack during sickle cell crisis. *Trop Med Int Health*. 2000;5(2):81–84
28. Lemanek KL, Ranalli M, Lukens C. A randomized controlled trial of massage therapy in children with sickle cell disease. *J Pediatr Psychol*. 2009;34(10):1091–1096
29. Alvim RC, Viana MB, Pires MAS, et al. Inefficacy of piracetam in the prevention of painful crises in children and adolescents with sickle cell disease. *Acta Haematol*. 2005; 113(4):228–233
30. Wambebe C, Khamofu H, Momoh JA, et al. Double-blind, placebo-controlled, randomised cross-over clinical trial of niprisan in patients with sickle cell disorder. *Phytomedicine*. 2001;8(4):252–261
31. Serjeant BE, Harris J, Thomas P, Serjeant GR. Propionyl-L-carnitine in chronic leg ulcers of homozygous sickle cell disease: a pilot study. *J Am Acad Dermatol*. 1997;37(3 pt 1):491–493
32. Chernoff RG, Ireys HT, DeVet KA, Kim YJ. A randomized, controlled trial of a community-based support program for families of children with chronic illness: pediatric outcomes. *Arch Pediatr Adolesc Med*. 2002;156(6):533–539
33. Zemel BS, Kawchak DA, Fung EB, Ohene-Frempong K, Stallings VA. Effect of zinc supplementation on growth and body composition in children with sickle cell disease. *Am J Clin Nutr*. 2002;75(2):300–307
34. Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. *J Pediatr*. 1998;133(2):275–278
35. Hirst C, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database Syst Rev*. 2009;(4): CD003427
36. Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia: prophylactic penicillin study II. *J Pediatr*. 1995;127(5): 685–690
37. Berkovitch M, Papadouris D, Shaw D, Onuaha N, Dias C, Olivieri NF. Trying to improve compliance with prophylactic penicillin therapy in children with sickle cell disease. *Br J Clin Pharmacol*. 1998;45(6):605–607
38. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. *N Engl J Med*. 1995; 333(11):699–703
39. Hsu LL, Batts BK, Rau JL. Positive expiratory pressure device acceptance by hospitalized children with sickle cell disease is comparable to incentive spirometry. *Respir Care*. 2005;50(5):624–627
40. Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The preoperative transfusion in sickle cell disease study group. *N Engl J Med*. 1995; 333(4):206–213
41. Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. *Br J Haematol*. 2007;136(3): 501–508
42. Waldron P, Pegelow C, Neumayr L, et al. Tonsillectomy, adenoidectomy, and myringotomy in sickle cell disease: perioperative morbidity: preoperative transfusion in sickle cell disease study group. *J Pediatr Hematol Oncol*. 1999;21(2):129–135
43. Vichinsky EP, Neumayr LD, Haberkern C, et al. The perioperative complication rate of orthopedic surgery in sickle cell disease: report of the National Sickle Cell Surgery Study Group. *Am J Hematol*. 1999;62(3): 129–138
44. Haberkern CM, Neumayr LD, Orringer EP, et al. Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the national preoperative transfusion study. Preoperative transfusion in sickle cell disease study group. *Blood*. 1997; 89(5):1533–1542
45. National Heart Lung and Blood Institute. Stroke prevention study in children with sickle cell anemia, iron overload stopped early [press release]. Available at: www.nih.gov/news/health/jun2010/nhlbi-03.htm. Accessed June 4, 2010
46. National Heart Lung and Blood Institute. NIH-funded study finds sickle cell treatment safe for young children [press release]. Available at: http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2788. Accessed May 12, 2011
47. Thornburg CD, Rogers ZR, Jeng MR, et al. Adherence to study medication and visits: fata from the BABY HUG trial. *Pediatr Blood Cancer*. 2010;54(2):260–264
48. Pavlakis SG, Rees RC, Huang X, et al. Transcranial doppler ultrasonography (TCD) in infants with sickle cell anemia: baseline data from the baby hug trial. *Pediatr Blood Cancer*. 2010;54(2):256–259
49. Ware RE, Rees RC, Sarnaik SA, et al. Renal function in infants with sickle cell anemia: baseline data from the BABY HUG trial. *J Pediatr*. 2010;156(1):66–70.e61
50. Martinez-Castaldi C, Silverstein M, Bauchner H. Child versus adult research: the gap in high-quality study design. *Pediatrics*. 2008;122(1):52–57
51. Cohen E, Goldman RD, Ragone A, et al. Child vs adult randomized controlled trials in specialist journals: a citation analysis of trends, 1985–2005. *Arch Pediatr Adolesc Med*. 2010;164(3):283–288
52. Gil KM, Porter L, Ready J, Workman E, Sedway J, Anthony KK. Pain in children and adolescents with sickle cell disease: an analysis of daily pain diaries. *Child Health Care*. 2000;29(4):225–241
53. Bennett DR. Pain management for sickle cell disease in children and adults. *Cochrane Database Syst Rev*. 2009;(3):CD14003350
54. Benjamin LJ, Dampier CD, Jacox A, et al. *Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease*. Glenview, IL: American Pain Society; 1999
55. Weitzman M. School absence rates as outcome measures in studies of children with chronic illness. *J Chronic Dis*. 1986;39(10):799–808
56. Fowler MG, Johnson MP, Atkinson SS. School achievement and absence in children with chronic health conditions. *J Pediatr*. 1985;106(4):683–687
57. Thies KM. Identifying the educational impli-

cations of chronic illness in school children. *J Sch Health*. 1999;69(10):392–397

58. Griffin TC, McIntire D, Buchanan GR. High-dose intravenous methylprednisolone therapy for pain in children and adolescents with sickle cell disease. *N Engl J Med*. 1994; 330(11):733–737
59. Wilimas JA, Flynn PM, Harris S, et al. A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease. *N Engl J Med*. 1994; 329(7):472–476
60. Silliman C, Peterson VM, Mellman DL, Dixon DJ, Hambridge KM, Lane PA. Iron chelation by deferoxamine in sickle cell patients with severe transfusion-induced hemosiderosis: a randomized, double-blind study of the dose-response relationship. *J Lab Clin Med*. 1993;122(1):48–54
61. Baum KF, MacFarlane DE, Maude GH, Serjeant GR. Topical antibiotics in chronic sickle cell leg ulcers. *Trans R Soc Trop Med Hyg*. 1987;81(5):847–849
62. John AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *Br Med J (Clin Res Ed)*. 1984;288(6430):1567–1570
63. Rabb LM, Grandison Y, Mason K, Hayes RJ, Serjeant B, Serjeant GR. A trial of folate supplementation in children with homozygous sickle cell disease. *Br J Haematol*. 1983;54(4):589–594
64. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: opportunities, challenges, and solutions. *Mol Genet Metab*. 2009;96(1):20–26
65. Caldwell PHY, Murphy SB, Butow PN, Craig JC. Clinical trials in children. *Lancet*. 2004; 364(9436):803–811
66. Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood*. 2010;115(26):5300–5311

APPENDIX 1 Medline Search Strategies

I. Acute events
1. Acute chest syndrome
   acute chest syndrome.mp.
   or acute chest.mp. or exp pneumonia/or exp lung diseases
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
2. Aplastic crisis
   exp anemia, aplastic
   or aplastic crisis.mp. or exp parvovirus/or parvovirus B19, human
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
3. Fever/sepsis
   exp fever
   or exp bacteremia/or exp sepsis/or septicemia.mp./ or exp meningitis/or exp dehydration/or exp gastroenteritis/or exp abdominal pain
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
4. Osteomyelitis
   exp osteomyelitis
   or bone infection.mp.
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
5. Pain episodes
   exp pain
   or vaso-occlusive crisis.mp. or vasoocclusive crisis.mp. or exp narcotics/or exp analgesics, opioid/or exp analgesics
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
6. Priapism
   exp priapism
   or exp penile erection/impotence/or penile prosthesis
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
7. Splenic sequestration
   splenic sequestration.mp.
   or exp splenectomy/or exp spleen/or exp splenic diseases/or exp hypersplenism
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
8. Stroke
   exp cerebrovascular accident
   or stroke.mp. or CVA.mp.
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")

II. Chronic conditions
1. Asthma
   exp Asthma
   or reactive airway disease.mp.
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
2. Avascular necrosis
   aseptic necrosis.mp.
   or avascular necrosis.mp. or avn.mp. or exp femur head necrosis/or exp osteonecrosis/or humeral head necrosis.mp.
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
3. Gall bladder disease
   exp cholelithiasis
   or exp cholecystitis/or exp choledocholithiasis/or exp cholestasis/or exp gallstones/or exp gallbladder/or exp cholecystectomy
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")

APPENDIX 1 Continued

4. Hepatic dysfunction
   exp liver
   or hepatic sequestration.mp
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
5. Leg ulcers
   exp Leg ulcer
   or leg ulcer.mp
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
6. Nephropathy
   exp proteinuria
   or exp renal insufficiency, chronic/or exp hematuria/or exp kidney papillary necrosis/or (kidney and infarction).mp.
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
7. Pulmonary hypertension
   exp hypertension, pulmonary
   or exp hypertrophy, right ventricular
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
8. Retinopathy
   retinopathy.mp.
   or exp retinal neovascularization/or exp corneal neovascularization/or exp neovascularization, physiologic/or exp choroidal neovascularization/or exp neovascularization, pathologic/or exp neovascularization.mp. or photocoagulation.mp./ or exp laser coagulation/or exp light coagulation/or laser photocoagulation.mp. or exp macular degeneration/or exp retinal detachment/or exp glaucoma/or exp diagnostic techniques, ophthalmological/or exp ophthalmoscopy/or vision tests
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
9. Silent infarcts/neuropsychological testing
   exp neuropsychological tests
   or exp brain/and exp magnetic resonance Imaging/or exp cognition/or silent stroke.mp or silent infarct.mp
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")

III. Routine health care maintenance and disease-modifying treatment options

1. Cardiac care
   exp cardiomegaly
   or exp hypertrophy, right ventricular/or exp ventricular dysfunction, right/or exp heart failure, congestive/or exp heart diseases/or exp echocardiography/or exp electrocardiography
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
2. Comprehensive care
   exp Primary health care
   or health maintenance.mp/or health supervision.mp.
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
3. Folate supplementation
   exp folic acid
   or folate.mp.
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
4. Genetic counseling/newborn screening
   exp genetic counseling
   or exp neonatal screening
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
5. Growth
   exp growth and development
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")

APPENDIX 1 Continued

6. Prevention of pneumococcal infections
   exp immunization
   or exp vaccines/or exp penicillins/or exp antibiotic prophylaxis
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
7. Pulmonary function testing
   exp respiratory function tests
   or pulmonary function test.mp or exp pulmonary fibrosis/or interstitial fibrosis.mp. or exp pulmonary diffusing capacity or exp lung diseases, obstructive/or exp bronchial hyperreactivity/or exp sleep apnea, obstructive/or hypoxia.mp. or exp sleep apnea syndromes
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
8. Transcranial Doppler screening
   exp ultrasonography, Doppler, transcranial
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
9. Transfusion
   chronic transfusion.mp.
   or exp iron overload/or exp chelation therapy/or exp deferoxamine/or exp iron chelating agents/or transfusion protocol.mp./ or hypertransfusion.mp. or transfusion.mp. or exp transfusion erythrocyte transfusion/or exp blood transfusion/or exp blood component transfusion/or exp blood transfusion, autologous/or exp exchange transfusion, whole blood
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
10. Hematopoietic stem cell transplant
   exp bone marrow transplantation
   or exp hematopoietic stem cell transplant
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")
11. Hydroxyurea
   exp hydroxyurea
   and sickle cell.mp.
   limit to (humans and "all child (0 to 18 years)")

APPENDIX 2 Articles Selected for Full Review

	Evidence Level
I. Acute events	
Acute chest syndrome[1–13]	
1. Sobota A, Graham DA, Heeney MM, Neufeld EJ. Corticosteroids for acute chest syndrome in children with sickle cell disease: variation in use and association with length of stay and readmission. *Am J Hematol*. 2010;85(1):24–28	III
2. Styles LA, Abboud M, Larkin S, Lo M, Kuypers FA. Transfusion prevents acute chest syndrome predicted by elevated secretory phospholipase A2. *Br J Haematol*. 2007;136(2):343–344	I
3. Sylvester KP, Patey RA, Milligan P, et al. Impact of acute chest syndrome on lung function of children with sickle cell disease. *J Pediatr*. 2006;149(1):17–22	II
4. Ballas SK, Files B, Luchtman-Jones L, et al. Safety of purified poloxamer 188 in sickle cell disease: Phase I study of a non-ionic surfactant in the management of acute chest syndrome. *Hemoglobin*. 2004;28(2):85–102	II
5. Crawford MW, Speakman M, Carver ED, Kim PCW. Acute chest syndrome shows a predilection for basal lung regions on the side of upper abdominal surgery. *Can J Anaesth*. 2004;51(7):707–711	III
6. Dean D, Neumayr L, Kelly DM, et al. Chlamydia pneumoniae and acute chest syndrome in patients with sickle cell disease. *J Pediatr Hematol Oncol*. 2003;25(1):46–55	III
7. Neumayr L, Lennette E, Kelly D, et al. Mycoplasma disease and acute chest syndrome in sickle cell disease. *Pediatrics*. 2003;112(1 pt 1):87–95	III
8. Jenkins TL. Sickle cell anemia in the pediatric intensive care unit: novel approaches for managing life-threatening complications. *AACN Clin Issues*. 2002;13(2):154–168	III
9. Wales PW, Carver E, Crawford MW, Kim PC. Acute chest syndrome after abdominal surgery in children with sickle cell disease: is a laparoscopic approach better? *J Pediatr Surg*. 2001;36(5):718–721	III
10. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group [published correction appears in *N Engl J Med*. 2000;343(11):824]. *N Engl J Med*. 2000;342(25):1855–1865	III
11. Morris C, Vichinsky E, Styles L. Clinician assessment for acute chest syndrome in febrile patients with sickle cell disease: is it accurate enough? *Ann Emerg Med*. 1999;34(1):64–69	III
12. Bernini JC, Rogers ZR, Sandler ES, Reisch JS, Quinn CT, Buchanan GR. Beneficial effect of intravenous dexamethasone in children with mild to moderately severe acute chest syndrome complicating sickle cell disease. *Blood*. 1998;92(9):3082–3089	I
13. Emre U, Miller ST, Gutierez M, Steiner P, Rao SP, Rao M. Effect of transfusion in acute chest syndrome of sickle cell disease. *J Pediatr*. 1995;127(6):901–904	II
Aplastic crisis[14–15]	
14. Smith-Whitley K, Zhao H, Hodinka RL, et al. Epidemiology of human parvovirus B19 in children with sickle cell disease. *Blood*. 2004;103(2):422–427	II
15. Wethers DL, Grover R, Oyeku S. Aplastic crisis and acute splenic sequestration crisis. *J Pediatr Hematol Oncol*. 2000;22(2):187–188	III
Fever and sepsis[16–24]	
16. Halasa NB, Shankar SM, Talbot TR, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. *Clin Infect Dis*. 2007;44(11):1428–1433	II
17. McGregor D, Barton M, Thomas S, Christie CD. Invasive pneumococcal disease in Jamaican children. *Ann Trop Paediatr*. 2004;24(1):33–40	III
18. Adamkiewicz TV, Sarnaik S, Buchanan GR, et al. Invasive pneumococcal infections in children with sickle cell disease in the era of penicillin prophylaxis, antibiotic resistance, and 23-valent pneumococcal polysaccharide vaccination [published correction appears in *J Pediatr*. 2004; 144(3):412]. *J Pediatr*. 2003;143(4):438–444	II
19. Norris CF, Smith-Whitley K, McGowan KL. Positive blood cultures in sickle cell disease: time to positivity and clinical outcome. *J Pediatr Hematol Oncol*. 2003;25(5):390–395	III
20. Hord J, Byrd R, Stowe L, Windsor B, Smith-Whitley K. Streptococcus pneumoniae sepsis and meningitis during the penicillin prophylaxis era in children with sickle cell disease. *J Pediatr Hematol Oncol*. 2002;24(6):470–472	III
21. West DC, Andrada E, Azari R, Rangaswami AA, Kuppermann N. Predictors of bacteremia in febrile children with sickle cell disease. *J Pediatr Hematol Oncol*. 2002;24(4):279–283	III
22. Neonato MG, Guilloud-Bataille M, Beauvais P, et al. Acute clinical events in 299 homozygous sickle cell patients living in France. French Study Group on Sickle Cell Disease. *Eur J Haematol*. 2000;65(3):155–164	III
23. Rahimy MC, Gangbo A, Ahouignan G, Anagonou S, Boco V, Alihonou E. Outpatient management of fever in children with sickle cell disease (SCD) in an African setting. *Am J Hematol*. 1999;62(1):1–6	III
24. Williams LL, Wilimas JA, Harris SC, Day SW, Dancy RM, Wang WC. Outpatient therapy with ceftriaxone and oral cefixime for selected febrile children with sickle cell disease. *J Pediatr Hematol Oncol*. 1996;18(3):257–261	III
Osteomyelitis[25–32]	
25. Berger E, Saunders N, Wang L, et al. Sickle cell disease in children: differentiating osteomyelitis from vaso-occlusive crisis. *Arch Pediatr Adolesc Med*. 2009;163(3):251–255	II
26. Almeida A, Roberts I. Bone involvement in sickle cell disease. *Br J Haematol*. 2005;129(4):482–490	III
27. Skaggs DL, Kim SK, Greene NW, Harris D, Miller JH. Differentiation between bone infarction and acute osteomyelitis in children with sickle-cell disease with use of sequential radionuclide bone-marrow and bone scans. *J Bone Joint Surg Am*. 2001;83-A(12):1810–1813	III
28. Chambers JB, Forsythe DA, Bertrand SL, Iwinski HJ, Steflik DE. Retrospective review of osteoarticular infections in a pediatric sickle cell age group. *J Pediatr Orthop*. 2000;20(5):682–685	III
29. Umans H, Haramati N, Flusser G. The diagnostic role of gadolinium enhanced MRI in distinguishing between acute medullary bone infarct and osteomyelitis. *Magn Reson Imaging*. 2000;18(3):255–262	III
30. William RR, Hussein SS, Jeans WD, Wali YA, Lamki ZA. A prospective study of soft-tissue ultrasonography in sickle cell disease patients with suspected osteomyelitis. *Clin Radiol*. 2000;55(4):307–310	III

APPENDIX 2 Continued

	Evidence Level
31. Frush DP, Heyneman LE, Ware RE, Bissett GS, 3rd. MR features of soft-tissue abnormalities due to acute marrow infarction in five children with sickle cell disease. *AJR Am J Roentgenol.* 1999;173(4):989–993	III
32. Sadat-Ali M, al-Umran K, al-Habdan I, al-Mulhim F. Ultrasonography: can it differentiate between vasoocclusive crisis and acute osteomyelitis in sickle cell disease? *J Pediatr Orthop.* 1998;18(4):552–554	III
Pain episodes[33–62]	
33. O'Brien SH, Fan L, Kelleher KJ. Inpatient use of laxatives during opioid administration in children with sickle cell disease. *Pediatr Blood Cancer.* 2010;54(4):559–562	III
34. Lemanek KL, Ranalli M, Lukens C. A randomized controlled trial of massage therapy in children with sickle cell disease. *J Pediatr Psychol.* 2009;34(10):1091–1096	I
35. McClellan CB, Schatz JC, Mark TR, et al. Criterion and convergent validity for 4 measures of pain in a pediatric sickle cell disease population. *Clin J Pain.* 2009;25(2):146–152	III
36. McClellan CB, Schatz JC, Puffer E, et al. Use of handheld wireless technology for a home-based sickle cell pain management protocol. *J Pediatr Psychol.* 2009;34(5):564–573	III
37. Nolan VG, Zhang Y, Lash T, et al. Association between wind speed and the occurrence of sickle cell acute painful episodes: Results of a case-crossover study. *Br J Haematol.* 2008;143(3):433–438	II
38. Qari MH, Aljaouni SK, Alardawi MS, et al. Reduction of painful vaso-occlusive crisis of sickle cell anaemia by tinzaparin in a double-blind randomized trial. *Thromb Haemost.* 2007;98(2):392–396	I
39. Quinn CT, Shull EP, Ahmad N, Lee NJ, Rogers ZR, Buchanan GR. Prognostic significance of early vaso-occlusive complications in children with sickle cell anemia. *Blood.* 2007;109(1):40–45	III
40. Alvim RC, Viana MB, Pires MAS, et al. Inefficacy of piracetam in the prevention of painful crises in children and adolescents with sickle cell disease. *Acta Haematol.* 2005;113(4):228–233	I
41. Buchanan ID, Woodward M, Reed GW. Opioid selection during sickle cell pain crisis and its impact on the development of acute chest syndrome. *Pediatr Blood Cancer.* 2005;45(5):716–724	III
42. Kopecky EA, Jacobson S, Joshi P, Koren G. Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. *Clin Pharmacol Ther.* 2004;75(3):140–146	II
43. Melzer-Lange MD, Walsh-Kelly CM, Lea G, Hillery CA, Scott JP. Patient-controlled analgesia for sickle cell pain crisis in a pediatric emergency department. *Pediatr Emerg Care.* 2004;20(1):2–4	II
44. Co JPT, Johnson KB, Duggan AK, Casella JF, Wilson M. Does a clinical pathway improve the quality of care for sickle cell anemia? *Joint Comm J Qual Safety.* 2003;29(4):181–190	II
45. Gil KM, Carson JW, Porter LS, et al. Daily stress and mood and their association with pain, health-care use, and school activity in adolescents with sickle cell disease. *J Pediatr Psychol.* 2003;28(5):363–373	III
46. Jacob E, Miaskowski C, Savedra M, Beyer JE, Treadwell M, Styles L. Management of vaso-occlusive pain in children with sickle cell disease. *J Pediatr Hematol Oncol.* 2003;25(4):307–311	III
47. Jacob E, Miaskowski C, Savedra M, Beyer JE, Treadwell M, Styles L. Changes in intensity, location, and quality of vaso-occlusive pain in children with sickle cell disease. *Pain.* 2003;102(1–2):187–193	III
48. Rees DC, Olujohungbe AD, Parker NE, et al. Guidelines for the management of the acute painful crisis in sickle cell disease. *Br J Haematol.* 2003;120(5):744–752	III
49. Stinson J, Naser B. Pain management in children with sickle cell disease. *Paediatr Drugs.* 2003;5(4):229–241	III
50. Weiner DL, Hibberd PL, Betit P, Cooper AB, Botelho CA, Brugnara C. Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease [published correction appears in *JAMA.* 200425;292(8):925]. *JAMA.* 2003;289(9):1136–1142	I
51. Anie KA, Steptoe A, Ball S, Dick M, Smalling BM. Coping and health service utilisation in a UK study of paediatric sickle cell pain. *Arch Dis Child.* 2002;86(5):325–329	III
52. Dampier C, Ely E, Brodecki D, O'Neal P. Home management of pain in sickle cell disease: a daily diary study in children and adolescents. *J Pediatr Hematol Oncol.* 2002;24(8):643–647	III
53. Franck LS, Treadwell M, Jacob E, Vichinsky E. Assessment of sickle cell pain in children and young adults using the adolescent pediatric pain tool. *J Pain Symptom Manage.* 2002;23(2):114–120	III
54. Orringer EP, Casella JF, Ataga KI, et al. Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA.* 2001;286(17):2099–2106	I
55. Wambebe C, Khamofu H, Momoh JA, et al. Double-blind, placebo-controlled, randomised cross-over clinical trial of NIPRISAN in patients with Sickle Cell Disorder. *Phytomedicine.* 2001;8(4):252–261	I
56. Eke FU, Obamyonyi A, Eke NN, Oyewo EA. An open comparative study of dispersible piroxicam versus soluble acetylsalicylic acid for the treatment of osteoarticular painful attack during sickle cell crisis. *Trop Med Int Health.* 2000;5(2):81–84	I
57. Hardwick WE, Jr, Givens TG, Monroe KW, King WD, Lawley D. Effect of ketorolac in pediatric sickle cell vaso-occlusive pain crisis. *Pediatr Emerg Care.* 1999;15(3):179–182	I
58. Adams-Graves P, Kedar A, Koshy M, et al. RheothRx (poloxamer 188) injection for the acute painful episode of sickle cell disease: a pilot study. *Blood.* 1997;90(5):2041–2046	I
59. Dinges DF, Whitehouse WG, Orne EC, et al. Self-hypnosis training as an adjunctive treatment in the management of pain associated with sickle cell disease. *Int J Clin Exp Hypn.* 1997;45(4):417–432	II

APPENDIX 2 Continued

	Evidence Level
60. Fertleman CR, Gallagher A, Rossiter MA. Evaluation of fast track admission policy for children with sickle cell crises: questionnaire survey of parents' preferences. *BMJ*. 1997;315(7109):650	II
61. Gil KM, Wilson JJ, Edens JL. The stability of pain coping strategies in young children adolescents, and adults with sickle cell disease over an 18-month period. *Clin J Pain*. 1997;13(2):110–115	III
62. Jacobson SJ, Kopecky EA, Joshi P, Babul N. Randomised trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet*. 1997;350(9088):1358–1361	I
Priapism[63–70]	
63. Maples BL, Hagemann TM. Treatment of priapism in pediatric patients with sickle cell disease. *Am J Health Syst Pharm*. 2004;61(4):355–363	III
64. Gbadoe AD, Atakouma Y, Kusiaku K, Assimadi JK. Management of sickle cell priapism with etilefrine. *Arch Dis Child*. 2001;85(1):52–53	III
65. Colombani JF, Peluchon P, Elana G, Delatre P. Priapism in a sickle cell prepuberal child. *Eur J Pediatr Surg*. 2000;10(1):68–71	III
66. Mantadakis E, Ewalt DH, Cavender JD, Rogers ZR, Buchanan GR. Outpatient penile aspiration and epinephrine irrigation for young patients with sickle cell anemia and prolonged priapism. *Blood*. 2000;95(1):78–82	III
67. Mantadakis E, Cavender JD, Rogers ZR, Ewalt DH, Buchanan GR. Prevalence of priapism in children and adolescents with sickle cell anemia. *J Pediatr Hematol Oncol*. 1999;21(6):518–522	III
68. Chakrabarty A, Upadhyay J, Dhabuwala CB, Sarnaik S, Perlmutter AD, Connor JP. Priapism associated with sickle cell hemoglobinopathy in children: long-term effects on potency. *J Urol*. 1996;155(4):1419–1423	III
69. Dunn EK, Miller ST, Macchia RJ, et al. Penile scintigraphy for priapism in sickle cell disease. *J Nucl Med*. 1995;36(8):1404–1407	III
70. Miller ST, Rao SP, Dunn EK, Glassberg KI. Priapism in children with sickle cell disease. *J Urol*. 1995;154(2 pt 2):844–847	III
Splenic sequestration[71–78]	
71. Rescorla FJ, West KW, Engum SA, Grosfeld JL. Laparoscopic splenic procedures in children: experience in 231 children. *Ann Surg*. 2007;246(4): 683–687; discussion 687-688	III
72. Al-Salem AH. Indications and complications of splenectomy for children with sickle cell disease. *J Pediatr Surg*. 2006;41(11):1909–1915	III
73. Hendricks-Ferguson VL, Nelson MA. Laparoscopic splenectomy for splenic sequestration crisis. *AORN J*. 2000;71(4):820–822	III
74. Wright JG, Hambleton IR, Thomas PW, Duncan ND, Venugopal S, Serjeant GR. Postsplenectomy course in homozygous sickle cell disease. *J Pediatr*. 1999;134(3):304–309	II
75. Rescorla FJ, Breitfeld PP, West KW, Williams D, Engum SA, Grosfeld JL. A case controlled comparison of open and laparoscopic splenectomy in children. *Surgery*. 1998;124(4):670–675; discussion 675-676	III
76. Sorrells DL, Morrissey TB, Brown MF. Septic complications after splenectomy for sickle cell sequestration crisis. *Pediatr Surg Int*. 1998;13(2-3):100–103	II
77. Lane PA, O'Connell JL, Lear JL, et al. Functional asplenia in hemoglobin SC disease. *Blood*. 1995;85(8):2238–2244	III
78. Lane PA. The spleen in children. *Curr Opin Pediatr*. 1995;7(1):36–41	III
Stroke[79–99]	
79. Goldenberg NA, Bernard TJ, Fullerton HJ, Gordon A, deVeber G. Antithrombotic treatments, outcomes, and prognostic factors in acute childhood-onset arterial ischaemic stroke: a multicentre, observational, cohort study. *Lancet Neurol*. 2009;8(12):1120–1127	III
80. Bernard TJ, Goldenberg NA, Armstrong-Wells J, et al. Treatment of childhood arterial ischemic stroke. *Ann Neurol*. 2008;63(6):679–696	III
81. DeVeber G, Kirkham F. Guidelines for the treatment and prevention of stroke in children. *Lancet Neurol*. 2008;7(11):983–985	III
82. Quinn CT, Sargent JW. Daytime steady-state haemoglobin desaturation is a risk factor for overt stroke in children with sickle cell anaemia. *Br J Haematol*. 2008;140(3):336–339	II
83. Hulbert ML, Scothorn DJ, Panepinto JA, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. *J Pediatr*. 2006;149(5):710–712	II
84. Strouse JJ, Hulbert ML, DeBaun MR, Jordan LC, Casella JF. Primary hemorrhagic stroke in children with sickle cell disease is associated with recent transfusion and use of corticosteroids. *Pediatrics*. 2006;118(5):1916–1924	II
85. Hoppe C, Klitz W, Cheng S, et al. Gene interactions and stroke risk in children with sickle cell anemia. *Blood*. 2004;103(6):2391–2396	III
86. Hutchison JS, Ichord R, Guerguerian A-M, Deveber G. Cerebrovascular disorders. *Sem Pediatr Neurol*. 2004;11(2):139–146	III
87. Driscoll MC, Hurlet A, Styles L, et al. Stroke risk in siblings with sickle cell anemia. *Blood*. 2003;101(6):2401–2404	III
88. Hoppe C, Klitz W, Noble J, Vigil L, Vichinsky E, Styles L. Distinct HLA associations by stroke subtype in children with sickle cell anemia. *Blood*. 2003;101(7):2865–2869	III
89. Steen RG, Emudianughe T, Hankins GM, et al. Brain imaging findings in pediatric patients with sickle cell disease. *Radiology*. 2003;228(1):216–225	III
90. Winrow N, Melhem ER. Sickle cell disease and stroke in a pediatric population. Evidence-based diagnostic evaluation. *Neuroimag Clin North Am*. 2003;13(2):185–196	III
91. Pegelow CH, Macklin EA, Moser FG, et al. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. *Blood*. 2002;99(8):3014–3018	II
92. Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R, Evans JP. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. *Lancet*. 2001;357(9269):1656–1659	III
93. Miller ST, Macklin EA, Pegelow CH, et al. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. *J Pediatr*. 2001;139(3):385–390	II
94. Powars DR. Management of cerebral vasculopathy in children with sickle cell anaemia. *Br J Haematol*. 2000;108(4):666–678	III
95. Powars DR, Conti PS, Wong WY, et al. Cerebral vasculopathy in sickle cell anemia: diagnostic contribution of positron emission tomography. *Blood*. 1999;93(1):71–79	III
96. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998;91(1):288–294	II

APPENDIX 2 Continued

	Evidence Level
97. Wang WC, Langston JW, Steen RG, et al. Abnormalities of the central nervous system in very young children with sickle cell anemia. *J Pediatr.* 1998;132(6):994–998	III
98. Moser FG, Miller ST, Bello JA, et al. The spectrum of brain MR abnormalities in sickle-cell disease: a report from the Cooperative Study of Sickle Cell Disease. *Am J Neuroradiol.* 1996;17(5):965–972	II
99. Pegelow CH, Adams RJ, McKie V, et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. *J Pediatr.* 1995;126(6):896–899	II
II. Chronic conditions	
Asthma[100–106]	
100. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. *Haematologica.* 2007;92(8):1115–1118	II
101. Duckworth L, Hsu L, Feng H, et al. Physician-diagnosed asthma and acute chest syndrome: associations with NOS polymorphisms. *Pediatr Pulmonol.* 2007;42(4):332–338	III
102. Sylvester KP, Patey RA, Broughton S, et al. Temporal relationship of asthma to acute chest syndrome in sickle cell disease. *Pediatr Pulmonol.* 2007;42(2):103–106	III
103. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. *Blood.* 2006;108(9):2923–2927	II
104. Glassberg J, Spivey JF, Strunk R, Boslaugh S, DeBaun MR. Painful episodes in children with sickle cell disease and asthma are temporally associated with respiratory symptoms. *J Pediatr Hematol Oncol.* 2006;28(8):481–485	II
105. Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. *Thorax.* 2005;60(3):206–210	III
106. Boyd JH, Moinuddin A, Strunk RC, DeBaun MR. Asthma and acute chest in sickle-cell disease. *Pediatr Pulmonol.* 2004;38(3):229–232	II
Avascular necrosis[107–113]	
107. de Gheldere A, Ndjoko R, Docquier P-L, Mousny M, Rombouts J-J. Orthopaedic complications associated with sickle-cell disease. *Acta Orthop Belg.* 2006;72(6):741–747	III
108. Hernigou P, Habibi A, Bachir D, Galacteros F. The natural history of asymptomatic osteonecrosis of the femoral head in adults with sickle cell disease. *J Bone Joint Surg.* 2006;88(12):2565–2572	II
109. Aguilar CM, Neumayr LD, Eggleston BE, et al. Clinical evaluation of avascular necrosis in patients with sickle cell disease: Children's Hospital Oakland Hip Evaluation Scale–a modification of the Harris Hip Score. *Arch Phys Med Rehabil.* 2005;86(7):1369–1375	III
110. Adekile AD, Gupta R, Yacoub F, Sinan T, Al-Bloushi M, Haider MZ. Avascular necrosis of the hip in children with sickle cell disease and high Hb F: magnetic resonance imaging findings and influence of α-thalassemia trait. *Acta Haematol.* 2001;105(1):27–31	III
111. Malizos KN, Siafakas MS, Fotiadis DI, Karachalios TS, Soucacos PN. An MRI-based semiautomated volumetric quantification of hip osteonecrosis. *Skeletal Radiol.* 2001;30(12):686–693	III
112. Soucacos PN, Beris AE, Malizos K, Koropilias A, Zalavras H, Dailiana Z. Treatment of avascular necrosis of the femoral head with vascularized fibular transplant. *Clin Orthop Rel Research.* 2001(386):120–130	II
113. Styles LA, Vichinsky EP. Core decompression in avascular necrosis of the hip in sickle-cell disease. *Am J Hematol.* 1996;52(2):103–107	III
Gallbladder disease[114–121]	
114. Dan D, Seetahal S, Harnanan D, et al. Laparoscopic cholecystectomy in sickle cell disease patients: does operating time matter? *Int J Surg.* 2009;7(1):70–73	III
115. Curro G, Meo A, Ippolito D, Pusiol A, Cucinotta E. Asymptomatic cholelithiasis in children with sickle cell disease: early or delayed cholecystectomy? *Ann Surg.* 2007;245(1):126–129	III
116. Al-Mulhim AS, Al-Mulhim FM, Al-Suwaiygh AA. The role of laparoscopic cholecystectomy in the management of acute cholecystitis in patients with sickle cell disease. *Am J Surg.* 2002;183(6):668–672	III
117. Sandoval C, Stringel G, Ozkaynak MF, Tugal O, Jayabose S. Perioperative management in children with sickle cell disease undergoing laparoscopic surgery. *J Soc Laparoendosc Surg.* 2002;6(1):29–33	III
118. Seguier-Lipszyc E, de Lagausie P, Benkerrou M, Di Napoli S, Aigrain Y. Elective laparoscopic cholecystectomy. *Surg Endosc.* 2001;15(3):301–304	III
119. Walker TM, Hambleton IR, Serjeant GR. Gallstones in sickle cell disease: observations from The Jamaican Cohort study. *J Pediatr.* 2000;136(1):80–85	II
120. Al-Salem AH, Qaisruddin S. The significance of biliary sludge in children with sickle cell disease. *Pediatr Surg Int.* 1998;13(1):14–16	III
121. Al-Salem AH, Qaisaruddin S, Al-Abkari H, Nourallah H, Yassin YM, Varma KK. Laparoscopic versus open cholecystectomy in children. *Pediatr Surg Int.* 1997;12(8):587–590	III
Hepatic dysfunction[122–123]	
122. Ahn H, Li C-S, Wang W. Sickle cell hepatopathy: clinical presentation, treatment, and outcome in pediatric and adult patients. *Pediatr Blood Cancer.* 2005;45(2):184–190	III
123. Samperi P, Consalvo C, Romano V, Gelardi S, Di Bella D, Schiliro G. Liver involvement in white patients with sickle-cell disease. *Arch Pediatr Adolesc Med.* 1996;150(11):1177–1180	III
Leg ulcers[124–125]	
124. Cackovic M, Chung C, Bolton LL, Kerstein MD. Leg ulceration in the sickle cell patient. *J Am Coll Surg.* 1998;187(3):307–309	III
125. Serjeant BE, Harris J, Thomas P, Serjeant GR. Propionyl-L-carnitine in chronic leg ulcers of homozygous sickle cell disease: a pilot study. *J Am Acad Dermatol.* 1997;37(3 pt 1):491–493	I

APPENDIX 2 Continued

	Evidence Level
Nephropathy[126–132]	
126. Miller ST, Wang WC, Iyer R, et al. Urine concentrating ability in infants with sickle cell disease: baseline data from the phase III trial of hydroxyurea (BABY HUG). *Pediatr Blood Cancer.* 2010;54(2):265–268	III
127. Ware RE, Rees RC, Sarnaik SA, et al. Renal function in infants with sickle cell anemia: baseline data from the BABY HUG trial. *J Pediatr.* 2010;156(1):66–70.e61	III
128. Marsenic O, Couloures KG, Wiley JM. Proteinuria in children with sickle cell disease. *Nephrol Dial Transplant.* 2008;23(2):715–720	III
129. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. *J Pediatr Hematol Oncol.* 2007;29(3):140–144	II
130. de Santis Feltran L, de Abreu Carvalhaes JT, Sesso R. Renal complications of sickle cell disease: managing for optimal outcomes. *Paediatr Drugs.* 2002;4(1):29–36	III
131. McBurney PG, Hanevold CD, Hernandez CM, Waller JL, McKie KM. Risk factors for microalbuminuria in children with sickle cell anemia. *J Pediatr Hematol Oncol.* 2002;24(6):473–477	III
132. Aoki RY, Saad ST. Enalapril reduces the albuminuria of patients with sickle cell disease. *Am J Med.* 1995;98(5):432–435	II
Pulmonary hypertension[133–143]	
133. Dham N, Ensing G, Minniti C, et al. Prospective echocardiography assessment of pulmonary hypertension and its potential etiologies in children with sickle cell disease. *Am J Cardiol.* 2009;104(5):713–720	II
134. Lee MT, Small T, Khan MA, et al. Doppler-defined pulmonary hypertension and the risk of death in children with sickle cell disease followed for a mean of three years. *Br J Haematol.* 2009;146(4):437–441	II
135. Liem RI, Nevin MA, Prestridge A, et al. Tricuspid regurgitant jet velocity elevation and its relationship to lung function in pediatric sickle cell disease. *Pediatr Pulmonol.* 2009;44(3):281–289	III
136. Minniti CP, Sable C, Campbell A, et al. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. *Haematologica.* 2009;94(3):340–347	III
137. Pashankar FD, Carbonella J, Bazzy-Asaad A, et al. Longitudinal follow up of elevated pulmonary artery pressures in children with sickle cell disease. *Br J Haematol.* 2009;144(5):736–741	II
138. Sedrak A, Rao SP, Miller ST, et al. A prospective appraisal of pulmonary hypertension in children with sickle cell disease. *J Pediatr Hematol Oncol.* 2009;31(2):97–100	III
139. Akgul F, Yalcin F, Babayiit C, Seyfeli E, Seydaliyeva T, Gali E. Right ventricular and pulmonary function in sickle cell disease patients with pulmonary hypertension. *Pediatr Cardiol.* 2006;27(4):440–446	III
140. Ambrusko SJ, Gunawardena S, Sakara A, et al. Elevation of tricuspid regurgitant jet velocity, a marker for pulmonary hypertension in children with sickle cell disease. *Pediatr Blood Cancer.* 2006;47(7):907–913	II
141. El-Beshlawy A, Abd El Raouf E, Mostafa F, et al. Diastolic dysfunction and pulmonary hypertension in sickle cell anemia: is there a role for L-carnitine treatment? *Acta Haematol.* 2006;115(1-2):91–96	II
142. Qureshi N, Joyce JJ, Qi N, Chang R-K. Right ventricular abnormalities in sickle cell anemia: evidence of a progressive increase in pulmonary vascular resistance. *J Pediatr.* 2006;149(1):23–27	II
143. Morris CR, Morris SM, Jr, Hagar W, et al. Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? [see comment]. *Am J Respir Crit Care Med.* 2003;168(1):63–69	II
Retinopathy[144,145]	
144. Gill HS, Lam W-C. A screening strategy for the detection of sickle cell retinopathy in pediatric patients. *Can J Ophthalmol.* 2008;43(2):188–191	II
145. Downes SM, Hambleton IR, Chuang EL, Lois N, Serjeant GR, Bird AC. Incidence and natural history of proliferative sickle cell retinopathy: observations from a cohort study. *Ophthalmology.* 2005;112(11):1869–1875	II
Silent infarcts and neuropsychological testing[146–162]	
146. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. *Br J Haematol.* 2009;146(3):300–305	III
147. Schatz J, Puffer ES, Sanchez C, et al. Language processing deficits in sickle cell disease in young school-age children. *Dev Neuropsychol.* 2009;34(1):122–136	II
148. Gold JI, Johnson CB, Treadwell MJ, et al. Detection and assessment of stroke in patients with sickle cell disease: neuropsychological functioning and magnetic resonance imaging. *Pediatr Hematol Oncol.* 2008;25(5):409–421	III
149. Wang WC, Pavlakis SG, Helton KJ, et al. MRI abnormalities of the brain in one-year-old children with sickle cell anemia. *Pediatr Blood Cancer.* 2008;51(5):643–646	III
150. White DA, Moinuddin A, McKinstry RC, Noetzel M, Armstrong M, DeBaun M. Cognitive screening for silent cerebral infarction in children with sickle cell disease. *J Pediatr Hematol Oncol.* 2006;28(3):166–169	III
151. Steen RG, Xiong X, Langston JW, Helton KJ. Brain injury in children with sickle cell disease: prevalence and etiology. *Ann Neurol.* 2003;54(5):564–572	III
152. Thompson RJ, Jr, Gustafson KE, Bonner MJ, Ware RE. Neurocognitive development of young children with sickle cell disease through three years of age. *J Pediatr Psychol.* 2002;27(3):235–244	II
153. Ashley-Koch A, Murphy CC, Khoury MJ, Boyle CA. Contribution of sickle cell disease to the occurrence of developmental disabilities: a population-based study. *Genet Med.* 2001;3(3):181–186	III
154. Noll RB, Stith L, Gartstein MA, et al. Neuropsychological functioning of youths with sickle cell disease: comparison with non-chronically ill peers. *J Pediatr Psychol.* 2001;26(2):69–78	II

APPENDIX 2 Continued

	Evidence Level
155. Pegelow CH, Wang W, Granger S, et al. Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. *Arch Neurol.* 2001;58(12):2017–2021	II
156. Wang W, Enos L, Gallagher D, et al. Neuropsychologic performance in school-aged children with sickle cell disease: a report from the Cooperative Study of Sickle Cell Disease. *J Pediatr.* 2001;139(3):391–397	II
157. Bernaudin F, Verlhac S, Freard F, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. *J Child Neurol.* 2000;15(5):333–343	II
158. Steen RG, Xiong X, Mulhern RK, Langston JW, Wang WC. Subtle brain abnormalities in children with sickle cell disease: relationship to blood hematocrit. *Ann Neurol.* 1999;45(3):279–286	II
159. Thompson RJ, Jr, Armstrong FD, Kronenberger WG, et al. Family functioning, neurocognitive functioning, and behavior problems in children with sickle cell disease. *J Pediatr Psychol.* 1999;24(6):491–498	II
160. DeBaun MR, Schatz J, Siegel MJ, et al. Cognitive screening examinations for silent cerebral infarcts in sickle cell disease. *Neurology.* 1998;50(6):1678–1682	II
161. Thompson RJ, Jr, Gustafson KE, Gil KM, Godfrey J, Murphy LM. Illness specific patterns of psychological adjustment and cognitive adaptational processes in children with cystic fibrosis and sickle cell disease. *J Clin Psychol.* 1998;54(1):121–128	III
162. Armstrong FD, Thompson RJ, Jr, Wang W, et al. Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. Neuropsychology Committee of the Cooperative Study of Sickle Cell Disease. *Pediatrics.* 1996;97(6 pt 1):864–870	III
III. Routine health care maintenance and long-term treatment options	
Cardiac care[163–164]	
163. Pegelow CH, Colangelo L, Steinberg M, et al. Natural history of blood pressure in sickle cell disease: Risks for stroke and death associated with relative hypertension in sickle cell anemia. *Am J Med.* 1997;102(2):171–177	II
164. Covitz W, Espeland M, Gallagher D, Hellenbrand W, Leff S, Talner N. The heart in sickle cell anemia. The Cooperative Study of Sickle Cell Disease (CSSCD). *Chest.* 1995;108(5):1214–1219	III
Comprehensive care[165–172]	
165. McPherson M, Thaniel L, Minniti CP, McPherson M, Thaniel L, Minniti CP. Transition of patients with sickle cell disease from pediatric to adult care: assessing patient readiness. *Pediatr Blood Cancer.* 2009;52(7):838–841	III
166. Yanni E, Grosse SD, Yang Q, et al. Trends in pediatric sickle cell disease-related mortality in the United States, 1983-2002. *J Pediatr.* 2009;154(4):541–545	III
167. Amrolia PJ, Almeida A, Halsey C, Roberts IAG, Davies SC. Therapeutic challenges in childhood sickle cell disease. Part 1: current and future treatment options. *Br J Haematol.* 2003;120(5):725–736	III
168. Amrolia PJ, Almeida A, Davies SC, Roberts IAG. Therapeutic challenges in childhood sickle cell disease. Part 2: a problem-orientated approach. *Br J Haematol.* 2003;120(5):737–743	III
169. Claster S, Vichinsky EP. Managing sickle cell disease. *BMJ.* 2003;327(7424):1151–1155	III
170. Chernoff RG, Ireys HT, DeVet KA, Kim YJ. A randomized, controlled trial of a community-based support program for families of children with chronic illness: pediatric outcomes. *Arch Pediatr Adolesc Med.* 2002;156(6):533–539	I
171. Section on Hematology/Oncology Committee on G, American Academy of P. Health supervision for children with sickle cell disease. *Pediatrics.* 2002;109(3):526–535	III
172. Wojciechowski EA, Hurtig A, Dorn L. A natural history study of adolescents and young adults with sickle cell disease as they transfer to adult care: a need for case management services. *J Pediatr Nurs.* 2002;17(1):18–27	III
Folate supplementation[173–176]	
173. van der Dijs FPL, Fokkema MR, Dijck-Brouwer DAJ, et al. Optimization of folic acid, vitamin B(12), and vitamin B(6) supplements in pediatric patients with sickle cell disease. *Am J Hematol.* 2002;69(4):239–246	III
174. Rodriguez-Cortes HM, Griener JC, Hyland K, et al. Plasma homocysteine levels and folate status in children with sickle cell anemia. *J Pediatr Hematol Oncol.* 1999;21(3):219–223	III
175. van der Dijs FP, Schnog JJ, Brouwer DA, et al. Elevated homocysteine levels indicate suboptimal folate status in pediatric sickle cell patients. *Am J Hematol.* 1998;59(3):192–198	II
176. Houston PE, Rana S, Sekhsaria S, Perlin E, Kim KS, Castro OL. Homocysteine in sickle cell disease: relationship to stroke. *Am J Med.* 1997;103(3):192–196	III
Genetic counseling and newborn screening[177–179]	
177. Kavanagh PL, Wang CJ, Therrell BL, Sprinz PG, Bauchner H. Communication of positive newborn screening results for sickle cell disease and sickle cell trait: variation across states. *Am J Med Genet Part C: Sem Med Genet.* 2008;148C(1):15–22	III
178. Gergen PJ, Macri CJ, Murrillo S. The need for sickle cell screening among pediatric Latino immigrants. *Arch Pediatr Adolesc Med.* 2002;156(7):729	III
179. Farrell M, Certain L, Farrell P. Genetic counseling and risk communication services of newborn screening programs. *Arch Pediatr Adolesc Med.* 2001;155(2):120–126	III
Growth[180–189]	
180. Mitchell MJ, Carpenter GJ, Crosby LE, et al. Growth status in children and adolescents with sickle cell disease. *Pediatr Hematol Oncol.* 2009;26(4):202–215	III
181. Rhodes M, Akohoue SA, Shankar SM, et al. Growth patterns in children with sickle cell anemia during puberty. *Pediatr Blood Cancer.* 2009;53(4):635–641	II
182. Al-Saqladi AW, Cipolotti R, Fijnvandraat K, Brabin BJ, Al-Saqladi AWM. Growth and nutritional status of children with homozygous sickle cell disease. *Ann Trop Paediatr.* 2008;28(3):165–189	III

APPENDIX 2 Continued

	Evidence Level
183. Zemel BS, Kawchak DA, Ohene-Frempong K, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. *Pediatr Res*. 2007;61(5 pt 1):607–613	II
184. Buison AM, Kawchak DA, Schall JI, et al. Bone area and bone mineral content deficits in children with sickle cell disease. *Pediatrics*. 2005;116(4):943–949	III
185. Barden EM, Kawchak DA, Ohene-Frempong K, Stallings VA, Zemel BS. Body composition in children with sickle cell disease. *Am J Clin Nutr*. 2002;76(1):218–225	III
186. Patey RA, Sylvester KP, Rafferty GF, Dick M, Greenough A. The importance of using ethnically appropriate reference ranges for growth assessment in sickle cell disease. *Arch Dis Child*. 2002;87(4):352–353	III
187. Singhal A, Parker S, Linsell L, Serjeant G. Energy intake and resting metabolic rate in preschool Jamaican children with homozygous sickle cell disease. *Am J Clin Nutr*. 2002;75(6):1093–1097	III
188. Zemel BS, Kawchak DA, Fung EB, Ohene-Frempong K, Stallings VA. Effect of zinc supplementation on growth and body composition in children with sickle cell disease. *Am J Clin Nutr*. 2002;75(2):300–307	I
189. Thomas PW, Singhal A, Hemmings-Kelly M, Serjeant GR. Height and weight reference curves for homozygous sickle cell disease. *Arch Dis Child*. 2000;82(3):204–208	II
Immunuization[190–196]	
190. Adamkiewicz TV, Silk BJ, Howgate J, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. *Pediatrics*. 2008;121(3):562–569	II
191. Zimmerman RK. Pneumococcal conjugate vaccine for young children [published correction appears in *Am Fam Physician*. 2002;65(5):799]. *Am Fam Physician*. 2001;63(10):1991–1998	III
192. Advisory Committee on Immunization P. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2000;49(RR-9):1–35	III
193. American Academy of Pediatrics. Committee on Infectious Diseases. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics*. 2000;106(2 pt 1):362–366	III
194. O'Brien KL, Swift AJ, Winkelstein JA, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM(197) among infants with sickle cell disease. Pneumococcal Conjugate Vaccine Study Group. *Pediatrics*. 2000;106(5):965–972	II
195. Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. *J Pediatr*. 1998;133(2):275–278	I
196. Bjornson AB, Falletta JM, Verter JI, et al. Serotype-specific immunoglobulin G antibody responses to pneumococcal polysaccharide vaccine in children with sickle cell anemia: effects of continued penicillin prophylaxis. *J Pediatr*. 1996;129(6):828–835	II
Penicillin prophylaxis[197–204]	
197. Hirst C, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database Syst*. 2009;(4):CD003427	I
198. Tate AR, Norris CK, Minniti CP. Antibiotic prophylaxis for children with sickle cell disease: a survey of pediatric dentistry residency program directors and pediatric hematologists. *Pediatr Dent*. 2006;28(4):332–335	III
199. de Montalembert M, Lenoir G. Antibiotic prevention of pneumococcal infections in asplenic hosts: admission of insufficiency. *Ann Hematol*. 2004;83(1):18–21	III
200. Overturf GD. American Academy of Pediatrics. Committee on Infectious Diseases. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. *Pediatrics*. 2000;106(2 pt 1):367–376	III
201. Pai VB, Nahata MC. Duration of penicillin prophylaxis in sickle cell anemia: Issues and controversies. *Pharmacotherapy*. 2000;20(1):110–117	III
202. Berkovitch M, Papadouris D, Shaw D, Onuaha N, Dias C, Olivieri NF. Trying to improve compliance with prophylactic penicillin therapy in children with sickle cell disease. *Br J Clin Pharmacol*. 1998;45(6):605–607	I
203. Woods GM, Jorgensen JH, Waclawiw MA, et al. Influence of penicillin prophylaxis on antimicrobial resistance in nasopharyngeal S. pneumoniae among children with sickle cell anemia. The Ancillary Nasopharyngeal Culture Study of Prophylactic Penicillin Study II. *J Pediatr Hematol Oncol*. 1997;19(4):327–333	II
204. Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II. *J Pediatr*. 1995;127(5):685–690	I
Pulmonary function testing[205–214]	
205. Spivey JF, Uong EC, Strunk R, et al. Low daytime pulse oximetry reading is associated with nocturnal desaturation and obstructive sleep apnea in children with sickle cell anemia. *Pediatr Blood Cancer*. 2008;50(2):359–362	III
206. Sylvester KP, Patey RA, Kassim Z, et al. Lung gas transfer in children with sickle cell anaemia. *Respir Physiol Neurobiol*. 2007;158(1):70–74	III
207. Uong EC, Boyd JH, DeBaun MR. Daytime pulse oximeter measurements do not predict incidence of pain and acute chest syndrome episodes in sickle cell anemia. *J Pediatr*. 2006;149(5):707–709	III
208. Hsu LL, Batts BK, Rau JL. Positive expiratory pressure device acceptance by hospitalized children with sickle cell disease is comparable to incentive spirometry. *Respir Care*. 2005;50(5):624–627	I
209. Quinn CT, Ahmad N. Clinical correlates of steady-state oxyhaemoglobin desaturation in children who have sickle cell disease. *Br J Haematol*. 2005;131(1):129–134	III
210. Sylvester KP, Patey RA, Milligan P, et al. Pulmonary function abnormalities in children with sickle cell disease. *Thorax*. 2004;59(1):67–70	III
211. Hargrave DR, Wade A, Evans JPM, Hewes DKM, Kirkham FJ. Nocturnal oxygen saturation and painful sickle cell crises in children. *Blood*. 2003;101(3):846–848	III

APPENDIX 2 Continued

	Evidence Level
212. Fitzgerald RK, Johnson A. Pulse oximetry in sickle cell anemia. *Crit Care Med.* 2001;29(9):1803–1806	III
213. Blaisdell CJ, Goodman S, Clark K, Casella JF, Loughlin GM. Pulse oximetry is a poor predictor of hypoxemia in stable children with sickle cell disease. *Arch Pediatr Adolesc Med.* 2000;154(9):900–903	III
214. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. *N Engl J Med.* 1995;333(11):699–703	I
Transcranial Doppler screening[215–240]	
215. Kwiatkowski JL. Transcranial Doppler ultrasonography in infants with sickle cell disease - Is earlier identification of children at risk of stroke possible? *Pediatr Blood Cancer.* 2010;54(2):187–188	III
216. Pavlakis SG, Rees RC, Huang X, et al. Transcranial Doppler ultrasonography (TCD) in infants with sickle cell anemia: baseline data from the BABY HUG trial. *Pediatr Blood Cancer.* 2010;54(2):256–259	III
217. Bernaudin F, Verlhac S, Chevret S, et al. G6PD deficiency, absence of α-thalassemia, and hemolytic rate at baseline are significant independent risk factors for abnormally high cerebral velocities in patients with sickle cell anemia. *Blood.* 2008;112(10):4314–4317	III
218. Hankins JS, Fortner GL, McCarville MB, et al. The natural history of conditional transcranial Doppler flow velocities in children with sickle cell anaemia. *Br J Haematol.* 2008;142(1):94–99	II
219. McCarville MB, Goodin GS, Fortner G, et al. Evaluation of a comprehensive transcranial Doppler screening program for children with sickle cell anemia. *Pediatr Blood Cancer.* 2008;50(4):818–821	III
220. Brambilla DJ, Miller ST, Adams RJ. Intra-individual variation in blood flow velocities in cerebral arteries of children with sickle cell disease. *Pediatr Blood Cancer.* 2007;49(3):318–322	III
221. Mazumdar M, Heeney MM, Sox CM, Lieu TA. Preventing stroke among children with sickle cell anemia: an analysis of strategies that involve transcranial Doppler testing and chronic transfusion. *Pediatrics.* 2007;120(4). Available at: www.pediatrics.org/cgi/content/full/120/4/e1107	III
222. Fullerton HJ, Gardner M, Adams RJ, Lo LC, Johnston SC. Obstacles to primary stroke prevention in children with sickle cell disease. *Neurology.* 2006;67(6):1098–1099	III
223. Kwiatkowski JL, Granger S, Brambilla DJ, et al. Elevated blood flow velocity in the anterior cerebral artery and stroke risk in sickle cell disease: extended analysis from the STOP trial. *Br J Haematol.* 2006;134(3):333–339	II
224. Lee MT, Piomelli S, Granger S, et al. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood.* 2006;108(3):847–852	II
225. Adams RJ, Brambilla D, Optimizing Primary Stroke Prevention in Sickle Cell Anemia Trial I. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med.* 2005;353(26):2769–2778	I
226. Bernaudin F, Verlhac S, Coic L, Lesprit E, Brugieres P, Reinert P. Long-term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler. *Pediatr Radiol.* 2005;35(3):242–248	II
227. Hoppe C. Defining stroke risk in children with sickle cell anaemia. *Br J Haematol.* 2005;128(6):751–766	III
228. Jones A, Granger S, Brambilla D, et al. Can peak systolic velocities be used for prediction of stroke in sickle cell anemia? *Pediatr Radiol.* 2005;35(1):66–72	III
229. Abboud MR, Cure J, Granger S, et al. Magnetic resonance angiography in children with sickle cell disease and abnormal transcranial Doppler ultrasonography findings enrolled in the STOP study. *Blood.* 2004;103(7):2822–2826	II
230. Adams RJ, Brambilla DJ, Granger S, et al. Stroke and conversion to high risk in children screened with transcranial Doppler ultrasound during the STOP study. *Blood.* 2004;103(10):3689–3694	II
231. McCarville MB, Li C, Xiong X, Wang W. Comparison of transcranial Doppler sonography with and without imaging in the evaluation of children with sickle cell anemia. *Am J Roentgenol.* 2004;183(4):1117–1122	III
232. Sloan MA, Alexandrov AV, Tegeler CH, et al. Assessment: transcranial Doppler ultrasonography: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2004;62(9):1468–1481	III
233. Kral MC, Brown RT, Nietert PJ, Abboud MR, Jackson SM, Hynd GW. Transcranial Doppler ultrasonography and neurocognitive functioning in children with sickle cell disease. *Pediatrics.* 2003;112(2):324–331	III
234. Kwiatkowski JL, Hunter JV, Smith-Whitley K, Katz ML, Shults J, Ohene-Frempong K. Transcranial Doppler ultrasonography in siblings with sickle cell disease. *Br J Haematol.* 2003;121(6):932–937	III
235. Riebel T, Kebelmann-Betzing C, Gotze R, Overberg US. Transcranial Doppler ultrasonography in neurologically asymptomatic children and young adults with sickle cell disease. *Eur Radiol.* 2003;13(3):563–570	III
236. Malouf AJ, Jr, Hamrick-Turner JE, Doherty MC, Dhillon GS, Iyer RV, Smith MG. Implementation of the STOP protocol for Stroke Prevention in Sickle Cell Anemia by using duplex power Doppler imaging. *Radiology.* 2001;219(2):359–365	III
237. Adams RJ. Lessons from the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study. *J Child Neurol.* 2000;15(5):344–349	III
238. Wang WC, Gallagher DM, Pegelow CH, et al. Multicenter comparison of magnetic resonance imaging and transcranial Doppler ultrasonography in the evaluation of the central nervous system in children with sickle cell disease. *J Pediatr Hematol Oncol.* 2000;22(4):335–339	III
239. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med.* 1998;339(1):5–11	I
240. Seibert JJ, Glasier CM, Kirby RS, et al. Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: an 8-year study [published correction appears in *Pediatr Radiol.* 1998;28(7):546]. *Pediatr Radiol.* 1998;28(3):138–142	II

APPENDIX 2 Continued

	Evidence Level
Transfusion[241–273]	
241. Inati A, Musallam KM, Wood JC, Taher AT. Iron overload indices rise linearly with transfusion rate in patients with sickle cell disease. *Blood*. 2010;115(14):2980–2981; author reply 2981-2982	III
242. McPherson ME, Anderson AR, Castillejo MI, et al. HLA alloimmunization is associated with RBC antibodies in multiply transfused patients with sickle cell disease. *Pediatr Blood Cancer*. 2010;54(4):552–558	III
243. Mirre E, Brousse V, Berteloot L, et al. Feasibility and efficacy of chronic transfusion for stroke prevention in children with sickle cell disease. *Eur J Haematol*. 2010;84(3):259–265	II
244. Adamkiewicz TV, Abboud MR, Paley C, et al. Serum ferritin level changes in children with sickle cell disease on chronic blood transfusion are nonlinear and are associated with iron load and liver injury. *Blood*. 2009;114(21):4632–4638	II
245. Aygun B, McMurray MA, Schultz WH, et al. Chronic transfusion practice for children with sickle cell anaemia and stroke. *Br J Haematol*. 2009;145(4):524–528	II
246. Brown K, Subramony C, May W, et al. Hepatic iron overload in children with sickle cell anemia on chronic transfusion therapy. *J Pediatr Hematol Oncol*. 2009;31(5):309–312	III
247. Hankins JS, McCarville MB, Loeffler RB, et al. R2* magnetic resonance imaging of the liver in patients with iron overload. *Blood*. 2009;113(20):4853–4855	III
248. Raphael JL, Bernhardt MB, Mahoney DH, et al. Oral iron chelation and the treatment of iron overload in a pediatric hematology center. *Pediatr Blood Cancer*. 2009;52(5):616–620	II
249. Taher A, Cappellini MD, Vichinsky E, et al. Efficacy and safety of deferasirox doses of >30 mg/kg per d in patients with transfusion-dependent anaemia and iron overload. *Br J Haematol*. 2009;147(5):752–759	II
250. Thuret I, Hacini M, Pegourie-Bandelier B, et al. Socio-psychological impact of infused iron chelation therapy with deferoxamine in metropolitan France: ISOSFER study results. *Hematology*. 2009;14(6):315–322	III
251. Vichinsky E, Pakbaz Z, Onyekwere O, et al. Patient-reported outcomes of deferasirox (Exjade, ICL670) versus deferoxamine in sickle cell disease patients with transfusional hemosiderosis. Substudy of a randomized open-label phase II trial. *Acta Haematol*. 2008;119(3):133–141	II
252. Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. *Br J Haematol*. 2007;136(3):501–508. doi:510.1111/j.1365-2141.2006.06455.x	I
253. Berdoukas V, Bohane T, Tobias V, et al. Liver iron concentration and fibrosis in a cohort of transfusion-dependent patients on long-term desferrioxamine therapy. *Hematol J*. 2005;5(7):572–578	II
254. Hankins J, Jeng M, Harris S, Li C-S, Liu T, Wang W. Chronic transfusion therapy for children with sickle cell disease and recurrent acute chest syndrome. *J Pediatr Hematol Oncol*. 2005;27(3):158–161	II
255. Wang WC, Morales KH, Scher CD, et al. Effect of long-term transfusion on growth in children with sickle cell anemia: results of the STOP trial. *J Pediatr*. 2005;147(2):244–247	II
256. Wood JC, Enriquez C, Ghugre N, et al. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. *Blood*. 2005;106(4):1460–1465	III
257. Talano J-AM, Hillery CA, Gottschall JL, Baylerian DM, Scott JP. Delayed hemolytic transfusion reaction/hyperhemolysis syndrome in children with sickle cell disease. *Pediatrics*. 2003;111(6 pt 1). Available at: www.pediatrics.org/cgi/content/full/111/6/e661	III
258. Wali YA, al Okbi H, al Abri R. A comparison of two transfusion regimens in the perioperative management of children with sickle cell disease undergoing adenotonsillectomy. *Pediatr Hematol Oncol*. 2003;20(1):7–13	II
259. Aygun B, Padmanabhan S, Paley C, Chandrasekaran V. Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. *Transfusion*. 2002;42(1):37–43	III
260. Files B, Brambilla D, Kutlar A, et al. Longitudinal changes in ferritin during chronic transfusion: a report from the Stroke Prevention Trial in Sickle Cell Anemia (STOP). *J Pediatr Hematol Oncol*. 2002;24(4):284–290	II
261. Miller ST, Wright E, Abboud M, et al. Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. *J Pediatr*. 2001;139(6):785–789	II
262. Olivieri NF. Progression of iron overload in sickle cell disease. *Sem Hematol*. 2001;38(1 Suppl 1):57–62	III
263. Olujohungbe A, Hambleton I, Stephens L, Serjeant B, Serjeant G. Red cell antibodies in patients with homozygous sickle cell disease: a comparison of patients in Jamaica and the United Kingdom. *Br J Haematol*. 2001;113(3):661–665	III
264. Reed W, Vichinsky EP. Transfusion therapy: a coming-of-age treatment for patients with sickle cell disease. *J Pediatr Hematol Oncol*. 2001;23(4):197–202	III
265. Vichinsky EP, Luban NL, Wright E, et al. Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. *Transfusion*. 2001;41(9):1086–1092	III
266. Harmatz P, Butensky E, Quirolo K, et al. Severity of iron overload in patients with sickle cell disease receiving chronic red blood cell transfusion therapy. *Blood*. 2000;96(1):76–79	III
267. Wayne AS, Schoenike SE, Pegelow CH. Financial analysis of chronic transfusion for stroke prevention in sickle cell disease. *Blood*. 2000;96(7):2369–2372	III
268. Singer ST, Quirolo K, Nishi K, Hackney-Stephens E, Evans C, Vichinsky EP. Erythrocytapheresis for chronically transfused children with sickle cell disease: an effective method for maintaining a low hemoglobin S level and reducing iron overload. *J Clin Apheresis*. 1999;14(3):122–125	II
269. Vichinsky EP, Neumayr LD, Haberkern C, et al. The perioperative complication rate of orthopedic surgery in sickle cell disease: Report of the National Sickle Cell Surgery Study Group. *Am J Hematol*. 1999;62(3):129–138	II
270. Waldron P, Pegelow C, Neumayr L, et al. Tonsillectomy, adenoidectomy, and myringotomy in sickle cell disease: perioperative morbidity. Preoperative Transfusion in Sickle Cell Disease Study Group. *J Pediatr Hematol Oncol*. 1999;21(2):129–135	II
271. Hilliard LM, Williams BF, Lounsbury AE, Howard TH. Erythrocytapheresis limits iron accumulation in chronically transfused sickle cell patients. *Am J Hematol*. 1998;59(1):28–35	II

APPENDIX 2 Continued

	Evidence Level
272. Haberkern CM, Neumayr LD, Orringer EP, et al. Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the National Preoperative Transfusion Study. Preoperative Transfusion in Sickle Cell Disease Study Group. *Blood.* 1997;89(5):1533–1542	II
273. Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group. *N Engl J Med.* 1995;333(4):206–213	I
Bone marrow transplant[274–283]	
274. Hsieh MM, Kang EM, Fitzhugh CD, et al. Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. *N Engl J Med.* 2009;361(24):2309–2317	II
275. Bernaudin F, Socie G, Kuentz M, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. *Blood.* 2007;110(7):2749–2756	II
276. Eggleston B, Patience M, Edwards S, et al. Effect of myeloablative bone marrow transplantation on growth in children with sickle cell anaemia: results of the multicenter study of haematopoietic cell transplantation for sickle cell anaemia. *Br J Haematol.* 2007;136(4):673–676	III
277. Fixler J, Vichinsky E, Walters MC. Stem cell transplantation for sickle cell disease: can we reduce the toxicity? *Pediatr Pathol Mol Med.* 2001;20(1):73–86	III
278. Steen RG, Helton KJ, Horwitz EM, et al. Improved cerebrovascular patency following therapy in patients with sickle cell disease: initial results in 4 patients who received HLA-identical hematopoietic stem cell allografts. *Ann Neurol.* 2001;49(2):222–229	II
279. Walters MC, Patience M, Leisenring W, et al. Stable mixed hematopoietic chimerism after bone marrow transplantation for sickle cell anemia. *Biol Blood Marrow Transplant.* 2001;7(12):665–673	II
280. Nietert PJ, Abboud MR, Silverstein MD, Jackson SM. Bone marrow transplantation versus periodic prophylactic blood transfusion in sickle cell patients at high risk of ischemic stroke: a decision analysis. *Blood.* 2000;95(10):3057–3064	III
281. Walters MC, Storb R, Patience M, et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. *Blood.* 2000;95(6):1918–1924	II
282. Walters MC, Patience M, Leisenring W, et al. Bone marrow transplantation for sickle cell disease. *N Engl J Med.* 1996;335(6):369–376	II
283. Walters MC, Sullivan KM, Bernaudin F, et al. Neurologic complications after allogeneic marrow transplantation for sickle cell anemia. *Blood.* 1995;85(4):879–884	II
Hydroxyurea[284–321]	
284. Drotar D. Treatment adherence in patients with sickle cell anemia. *J Pediatr.* 2010;156(3):350–351	III
285. Gordeuk VR, Campbell A, Rana S, et al. Relationship of erythropoietin, fetal hemoglobin, and hydroxyurea treatment to tricuspid regurgitation velocity in children with sickle cell disease. *Blood.* 2009;114(21):4639–4644	III
286. O'Brien SH, Hankins JS. Decision analysis of treatment strategies in children with severe sickle cell disease. *J Pediatr Hematol Oncol.* 2009;31(11):873–878	III
287. Thornburg CD, Dixon N, Burgett S, et al. A pilot study of hydroxyurea to prevent chronic organ damage in young children with sickle cell anemia. *Pediatr Blood Cancer.* 2009;52(5):609–615	II
288. Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med.* 2008;148(12):932–938	III
289. Heeney MM, Ware RE, Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. *Pediatr Clin North Am.* 2008;55(2):483–501	III
290. Mueller BU. When should hydroxyurea be used for children with sickle cell disease?[comment]. *Pediatrics.* 2008;122(6):1365–1366	III
291. Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics.* 2008;122(6):1332–1342	III
292. Puffer E, Schatz J, Roberts CW. The association of oral hydroxyurea therapy with improved cognitive functioning in sickle cell disease. *Child Neuropsychol.* 2007;13(2):142–154	II
293. Zimmerman SA, Schultz WH, Burgett S, Mortier NA, Ware RE. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. *Blood.* 2007;110(3):1043–1047	II
294. de Montalembert M, Brousse V, Elie C, et al. Long-term hydroxyurea treatment in children with sickle cell disease: tolerance and clinical outcomes. *Haematologica.* 2006;91(1):125–128	II
295. Kratovil T, Bulas D, Driscoll MC, Speller-Brown B, McCarter R, Minniti CP. Hydroxyurea therapy lowers TCD velocities in children with sickle cell disease. *Pediatr Blood Cancer.* 2006;47(7):894–900	II
296. Lanzkron S, Haywood C, Jr, Segal JB, Dover GJ. Hospitalization rates and costs of care of patients with sickle-cell anemia in the state of Maryland in the era of hydroxyurea. *Am J Hematol.* 2006;81(12):927–932	III
297. Bakanay SM, Dainer E, Clair B, et al. Mortality in sickle cell patients on hydroxyurea therapy. *Blood.* 2005;105(2):545–547	III
298. Fitzhugh CD, Wigfall DR, Ware RE. Enalapril and hydroxyurea therapy for children with sickle nephropathy. *Pediatr Blood Cancer.* 2005;45(7):982–985	III
299. Gulbis B, Haberman D, Dufour D, et al. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood.* 2005;105(7):2685–2690	II
300. Hankins JS, Ware RE, Rogers ZR, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood.* 2005;106(7):2269–2275	II
301. Meyappan JD, Lampl M, Hsu LL. Parents' assessment of risk in sickle cell disease treatment with hydroxyurea. *J Pediatr Hematol Oncol.* 2005;27(12):644–650	III
302. Brachet C, Azzi N, Demulder A, et al. Hydroxyurea treatment for sickle cell disease: impact on haematopoietic stem cell transplantation's outcome. *Bone Marrow Transplant.* 2004;33(8):799–803	II
303. Heeney MM, Whorton MR, Howard TA, Johnson CA, Ware RE. Chemical and functional analysis of hydroxyurea oral solutions. *J Pediatr Hematol Oncol.* 2004;26(3):179–184	III

APPENDIX 2 Continued

	Evidence Level
304. Kattamis A, Lagona E, Orfanou I, et al. Clinical response and adverse events in young patients with sickle cell disease treated with hydroxyurea. *Pediatr Hematol Oncol.* 2004;21(4):335–342	II
305. Saad STO, Lajolo C, Gilli S, et al. Follow-up of sickle cell disease patients with priapism treated by hydroxyurea. *Am J Hematol.* 2004;77(1):45–49	III
306. Ware RE, Zimmerman SA, Sylvestre PB, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr.* 2004;145(3):346–352	II
307. Zimmerman SA, Schultz WH, Davis JS, et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood.* 2004;103(6):2039–2045	II
308. Schultz WH, Ware RE. Malignancy in patients with sickle cell disease. *Am J Hematol.* 2003;74(4):249–253	III
309. Santos A, Pinheiro V, Anjos C, et al. Scintigraphic follow-up of the effects of therapy with hydroxyurea on splenic function in patients with sickle cell disease. *Eur J Nucl Med Molec Imag.* 2002;29(4):536–541	II
310. Wang WC, Helms RW, Lynn HS, et al. Effect of hydroxyurea on growth in children with sickle cell anemia: results of the HUG-KIDS Study. *J Pediatr.* 2002;140(2):225–229	II
311. Ware RE, Eggleston B, Redding-Lallinger R, et al. Predictors of fetal hemoglobin response in children with sickle cell anemia receiving hydroxyurea therapy. *Blood.* 2002;99(1):10–14	II
312. Ferster A, Tahriri P, Vermylen C, et al. Five years of experience with hydroxyurea in children and young adults with sickle cell disease. *Blood.* 2001;97(11):3628–3632	II
313. Powars DR. Hydroxyurea in very young children with sickle cell anemia is not a cure-all. *J Pediatr.* 2001;139(6):763–764	III
314. Wang WC, Wynn LW, Rogers ZR, Scott JP, Lane PA, Ware RE. A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr.* 2001;139(6):790–796	II
315. Kinney TR, Helms RW, O'Branski EE, et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. *Blood.* 1999;94(5):1550–1554	II
316. Koren A, Segal-Kupershmit D, Zalman L, et al. Effect of hydroxyurea in sickle cell anemia: a clinical trial in children and teenagers with severe sickle cell anemia and sickle cell β-thalassemia. *Pediatr Hematol Oncol.* 1999;16(3):221–232	II
317. Maier-Redelsperger M, Labie D, Elion J. Long-term hydroxyurea treatment in young sickle cell patients. *Curr Opin Hematol.* 1999;6(2):115–120	III
318. Ware RE, Zimmerman SA, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood.* 1999;94(9):3022–3026	II
319. Olivieri NF, Vichinsky EP. Hydroxyurea in children with sickle cell disease: impact on splenic function and compliance with therapy. *J Pediatr Hematol Oncol.* 1998;20(1):26–31	II
320. de Montalembert M, Belloy M, Bernaudin F, et al. Three-year follow-up of hydroxyurea treatment in severely ill children with sickle cell disease. The French Study Group on Sickle Cell Disease. *J Pediatr Hematol Oncol.* 1997;19(4):313–318	II
321. Ferster A, Vermylen C, Cornu G, et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. *Blood.* 1996;88(6):1960–1964	I

Management of Children With Sickle Cell Disease: A Comprehensive Review of the Literature

Patricia L. Kavanagh, Philippa G. Sprinz, Samuel R. Vinci, Howard Bauchner and C. Jason Wang

Pediatrics 2011;128;e1552; originally published online November 28, 2011;
DOI: 10.1542/peds.2010-3686