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**The Management of Sickle Cell Disease Complications:  
A Systematic Review, 2012**

Prepared for the National Heart, Lung, and Blood Institute

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## Included Studies

**Table 1. Baseline Characteristics of Included Studies (sorted by study design and then alphabetized by first author's last name)**

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Adams, 1998 <sup>1</sup>	RCT	Children	8.3±3.3	130	To test the effectiveness of transfusions compared to standard care to prevent 1st stroke in patients with sickle cell anemia (SCA) who were identified as high risk via transcranial Doppler (TCD) ultrasound (US)	Transfusion vs. standard care	Inclusion: To enter the study, children with SCA and no history of stroke had to have undergone 2 TCD studies that showed that the time-averaged mean blood-flow velocity in the internal carotid or middle cerebral artery was 200 cm/s or higher. Exclusion: Included contraindication to long-term transfusion	46	Homozygous sickle cell disease (HbSS), sickle hemoglobin beta-zero thalassemia (HbSβ <sup>0</sup> -thal)	0.8	100	Median: 21.1 mo
Adams, 2005 <sup>2</sup>	RCT	Children	12.2±3.2	79	To assess what duration of transfusion should be continued in children with SCA who have abnormalities on TCD US examination	Continued transfusion vs. halted transfusion	Adequate participation in a transfusion program (≥24 transfusions in 30 mo and sickle cell hemoglobin (HbS))	42	HbSS, HbSB-thal	6.3	100	4.5±2.6 mo
Adams-Graves, 1997 <sup>3</sup>	RCT	% adults NR	Range: 15–55	50	To assess the safety and efficacy of RheothRx (Poloxamer 188) injections in treating acute painful crises in patients with sickle cell disease (SCD)	RheothRx vs. placebo	Inclusion: Patients with SCD, age 15+ yr, history of at least 1 previous documented acute painful crisis, have moderate or severe pain lasting 4+ h but no longer than 18 h upon presentation, have a painful episode that required parenteral analgesics, have an acceptable medical history of vital signs. Exclusion: Pregnancy, liver disease, requiring daily narcotics for any reason, history of >15 painful crises per yr for the last 2 yr, have a painful episode with life-threatening complications, having pain involving the chest that was possibly pulmonary or cardiac in origin, having had a painful event requiring hospitalization within the preceding 2 weeks, having received hydroxyurea (HU) in the preceding 3 mo	50	HbSS (92%), sickle HbSC (2%), HbSβ <sup>0</sup> -thal (6%)	0	100	Acutely
Al-Jam'a, 1999 <sup>4</sup>	RCT	% adults NR	21	43	To evaluate the efficacy of isoxsuprine on pain control	2	Inclusion: Patients ≥12 yr old with painful crises requiring hospital admissions Exclusion: infection or temperature >38.3 °C, pregnancy or possibility of conception and lactation, recent arterial hemorrhage, use of β-blockers, and likelihood of general anesthesia in 24 h, not on hydroxyurea or on chronic transfusion program	77	HbSS, hemoglobin S beta-thalassemia (HbSβ-thal)	NR	100	Brief/acute

\* When there is no exclusion in the table, exclusion criteria were not reported in the articles.

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Alvim, 2005 <sup>5</sup>	RCT	Children	Median: 12.1	73	To assess the efficacy of piracetam in the prevention of painful crises in children with SCD	1, pediatric patients with SCD with recurrent pain receiving piracetam vs. placebo	Inclusion: Children and young adults with SCD, recurrent pain episodes. Exclusion: Noncompliance, renal, hepatic, cardiac, or coagulation disorders either secondary to SCD or not, regular blood transfusions, use of HU, age above 20 yr or below 5 yr, and cognitive dysfunction that hindered reporting of pain	45	HbSS (57.5%), HbSC (35.5%), HbSβ <sup>0</sup> -thal (7%)	0	100	11 mo
Barst, 2010 <sup>6</sup>	RCT	% adults NR	Range: 34–54	26	To assess the effect of bosentan for the treatment of sickle cell pulmonary hypertension (PHTN)	4; ASSET 1 (patients with pulmonary arterial hypertension (PAH): bosentan or placebo); ASSET 2 (patients with PHTN: bosentan or placebo)	Inclusion: Individuals with ≥12 yr of age with PAH or PHTN. Exclusion: Left ventricular ejection fraction <40%, systolic pressure <85 mmHg, uncontrolled hypertension with systolic pressure >160 mmHg and/or diastolic pressure >100 mmHg, total lung capacity <50% of predicted, hemoglobin <60 g/L alanine transaminase (ALT) ≥3 upper limit of normal or albumin >20% below upper limit of normal	35	HbSS or HbSβ	NR (4 patients (2 each in ASSET 1 and 2 bosentan arms) discontinued medication)	100	4 mo
Bartolucci, 2009 <sup>7</sup>	RCT	% adults NR	33	54	To test the efficacy and safety of ketoprofen for adults with SCD and severe vaso-occlusive crises (VOCs) requiring hospitalization	2	Inclusion: Patients with HbSS, age 15+ yr, presenting with severe VOCs. Exclusion: VOC lasting >72 h or <24 h; parenteral hydration >24 h; blood transfusion during the previous month; any nonsteroidal anti-inflammatory drug (NSAID) intake during the previous 7 d; pregnancy; a history of drug abuse; hypertension; fever >39°C; leukocyte count >30×10 <sup>9</sup> /L or <4×10 <sup>9</sup> /L; the presence at inclusion of an acute chest syndrome (ACS); severe anemia requiring a blood transfusion at inclusion; a psychiatric disorder or progressive visceral disease; and ketoprofen allergy or NSAID contraindication	63	NR	NR (but 14 of 54 patients were excluded from analysis because of treatment failures)	100	Peri-hospitalization
Baum, 1987 <sup>8</sup>	RCT	% adults NR	Range: 14–49	30	To assess the efficacy of antimicrobial therapy compared to placebo in treating chronic SCD leg ulcers	2, antimicrobial therapy vs. placebo	Inclusion: HbSS patients with leg ulcers of at least 3 mo duration, and in whom bacterial swabs revealed at least 1 skin pathogen of the following: <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , and <i>S. pyogenes</i> . Exclusion: Patients with large leg ulcers that deviated from a single plane, patients with evidence of chronic renal failure	36	HbSS	7	100	8 weeks

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Bellet, 1995 <sup>9</sup>	RCT	Children	15.9	29	To determine the incidence of thoracic bone infarction in patients with SCD who were hospitalized with acute chest or back pain above the diaphragm and to test the hypothesis that incentive spirometry can decrease the incidence of atelectasis and pulmonary infiltrates	2	Inclusion: All patients who received health care at the Comprehensive Sickle Cell Center at Children's Hospital Medical Center, Cincinnati who had acute chest or back pain above the diaphragm and who were admitted to the hospital were enrolled in the study between Oct. 1, 1990, and Aug. 1, 1994	51.7	HbSS=7 (9.3%), HbSC (10.3%), HbSβ-thal (6.9%), sickle hemoglobin D disease (HbSD) (3.4%)	6.9	100	NR
Benjamin, 1986 <sup>10</sup>	RCT	Adults	26.7	63	To examine the effects of cetiedil citrate (cetiedil) on the course of VOCs in patients with SCD	4, cetiedil at 0.2 mg/kg vs. 0.3 mg/kg vs. 0.4 mg/kg vs. placebo	Inclusion: Patients with SCD, presenting 4–24 h after onset of a painful VOC severe enough to require hospitalization. Exclusion: Pregnancy, women of childbearing potential, incarcerated persons, patients with a history of drug abuse or dependency, transfusion within 90 d preceding the trial, acute cerebrovascular accident (CVA), overt infection, renal failure with a serum creatinine concentration >2 mg %, clinical or roengenographic evidence of pulmonary edema, glaucoma, urinary retention, or a history of high sensitivity to anticholinergic or atropine-like drugs	57	HbSS (87%), HbSC (5%), HbSβ <sup>0</sup> -thal (2 %), sickle hemoglobin beta-plus thalassemia (HbSβ <sup>+</sup> -thal) (6%)	6 (4 patients of the original 67 patients)	100	During hospitalization
Bernini, 1998 <sup>11</sup>	RCT	Children	Median: 6.7	38 (43 episodes)	To evaluate the efficacy and toxicity of intravenous (IV) dexamethasone (0.3 mg/kg every 12 h × 4 doses) in children with SCD hospitalized with mild to moderately severe ACS	Intravenous dexamethasone vs. normal saline placebo	Inclusion: Age 1–21 yr, sickle cell hemoglobinopathy. Exclusion: Children with severe ACS, exacerbation of reactive airways disease, strong suspicion of bacterial infection, or any condition that might preclude the use of glucocorticoids	85	HbSS (89%), HbSC (8%), HbSβ <sup>0</sup> -thal (3%)	36.8 (lost to followup after discharge)	100	7 days after discharge
Cabannes, 1983 <sup>12</sup>	RCT	Children	11.4	30	To assess acute painful sickle cell crises in children	2	Inclusion: Children admitted to the University Hospital Hematology Clinic suffering from repeated sickle cell crises and who were suffering from an acute exacerbation	50	HbSS (63.3%), HbSC (13.3%), sickle hemoglobin beta-thalassemia (HbSβ-thal) (23.3%)	NR	100	NR

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Charache, 1995 <sup>13</sup>	RCT	Adults	NR	299	To test the efficacy of HU in reducing the frequency of painful crises in adults with a history of 3 or more such crises per yr	2	Patients had to be at least 18 yr old and had to have SCA; patients known to have HbSβ <sup>+</sup> -thal or HbSβ <sup>0</sup> -thal were excluded, but those with hemoglobin S alpha-thalassemia (HbSα-thal) were not. If patients had received transfusions, hemolysates of their red cells could not contain >15% hemoglobin A (HbA) at the time treatment was initiated. The patients had to have reported at least 3 crises to the study physician in the yr before entry into the study; for purposes of eligibility, documentation of crises was not necessary. There was no upper limit on the number of crises per yr. Other reasons for exclusion from the study included pregnancy; known narcotic addiction or regular consumption of >30 oxycodone capsules (or the equivalent) every 2 weeks; participation in a long-term program of transfusion; concurrent treatment with another potential anti-sickling agent; pretreatment blood counts that could not be distinguished from levels considered to indicate marrow depression; a history of stroke during the preceding 6 yr; prior HU therapy; and the presence of antibody to the human immunodeficiency virus (HIV)	49	HbSS, HbSα-thal	NR (but at study analysis time, only 134 patients of 299 patients had finished 24-mo followup)	100	21 mo
Co, 1979 <sup>14</sup>	RCT	Adults	Range: 18–29	10	To evaluate painful crises in patients with SCA	2	Inclusion: Patients had at least 2 areas of pain in each of 2 extremities with a similar degree of pain, provided the crises lasted >4 h and <24 h at the time of presentation to the hospital	60	HbSS	NR	100	NR
Cooperative Urea Trials Group, 1974 <sup>15</sup>	RCT	% adults NR	22.4±5.6 and 20±6.4 in groups 1 and 2	37	To assess the efficacy of raising blood urea nitrogen (BUN) level to 150 mg/dL or more in treating sickle cell crisis	2, urea treatment (group 1) vs. invert sugar (group 2)	Inclusion: Patients with SCD, with a painful crisis. Exclusion: Age <5 yr, painful crisis <2 weeks before the present episode, crisis pain <4 h or >24 h in duration, BUN or plasma urea nitrogen >30 mg/dL, a hematocrit reading <20% or >32% and not >3% below the baseline for the patient, pregnancy, overt infection, clinical or roentgenographic evidence of pulmonary edema or congestive heart failure, central nervous system (CNS) disease that was progressive or made evaluation difficult, hemoptysis, active liver disease, or only a single locus of pain in the abdomen or chest, known or probable narcotics addiction, patients with aplastic crises, hematuria, and priapism	54	NR	NR	100	Acute, during hospitalization
de Abood, 1997 <sup>16</sup>	RCT	Adults	Range: 17–39	43	To examine the effects of Depo-Provera (depot medroxy progesterone acetate (DMPA)) and microgynon (contraceptive medicine) on the incidence of painful crises in patients with SCD	3, DMPA vs. oral contraceptive pills (OCPs) vs. control (surgical sterilization)	Inclusion: Female patients with SCD, desiring a reversible method of contraception, history of at least 1 painful episode per mo	0	HbSS	0	100	12 mo

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Eke, 2000 <sup>17</sup>	RCT	Children	7.5	58	To compare the efficacy and tolerability of oral piroxicam with soluble aspirin in patients with SCA and severe osteoarticular painful attacks requiring hospitalization in a randomized, paralleled study	2	Inclusion: Eligible patients were children enrolled in the sickle cell register at the University of Port Harcourt Teaching Hospital. Exclusion: A history of allergy or hypersensitivity to either of the 2 drugs; a history of asthma, rhinitis, angioneurotic edema, and urticaria; and hepatic or renal failure	64	HbSS (98%), HbSC (2%)	NR	100	0.13 mo
Farber, 1991 <sup>18</sup>	RCT	% adults NR	Not clearly mentioned	116	To perform a randomized prospective clinical trial to study the effects of argon laser scatter photocoagulation therapy for proliferative sickle cell retinopathy (PSR)	2	Inclusion: All patients enrolled in the study had unilateral or bilateral peripheral PSR associated with HbSS, HbSC, or HbS $\beta$ -thal. Exclusion: Eyes with cloudy media (e.g., cataract, vitreous hemorrhage), previous photocoagulation, ocular surgery, or retinal detachment were excluded from the study, as were patients with systemic diseases that could influence the retinopathy (e.g., diabetes mellitus, hypertension). Also excluded was 1 eye of a patient randomized to the control group but treated in error. Patients with bilateral disease had their right eye randomized to either scatter photocoagulation or no treatment, with the other eye receiving the opposite modality	53	HbSS (18.1), HbSC (80.2), HbS $\beta$ -thal (1.7)	9.5	100	47.4 mo for treated eyes and 42.4 mo for control eyes
Foucan, 1998 <sup>19</sup>	RCT	Adults	30 $\pm$ 8 in treatment, 28 $\pm$ 6 in control	22	To evaluate the effect of angiotensin-converting enzyme inhibition on microalbuminuria in sickle cell patients	2, captopril vs. placebo	Inclusion: Patients with sickle cell anemia were 18 yr of age or older, had a diagnosis of SCA based on clinical and biological data including hemoglobin electrophoresis, and had urinary albumin excretion between 30 and 300 mg per 24 h on 3 separate occasions during the 6-mo period preceding the study. Exclusion: Patients with hypertension, if they had evidence of heart, kidney, liver, or systemic disease, and if they were pregnant	31.8	HbSS	4.5	100	6 mo
Fox, 1993 <sup>20</sup>	RCT	% adults NR	NR	88 (134 eyes)	To assess the efficacy of sectoral scatter laser photocoagulation in treating PSR	2, treatment vs. control	Inclusion: HbSC patients with PSR. Exclusion: Eyes with cataracts or vitreous hemorrhage, retinal detachment, previous photocoagulation, patients with diabetes mellitus (DM) or systemic hypertension	NR	HbSC	NR	100	35 mo
Gonzalez, 1988 <sup>21</sup>	RCT	Adults	29.3 $\pm$ 7.7	18	To compare the efficacy of intramuscular (IM) analgesic activity of butorphanol and morphine in patients with SCD	2, butorphanol vs. morphine	Inclusion: Adult patients with SCD, presenting to the emergency department with pain consistent with sickle cell crisis with no other identifiable cause by clinical history and examination. Exclusion: Allergy to medication, chronic narcotic therapy, history of drug or alcohol abuse, opioid tolerance, pregnancy, breast feeding, history of an acute myocardial infarction (AMI) within the past 6 mo or daily use of a narcotic analgesic during the last week	67	NR	0	100	Acute

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Gonzalez, 1991 <sup>22</sup>	RCT	Adults	18–65	Phase 1: 20 Phase 2: 25	The purpose of this study is a prospective assessment of morphine sulfate administration by intermittent needle therapy IV (INT-IV) injections vs. patient-controlled analgesia (PCA) in patients in the emergency department (ED) with sickle cell crisis pain	2 for each phase	Inclusion: Patients aged 18–65 yr who presented to the emergency department with sickle cell crisis pain. Exclusion: History of drug or alcohol abuse, allergy to morphine, pregnancy, or long-term use of narcotic analgesic	40 in each phase	NR	0	100	8 h
Griffin, 1994 <sup>23</sup>	RCT	Children	Mean: 7.7 Range: 2–19	36 (56 episodes)	To test the hypothesis that the administration of high doses of corticosteroids early in a VOC might lessen the duration or severity of pain in children and adolescents with SCD	2	Inclusion: <21 yr of age with SCD who are being followed at Children's Medical Center of Dallas were eligible if they had acute pain that remained despite management at home and in the emergency room (ER) with fluid and analgesics. Exclusion: Pain present >4 d before admission, bacterial infection suspected on basis of clinical exam or if ACS present	Unclear	HbSS (75%), HbSC (19%), HbSβ-thal (5%)	0	100	0.5 mo
Grisham, 1996 <sup>24</sup>	RCT	Children	14	15 (20 pain episodes)	To compare the safety and efficacy of ketorolac tromethamine and meperidine in sickle cell VOC in children	2	Inclusion: Eligible patients were children age 10 yr and older with SCA who were seen at the ED with VOCs. Exclusion: Patients with reactive airways disease, hepatic, renal or bleeding disorders, or allergies to NSAIDs	55	HbSS	0	100	NR
Hardwick, 1999 <sup>25</sup>	RCT	Children	11.7	29 (41 visits)	To determine if a single dose of IV ketorolac given upon presentation to the emergency department would (1) reduce the total dose of morphine required by the child in a VOC, (2) decrease the rate of hospitalization for these patients, and (3) decrease the rate of ED re-admission for discharged patients	2	Inclusion: Consecutive patients between the ages of 5 and 17 yr inclusive with SCA, who presented with pain crisis, were considered for inclusion in the study. Patients could be enrolled in the study more than once if their visits were separated by at least 1 mo. Exclusion: Patients with a known or suspected complication (e.g., aplastic crisis, ACS, and infection). Also excluded were patients with an allergy to 1 of the study medications and those with a history of renal disease, peptic ulcer disease, bleeding disorder, or use of analgesics or CNS-active medications within 3 h of enrollment.	56% of patient visits were men	NR	0	100	NR
Jacobson, 1991 <sup>26</sup>	RCT	% adults NR	27	44 (64 eyes)	To review long-term followup of patients enrolled in a randomized prospective trial of feeder vessel photocoagulation for PSR in order to demonstrate its efficacy	2	Inclusion: Patients with homozygous SCD, HbSC, or HbSβ-thal in association with peripheral PSR were eligible for the study	44.8	HbSS (13.7%), HbSC (68.9%), HbSβ-thal (17.2%)	34	100	108 mo
Jacobson, 1997 <sup>27</sup>	RCT	Children	11.2±3.5	50	To compare the clinical efficacy and safety of oral morphine with continuous IV morphine in children with severe episodes of sickle cell pain	2	Inclusion: Children with SCD who presented to the ED of the Hospital for Sick Children, Toronto, Canada, with painful episodes requiring admission to the hospital and parenteral opioid therapy were eligible. Exclusion: Children with intractable nausea or vomiting and those who were unable to tolerate oral or IV morphine	56	NR	0	100	NR

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La Grenade, 1993 <sup>28</sup>	RCT	% adults NR	31	32 (44 ulcerated legs, 49 ulcers)	To assess the efficacy of solcoseryl compared to duoderm and standard care in treating chronic SCD leg ulcers	3, control therapy vs. solcoseryl vs. duoderm	Inclusion: HbSS patients, age >15 yr, with ulceration of at least 6 mo and an ulcer size of at least 3 cm in its smallest dimension	80	HbSS	NA	100	6 mo
Lezcano, 2006 <sup>29</sup>	RCT	Children	Transfusion group=8.0 (standard deviation (SD)=3.6). Episodic/ no-transfusion group=8.1 (SD=3.0)	112	To determine whether regular blood transfusion was associated with significant reduction in free hemoglobin in plasma	2 arms ((transfusion group: ≥9 transfusions/yr, n=50) vs. (episodic/no transfusion group: <4 transfusions/yr, n=62))	Inclusion: Children with SCD at high risk of stroke based on TCD	NA	HbSS	NA	100	Median: 21.1 mo
McMahon, 2010 <sup>30</sup>	RCT	Adults	Range: 20–60	23	To compare the efficacy of arginine butyrate and standard local therapy to local therapy alone in treating chronic SCD leg ulcers	2, arginine butyrate + standard care vs. standard care only	Inclusion: Adult patients with HbSS or HbSβ-thal, presence of 1 or more leg ulcers that had been refractory to healing with National Institutes of Health (NIH)-defined standard local care for at least 6 mo, or ulcers that had recurred and not healed with at least 3 mo of standard care. Exclusion: Renal or hepatic compromise or current chronic transfusion therapy (CTX)	Unclear (due to cross-over)	HbSS (91%), HbSβ-thal (9%)	0	100	6 mo
Miller, 2001 <sup>31</sup>	RCT	Children	8.3±3.3	130	To determine the efficacy of CTX on incidence of pain and ACS	2, CTX vs. observation	Inclusion: Children with SCA and no history of stroke had to have undergone 2 TCD studies that showed that the time-averaged mean blood-flow velocity in the internal carotid or middle cerebral artery was 200 cm/s or higher	60	HbSS, HbSβ <sup>0</sup> -thal, % NR	NR	100	19.6±6.5 mo
Myers, 1999 <sup>32</sup>	RCT	Adults	Mean: 32.8	16	To investigate the effectiveness of relaxation training and massage therapy as adjunctive interventions in the management of chronic pain associated with SCD	2, relaxation training or massage therapy	Inclusion: Patients with HbSS, HbSC and HbSβ-thal	NR	HbSS (62%), HbSC (12%), HbSβ-thal (25%)	NR (12 patients (75%) completed the study protocol)	100	Mean: 4.5 mo
Neumayr, 2006 <sup>33</sup>	RCT	Adults	26	38	To test the effectiveness of hip core decompression	Surgery plus physical therapy vs. physical therapy	Physical therapy alone appeared to be as effective as hip core decompression followed by physical therapy in improving hip function and postponing the need for additional surgical intervention at a mean of 3 yr after treatment	50	HbSS, HbSβ-thal	17	76	36 mo
Odebiyi, 2007 <sup>34</sup>	RCT	Adults and children	21.9	20	To determine the effectiveness of sodium salicylate iontophoresis in the management of patients with hip pain and sickle cell disorders	2	Inclusion: Patients diagnosed with SCA with hip joint pain. Exclusion: Participants with metal implant in situ, skin lesions, renal problems, and individuals having crisis at the time of the study	55	NR	NR	100	1.25 mo

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Opio, 1972 <sup>35</sup>	RCT	26% adults	Mean: 15	19 (23 pain episodes)	To assess the effectiveness and efficacy of urea for the treatment of sickle cell bone pain	2	Inclusion: Patients who had HbSS attended the sickle cell clinic at Mulago Hospital, Kampala; were older than age 7 yr with typical bone pain crisis, usually <72 h duration and requiring hospitalization. Exclusion: Patients with established infection, requiring blood transfusion, or with other complications	65% pain episodes	HbSS	NR (1 patient was excluded)	100	NR
Orringer, 2001 <sup>36</sup>	RCT	% adults NR	Range: 9–53	249	To compare the duration of painful episodes in patients with SCD treated with purified poloxamer 188 to that of similar episodes experienced by patients who receive a placebo	2, purified poloxamer 188 vs. placebo	Inclusion: Age 8–65 yr, adequate liver function, adequate renal function, documented SCD, sudden onset of acute pain involving 1 or more sites typical of VOC, severe pain requiring parenteral analgesics, consent to use reliable contraception while enrolled in study and for 30 d thereafter, provided written informed consent. Exclusion: Clinically significant bleeding, chronic bacterial osteomyelitis, pregnancy or breastfeeding, inadequate venous access, history of major surgery (<2 weeks prior), episode of pain requiring hospitalization (<2 weeks prior), current hospitalization, participation in another investigational drug study, enrollment in a hypertension program, recent CVA/seizures, other SCD complications	41	HbSS/ HbSβ <sup>0</sup> -thal 77.5, HbSC 14.1, HbSβ <sup>+</sup> -thal 8.3	0	100	1 mo
Pegelow, 2001 (Stroke Prevention Trial in Sickle Cell Anemia (STOP)) <sup>37</sup>	RCT	Children	8.3±3.3	127	To determine if CTX affects the rate at which silent infarcts develop and to evaluate the contribution of magnetic resonance imaging (MRI) of the brain to stroke prediction by TCD US	2, CTX vs. standard care	Inclusion: SCD pediatric with abnormal TCD findings	46	HbSS, HbSβ-thal. Proportions NR	0	100	36 mo
Perlin, 1993 <sup>38</sup>	RCT	Adults	Range: 17–39	20	To compare infusional/patient-controlled mode of meperidine administration with IM meperidine control in patients with sickle cell pain crisis	2	Inclusion: Patients with SCD and pain crisis who were at least 18 yr of age. Exclusion: Pregnancy, abnormal renal function, and narcotic abuse	65	HbSS (85%), HbSC (10%), HbS-thal (5%)	35	100	Fixed: 0.1 mo
Perlin, 1994 <sup>39</sup>	RCT	Adults	Range: 19–41	21	To assess the efficacy of continuous IV infusion of ketorolac in treating patients with SCD with acute VOC pain	2, IV ketorolac vs. placebo	Inclusion: Patients with SCD with severe VOC pain. Exclusion: Age <15 yr, active peptic ulcer disease, systemic bleeding disorders, impaired renal function (BUN >20 mg/dL and/or serum creatinine >1 mg/dL, or other medical condition likely to complicate participation in study	52	NR	14	100	Acutely, during hospitalization

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Qari, 2007 <sup>40</sup>	RCT	% adults NR	Study group: 22.8±4.5; control group: 21.6±3.8	253	To test the safety and efficacy of low molecular weight heparin tinzaparin for management of acute painful VOC	2	Inclusion: HbSS patient with painful VOC severe enough to require narcotic analgesia. Exclusion: Medical or surgical contraindications for low-molecular-weight heparin (LMWH), pregnancy, low platelet count, complicated SCA, history of CVA, current aplasia, ACS, exchange transfusion, sequestration, anticoagulant therapy for other etiology, patients with painful crisis within 1 mo of this admission, women on contraceptive pills	48	HbSS	NR	100	NR
Sangare, 1993 <sup>41</sup>	RCT	Adults	21	100	To compare parenteral piroxicam and parenteral lysine acetylsalicylate in the treatment of acute painful articular attacks	2, piroxicam and lysine acetylsalicylate	Inclusion: Presence of painful osteoarticular attacks, clinical manifestation related to SCD, and biologic findings such as HbSS or HbSC Exclusion: Hypersensitivity to piroxicam or other NASIDs, concomitant peptic ulcer, severe gastrointestinal disease, or renal, hepatic or cardiac impairment, or pregnancy	61	HbSS, HbSC; respective percentages not reported	0	100	3 d
Schnog, 2001 <sup>42</sup>	RCT	Adults	HbSS 37±9 yr, HbSC 33±10 yr	29	To perform a randomized, double-blind, placebo-controlled, crossover pilot study to assess the potential efficacy of low adjusted-dose acenocoumarol treatment (international normalized ratio (INR) tested between 1.6 and 2.0) in adult patients with SCD	2	Exclusion: Age <16 yr, presence of chronic concomitant illness, blood transfusions in the last 4 mo, use of other medication (except acetaminophen, codeine, and vitamin B supplementation), pregnant or desire to become pregnant, recent trauma/surgery, sickle retinopathy, refusal of blood transfusion	Unclear	HbSS (64), HbSC (36)	24	100	7 mo
Serjeant, 1985 <sup>43</sup>	RCT	Adults	24.27	11	A double-blind, placebo-controlled crossover study was conducted in 11 patients with stuttering attacks of priapism and HbSS disease to analyze the value of stilboestrol in aborting/ preventing the attacks	2	Inclusion: Patients with SCD and stuttering priapism (SP) coming to the sickle cell clinic of University Hospital of West Indies and peripheral sickle cell clinics operated by staff of the Medical Research Council (MRC) labs	100	HbSS	0	100	Unclear
Serjeant, 1997 <sup>44</sup>	RCT	Adults	Range: 17–40	15	To compare the efficacy of propionyl-L-carnitine to placebo in treating chronic SCD leg ulcers	2, propionyl-L-carnitine vs. placebo	Inclusion: Adult patients with SCD with leg ulcers of at least 6 mo duration and at least 3 cm in diameter at the onset of treatment	80	HbSS	13	100	6 mo
Teuscher, 1989 <sup>45</sup>	RCT	Children	NR	36	To assess the efficacy of pentoxifyllin in treating VOC in SCD	2, active therapy vs. placebo	Inclusion: Pediatric patients with SCD >5 yr of age, evidence of severe VOC. Exclusion: <5 yr of age, unwillingness to comply to a hospital-based treatment, onset >48 h, another pain crisis in the past 14 d previous other specific treatments for SCD, severe clinically detectable bacterial infections, cardiovascular complications, hemoglobin <3, pregnancy, known drug misuse, severe renal or hepatic insufficiency, hypertension, oral contraceptives, known sensitivity for methylxanthines, participation in another clinical trial within the last 4 weeks	NR	HbSS	5	100	Acute, during hospitalization

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Uzun, 2010 <sup>46</sup>	RCT	Adults	24.9±6.1	68	To compare meperidine and tramadol with respect to their effects on the hemodynamics and pain relief in patients with SCD who were admitted to the emergency department with painful crisis	2	Inclusion: Patients with SCD who presented to the ED of our tertiary referral hospital with acute painful episode over an 18-mo period were included in this study. Exclusion: Patients <16 yr of age; known allergies to the study drugs; pregnancy; antidepressant/ monoamine oxidase inhibitor therapy; serious cardiac, pulmonary, or neurologic disorder; renal failure	72.1	HbS-thal (1.5%), HbSS (98.5%)	NR	100	NR
van Beers, 2007 <sup>47</sup>	RCT	Adults	26	25	To determine the efficacy of PCA in VOC in a prospective RCT in patients with SCD	2	Inclusion: Consecutive patients with SCD requiring parenteral analgesia for pain during a VOC were considered eligible for the study Exclusion: Patients who already received opioids for >24 h or patients who were allergic or intolerant to morphine	44	HbSS (64%), HbSC (24%), HbSβ-thal (12%)	8	100	NR
Vichinsky, 2001 <sup>48</sup>	RCT	Children	8.3±3.3	130	To determine if a prospective multicenter trial could successfully implement a transfusion program utilizing phenotypically matched blood to reduce alloimmunization and transfusion complications	2	As per STOP. Not detailed in this study	46	HbSS	1.5%	100	21 SD 5.7 mo
Wade, 1996 <sup>49</sup>	RCT	Adults	25±8	7	To evaluate Fluosol in the treatment of sickle cell crises (a perfluorocarbon that solubilizes large volumes of oxygen and enhances O <sub>2</sub> delivery)	2	Inclusion: Subjects homozygous for HbS and 16 yr or older Exclusion: significant pulmonary disease with baseline oxygen saturation of <92%; significant hepatic disease demonstrated by transaminases greater than 3 × normal or bilirubin >4.0 mg/dL; significant renal disease indicated by serum creatinine >2.0 mg/dL; known narcotic abuse or dependency during the 6 months prior to enrollment; concurrent participation in a program of exchange transfusions; sensitivity to egg yolk or poloxamer 188; or pregnancy. Patients who presented with fever (>38°C), evidence of acute infection, focal infarction or ACS were not treated during that crisis.	43	HbSS	0	100	2 d
Wang, 1988 <sup>50</sup>	RCT	% adults NR	Median: 17.5	22 (60 trials in 4 severity categories)	To analyze the value of transcutaneous electrical nerve stimulation (TENS) in treatment of sickle cell pain crisis as an alternate or adjunctive form of treatment not associated with significant toxicity	2	Inclusion: Patients with SCD reporting pain on a scale of 0–10, which was criteria for stratification by severity	45	HbSS (90%), HbSC (5%), HbSβ-thal (5%)	0	100	4 h

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Weiner, 2003 <sup>51</sup>	RCT	Children	Range: 10–21	20	To assess the efficacy and safety of inhaled nitric oxide (iNO) for acute VOC in pediatric patients with SCD	2, iNO vs. placebo	Inclusion: Sickle cell hemoglobinopathy patient, ages 10–21 yr, who had experienced uncomplicated severe acute VOC. Exclusion: ED treatment for VOC within the previous 24 h, VOC concomitant with other acute processes, including but not limited to ACS and potential serious infection, transfusion or use of investigational drugs other than HU within the last 30 d, allergy to morphine, smoking more than half a pack per d, and pregnancy	55	HbSS (50%), HbSC (45%), HbSβ-thal (5%)	0	100	Duration of hospitalization
Wethers, 1994 <sup>52</sup>	RCT	Adults	34	55	To compare the efficacy of arginyl-glycyl-aspartic acid (RGD) peptide matrix to that of placebo in treating SCD leg ulcers	2, RGD peptide matrix vs. placebo	Inclusion: Adult patients with SCD with isolated full-thickness lower leg or ankle ulcers that did not involve tendon or bone and had persisted for at least 1 mo. Exclusion: Other medical conditions that may delay healing (e.g., immune system diseases, uncontrolled diabetes, receiving medications that might adversely affect healing like steroids or anti-neoplastics, history of CTX) within the 3 mo preceding study commencement	60	HbSS (91%), HbSβ-thal (3.6%), HbSC (1.8%), HbSC Harlem (1.8%), HbSD (1.8%)	13	100	10 weeks
Wright, 1992 <sup>53</sup>	RCT	Adults	Mean: 30.8	18	To determine if a single dose of intramuscular ketorolac given on presentation to the emergency department has a narcotic-sparing effect in adult patients with sickle cell VOC pain	2	Inclusion: Eligible patients included adult patients with SCA who presented to the ED at either Vanderbilt or Metropolitan Nashville Hospital with a complaint of crisis pain and who rated their pain on a categorical scale as moderate or severe in intensity. Exclusion: Patients with an allergy to one of the study drugs; also those with a history of peptic ulcer disease, bleeding disorders, or use of analgesics during 3 h period before administration of study medication	37.5	HbSS	0	100	<1 mo (4 h)
Zipursky, 1992 <sup>54</sup>	RCT	Children	10.7 (4.8)	28 (5 patients studied twice)	To describe the effect of oxygen inhalation on the prevention and reversal of red blood cell (RBC) sickling in a randomized blinded study of patients in VOC	2	Inclusion: Eligible pediatric patients had HbSS, were clinically stable and were admitted to the Sickle Cell Disease Comprehensive Care Clinic of the Hospital for Sick Children for VOC pain. Exclusion: Patients with clinical or radiological signs of chest crises	NR	HbSS	NR (3 patients did not have sickle cell counts available)	100	NR

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Robieux, 1992 <sup>55</sup>	RCT within 1 arm of the observational prospective	Children	Range: 3–18	66	To compare the efficacy and safety of a continuous intravenous (CIV) infusion of morphine and intermittent parenteral opioids (IPO) in children with sickle cell VOC; to determine whether 50% O <sub>2</sub> administration through a face mask can reduce the duration of severe pain in patients receiving CIV infusions of morphine and to measure morphine concentration at steady state for pharmacokinetic and pharmacodynamic analysis in patients receiving CIV infusions of morphine	2, CIV infusion of morphine, vs. intermittent, and O <sub>2</sub> vs. air in the CIV group	Inclusion: Children with SCD disease, presenting with severe VOC. Exclusion: O <sub>2</sub> saturation <92%	NR	NR	NR	100	Acutely
Acurio, 1992 <sup>56</sup>	R, Obs	Adults	25 at onset of hip symptoms, 30 at surgery	25	To review and analyze the risk to benefit ratio of hip arthroplasty in SCD by reporting 25 hip arthroplasties in 25 patients with sickle-cell hemoglobinopathy and osteonecrosis	1	Inclusion: patients with osteonecrosis secondary to sickle-cell hemoglobinopathy	60	HbSS 44, HbSβ-thal 24, HbSC 12	0	100	103.2 mo
Adetayo, 2009 <sup>57</sup>	R, Obs	% adults NR	20.56 (9.33)	54	To present the outcome of management of acute prolonged priapism in patients with HbSS	2	Inclusion: Sickle cell patients of the Urology Unit at Lagos University Hospital from 1988 to 2001 with prolonged priapism	100	NR	15	100	6 mo
Adeyokunnu, 1981 <sup>58</sup>	R, Obs	Children	Range: 3–16	45	To assess priapism complicating SCD in Nigerian children	1	Inclusion: Nigerian children who presented with priapism at the Pediatric Dept. of University College Hospital, Ibadan between Apr. 1972 and Mar. 1980	100	The genotypes were known in 42 of 45 children. HbSS (90.5%), HbSC (7.1%), HbSF (2.4%)	15.6	100	Up to 3 yr
Al Hawsawi, 1998 <sup>59</sup>	R, Obs	Children	NA	9	To evaluate the prevalence and epidemiology of stroke in Saudi/ Yemeni patients with SCD	1	Children with SCD and had stroke	78	HbSS (67%), HbSβ-thal (33%)	0	100	18 mo
Al Jama, 2002 <sup>60</sup>	R, Obs	Adults	22	8	To describe massive splenic infarctions in patients with SCD	1, patients with SCD with massive splenic infarction	Inclusion: patients with SCA and massive splenic infarction	50	NR	0	100	Range: 6–60 mo
Al Salem, 1996 <sup>61</sup>	R, Obs	% adults NR	10.4	19	To describe the clinical course and treatment of 19 patients with SCD and acute splenic sequestration crisis (ASSC)	1	Inclusion: Patients with hematologically proven SCD who had ASSC during their management at Qatif Central Hospital over a period of 5 yr, from 1989 to 1993	74	HbSS (88%), HbS-thal (12%)	NA	100	Range: 6–60 mo

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Al-Mulhim, 2002 <sup>62</sup>	R, Obs	% adults NR	19 (range: 12–30)	35	To determine the safety, efficacy, morbidity and mortality of laparoscopic cholecystectomy (LC) in acute cholecystitis patients with SCD	1	Inclusion: Patients with SCD admitted to King Fahad Hospital, Hofuf between Apr. 1994 and Dec. 1998 with acute cholecystitis and had LC within the first 5 d of presentation	25.7	NR	NA	100	Fixed: 57 mo
Al-Salem, 1995 <sup>63</sup>	R, Obs	Children	14.4	22	To review Qatif Central Hospital experience with single preoperative transfusions in children with SCD undergoing cholecystectomy	1	Inclusion: All children ( $\leq 18$ ) with SCD (HbSS) who underwent cholecystectomy between 1988 and 1992 at Qatif Central Hospital	45	HbSS	NA	100	NR
Al-Salem, 1996 <sup>64</sup>	R, Obs	% adults NR	12.9	43	To present our experience with 43 patients with SCD who had splenectomy as part of their management	1	Not specified clearly	72	HbSS (88%), HbS $\beta$ -thal (12%)	0	100	72 mo
Al-Salem, 1998 <sup>65</sup>	R, Obs	50% adults	16.5	10	To describe the experience at Qatif Central Hospital with 10 cases of splenic abscess in patients with SCD	1	Inclusion: Patients with SCD treated at Qatif Central Hospital between June 1989 and June 1996 for splenic abscess	80	HbSS (40%), HbS $\alpha$ -thal (60%)	NA	100	NR
Al-Salem, 1999 <sup>66</sup>	R, Obs	20% adults	12.5 (range: 1.5–60)	143	To describe the experience with splenectomy performed for various hematological disorders over a period of 9 yr at the Qatif Central Hospital	NA	Inclusion: Patients who had splenectomy for hematological diseases at Qatif Central Hospital between 1988 and 1997. Exclusion: Patients with hypersplenism resulting from portal hypertension	58	HbSS (70%), HbS $\beta$ -thal (9%)	NR	79	Range: 8–104.4 mo
Al-Salem, 1999 <sup>67</sup>	R, Obs	33% adults	12.6	113	To assess efficacy and examine outcomes of splenectomy used in patients with SCD with splenic complications	1, patients with SCD with splenic complications who received a splenectomy	Inclusion: Patients with SCD who received splenectomy between 1987 and 1997 for splenic complications	61	HbSS (88.5%), HbS $\beta$ -thal (11.5%)	0	100	60+ mo
Al-Salem, 2000 <sup>68</sup>	R, Obs	Children	9.7	31	To describe experience with LC in children with SCD	1	Inclusion: Patients aged <15 yr with SCD who underwent LD	61	NR	NR	100	NR
Al-Suleiman, 2005 <sup>69</sup>	R, Obs	% adults NR	Mean: 20.4 (4.8)	135 (190 admissions for ACS)	To report the clinical features and outcome of ACS episodes in adult patients with SCD admitted to King Fahad Hospital, Hofuf, in eastern Saudi Arabia	1	Inclusion: Patients aged 12 and older with SCD and ACS admitted to King Fahad Hospital, Hofuf, in eastern Saudi Arabia	58.5	HbSS (87%), HbS $\beta^0$ -thal (10%), HbS $\beta^+$ -thal (3%)	NA	100	NR
Alvarez, 2006 <sup>70</sup>	R, Obs	Children 100	12.2 $\pm$ 4.7	120	To determine the prevalence of microalbuminuria in children and young adults with SCD in our multiethnic population, including African Americans and patients from the Caribbean (Hispanics and non-Hispanics), and to identify possible microalbuminuria associated factors	1	Inclusion: All children and young adults with sickle cell hemoglobinopathies who were screened with spot urine specimens for creatinine, albumin, protein, and $\beta$ -2 microglobulin during outpatient clinic visits while free of pain and infection	50	HbSS 89 (69.1%), HbSC 22 (18.3%), HbS $\beta^+$ -thal 3 (0.025%), HbS $\beta^0$ -thal 6 (0.05%)	NR	100	NR

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Bader-Meunier, 2009 <sup>71</sup>	R, Obs	Children	Median: 4.5	24	To assess the efficacy of CTX on cerebral vasculopathy in children with SCD	1, SCD pediatric patients receiving CTX for cerebral vasculopathy	Inclusion: Pediatric patients with SCD who had cerebral vasculopathy on MRA received regular exchange transfusion, were followed for a minimum of 1 yr after onset of transfusion therapy, and had at least 2 available MRAs	58	HbSS	0	100	29 mo
Bernaudin, 1997 <sup>72</sup>	R, Obs	Children	Median: 8.6	26	To evaluate the role of bone marrow transplant (BMT) in preventing recurrence of complications of SCD in severe cases	1	Inclusion: Patients with severe HbSS disease with multiple complications	46	HbSS	0	100	54.5 mo
Bhattacharya, 1993 <sup>73</sup>	R, Obs	Children	Median: 16.7	22	To review experience with preoperative transfusion in patients with SCD undergoing cholecystectomy	1	Inclusion: Patients with sickle cell hemoglobinopathy who underwent cholecystectomy at Children's Hospital, Boston, between 1978 and 1991	50	HbSS (90%), HbSC (5%), HbSβ-thal (5%)	0	100	Unclear
Bishop, 1988 <sup>74</sup>	R, Obs	Adults	31	11	To review and report the results of total hip arthroplasty in patients who have sickle cell hemoglobinopathy to analyze the risk for complications and overall results	1	Inclusion: Patients with sickle cell undergoing primary total hip arthroplasty between 1974 and 1984 who returned for followup	45	HbSS (55%), HbSC (18%), HbSβ-thal (27%)	0	100	90 mo
Brookoff, 1992 <sup>75</sup>	R, Obs	Adults	NR	295	To assess the effect of a structured analgesic regimen on hospital use by patients with SCD	2	Inclusion: Patients with the diagnosis of HbSS with crisis (International Classification of Diseases, Ninth Revision (ICD-9) 282.62) who were admitted to the Hospital of the University of Pennsylvania between Jan. 1 and June 30 in the years between 1985 and 1990	NR	HbSS	NA	100	36 mo
Brousse, 2009 <sup>76</sup>	R, Obs	Children	7	18	To assess the efficacy of regular blood transfusions in primary and secondary prevention of CVAs in patients with SCD	2, patients who had a 1st stroke vs. patients without history of stroke but a normal TCD	Inclusion: HbSS pediatric patients with either abnormal TCD findings or history of stroke	50	HbSS	0	100	59.6 mo in the secondary prevention group, and 14.3 mo in the primary prevention group

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Buchanan, 1989 <sup>77</sup>	R, Obs	Children	12	12	To determine the effects of blood transfusions on splenic function in older patients with SCD	2, intensive transfusion therapy with the aim of maintaining HbS <20% vs. less intensive transfusion therapy with pretransfusion HbS usually between 30 and 40%	NR	NR	HbSS	0	100	NR
Buchanan, 2005 <sup>78</sup>	R, Obs	Children	11	175	To evaluate the development of ACS in patients with SCD admitted for VOC and treated with either morphine sulfate or Nalbuphine hydrochloride and assess the efficacy in pain relief between the different analgesics by comparing the number of days of inpatient hospitalization as a proxy for pain control	2	Inclusion: Patients between the ages of 5 and 19 yr; identified with admission ICD-9 codes 282.60 and 282.62 for SCD and sickle cell pain crisis. Exclusion: Patients were transferred from another hospital for continued care; readmitted within 4 weeks after treatment for ACS on the previous admission; had a positive chest x ray on admission; were on chronic red cell transfusions; had other underlying diseases that could confound the primary outcome such as severe hepatic dysfunction, renal dysfunction, cardiac dysfunction, or status post-BMT; were on daily opioid therapy at home; if they had neurologic symptoms suggesting a transient ischemic attack (TIA) or an acute stroke (e.g., CVA); unable to grade their level of pain due to intellectual or physical limitations; were not admitted for a sickle cell pain event; not treated with 1 of the study medications	48.5	HbSS	NA	100	Fixed: 36 mo
Cackovic, 1998 <sup>79</sup>	Obs, R	% adults NR	20.7	18	To determine the cost of care for leg ulcers in patients with SCD	1, patients with SCD	Inclusion: Patients with SCD with nonhealing leg ulcers	67	NR	0	100	Unclear
Castro, 2003 <sup>80</sup>	R, Obs	Adults	37 (with pulmonary hypertension (PHTN)) and 31 (without PHTN)	34	To determine the relationship of PHTN to patient survival	1	Inclusion: Right-sided cardiac catheterization in adults with SCD	47	HbSS (72%), HbSC (12%), HbSβ-thal (3%), HbSD (3%)	0	100	23 mo for patients with PHTN and 45 mo for those without
Charache, 1979 <sup>81</sup>	R, Obs	% adults NR	22.6	28	To review and compare the clinical course and treatment of pediatric and adult patients with sickle cell and ACS	1	Inclusion: All adult or adolescent patients with SCA who were hospitalized with lung infiltrates between Sept. 1972 and Dec. 1975. Exclusion: Children <14 yr	57	HbSS	NA	100	NR

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Clarke, 1989 <sup>82</sup>	R, Obs	Adults	33 (range: 19–57)	15	To study total replacement of the hip for avascular necrosis (AVN) in SCD	1	Inclusion: Patients with SCD and had hip arthroplasties at the Johns Hopkins University from 1978 to 1988.	73.3	HbSS (46.7%), HbSC (33.3%), HbSC-thal (20%)	NR	100	24 mo
Cole, 1986 <sup>83</sup>	R, Obs	Children	NR	38 patients (98 pain episodes)	To describe our 5-yr experience with IV narcotic therapy, usually administered as a CIV infusion, for children and adolescents with severe sickle cell pain crisis	1	Inclusion: Patients with SCD admitted to the Children's Medical Center of Dallas for parenteral narcotic therapy from Nov. 1979 to Nov. 1984	55	HbSS, HbSC, HbSβ <sup>0</sup> -thal, HbSβ <sup>+</sup> -thal	NA	100	NR
Couillard, 2007 <sup>84</sup>	R, Obs	Children	NR	16	To evaluate the tolerability of long-term steroid treatment in children with SCD and autoimmune and/or systemic diseases	1	Inclusion: Patients with SCD, <18 yr of age, who were treated with steroids between Jan. 2000 and Dec. 2005	37.5	HbSS (94%), HbSC (6%)	NR	100	NR
Crawford, 2004 <sup>85</sup>	R, Obs	Children	9.4	16	To characterize the clinical and radiological presentation of ACS complicating cholecystectomy and splenectomy	1	Inclusion: Children who experienced ACS after undergoing cholecystectomy or splenectomy during the 15-yr period from Jan. 1988 through Dec. 2002. All children diagnosed with postoperative ACS were included in the analysis	31	HbSS (63%), HbSC (25%), HbSβ-thal (13%)	0	100	Average of 9 d
Crawford, 2006 <sup>86</sup>	R, Obs	Children	13.2	22	Retrospective study to compare postoperative PCA morphine consumption and pain intensity in sickle and nonsickle children who were referred to our Acute Pain Service (APS) after undergoing LC for symptomatic cholelithias	2	Inclusion: All children who were referred for PCA following LC during the period of Dec. 1996 to Dec. 2003. Exclusion: Patients who underwent open cholecystectomy	22.7	HbSS	0	54.5	NR
Curro, 2006 <sup>87</sup>	R, Obs	Children	Range: 9–16	42	To evaluate whether the outcome in children with chronic hemolytic anemia (CHA) and cholelithiasis undergoing LC is related to the operation timing	3, asymptomatic patients who received elective LC, vs. symptomatic patients, vs. emergency admitted patients	Inclusion: Pediatric patients with hemolytic anemia	NR	NR	0	50	55 mo
Curro, 2007 <sup>88</sup>	R, Obs	Children	14.9	30	To evaluate the role of elective LC in children with SCD and asymptomatic cholelithiasis	2	We reviewed the records of 30 children with SCD diagnosed with cholelithiasis from June 1995 to Sept. 2005	NR	NR	0	100	12–80 mo

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de Montalembert, 2004 <sup>89</sup>	R, Obs	Children	11.24±1.04	22	To investigate whether the heart also suffers from ischemia in SCD, as has already been shown for other organs (bone, brain, etc.), and to look for risk factors predisposing to this complication	1	In this study, children with chest pain, heart failure, abnormal electrocardiogram (ECG), left ventricular dilatation, or hypokinetic left ventricle were selected for myocardial perfusion studies	54.5	HbSS (95.5%), HbSβ-thal (4.5%)	0	100	NR
Delatte, 1999 <sup>90</sup>	R, Obs	Children	9.3	6	To analyze the incidence of ACS, a phenomenon of pulmonary sequestration inpatients with SCD, which is frequently missed in the postoperative SCD child, in pediatric patients	1	Not clearly reported	67	HbSS (50%), HbSC (33%), HbSβ-thal (17%)	0	100	0.2 mo
Duncan, 1992 <sup>91</sup>	R, Obs	83% adults	Range: 12–38	12	To report the results of biliary surgery in 12 patients with SCA	1	NR	16.6	HbSS	0	100	Perioperatively
Dunn, 1995 <sup>92</sup>	R, Obs	39% adults	Range: 5–38	13	To assess the role of penile scintigraphy in diagnosing priapism in patients with SCD	1, patients with SCD with priapism	NR	100	NR	0	100	Unclear
Ebong, 1977 <sup>93</sup>	R, Obs	% adults NR	13.7 (range: 7–27)	22	To study AVN of the femoral head associated with hemoglobinopathy	1	NR	54.5	HbSS (18.2%), HbAS (18.2%), HbSC (63.6%)	NR	81.8	NR
Ebong, 1986 <sup>94</sup>	R, Obs	Adults	20.8	75	To study aseptic necrosis of the femoral head in SCD	1	Inclusion: Patients with typical radiological features of AVN. Exclusion: Patients with negative radiological feature or patients with symptoms that were indistinguishable from septic arthritis	60	HbSS (49.3%), HbSC (51.7%)	0	100	6–48 mo
Emre, 1993 <sup>95</sup>	R, Obs	Children	6	37	To determine predictors of severity of ACS	1	Inclusion: Patients with SCD and ACS 51	HbSS (68%), HbSC (30%), HbSβ-thal (2%)	NR	NR	100	NR
Enninfu-Eghan, 2010 <sup>96</sup>	R, Obs	Children	2–18	475 pre-TCD 530 post-TCD	To assess the impact of TCD program on the incidence of first stroke and the rate of transfusion for stroke prevention in children with SCD	2, cohort	Inclusion: Patients <22 years of age with SCD-SS or SCD-Sβ <sup>0</sup> -thal Exclusion: Patients who had had a stroke before the study period	52	HbSS, HbSβ <sup>0</sup> -thal; respective percentages not reported	NA	100	8 yr before and 8 after intervention

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Finkelstein, 2007 <sup>97</sup>	R, Obs	Children	8.9 (4.0)	17	To explore the potential association between a dose-response effect of morphine exposure and the development of ACS in children with SCD who presented with VOC	1	All medical records of children (age <18 yr) with SCD who presented to the emergency department at the Hospital for Sick Children, Toronto, Ontario, Canada, for painful VOC (ICD-9, Clinical Modification (CM) (ICD-9-CM) code 282.62 or ICD, Tenth Revision, CM (ICD-10-CM) code D57.0) between Apr. 1, 2000, and Mar. 31, 2006, were reviewed. Data from patients who were treated with IV morphine and subsequently developed ACS were included in the analysis	23.6	HbSS (82.3%), HbSβ-thal (11.8%), HbSD (5.9%)	NA	100	Fixed: 72 mo
Frei-Jones, 2008 <sup>98</sup>	R, Obs	Children	14.5	105	To describe ED management of older children with SCD experiencing a vaso-occlusive episode (VOE) and factors associated with disposition and ED return	2	Inclusion: Patients between 8 and 19 yr of age were eligible. Inclusion criteria were an uncomplicated VOE during which the patient received at least 1 dose of IV morphine in the ED. Exclusion: Exclusion criteria, meant to eliminate factors other than a VOE that could influence the admission decision, included a documented temperature above 38.5°C, ACS, current CTX, isolated priapism, pain due to trauma or another reason other than VOE, initial treatment at another facility with transfer to Children's Medical Center Dallas, or pain relieved without administration of IV morphine	52	HbSS (70%), HbSC (22%), HbSβ <sup>+</sup> -thal (6%), HbSβ <sup>0</sup> -thal (2%)	NA	100	12 mo
Gholson, 1995 <sup>99</sup>	R, Obs	75% adults	25.5	8	To examine the outcomes of patients with SCD with sickle cell-associated cholelithiasis and choledocholithiasis	1, patients with SCD with suspicion of having choledocholithiasis	Inclusion: Patients with SCD suspected of having choledocholithiasis	NR	HbSS (87.5%), HbSβ-thal (12.5%)	0	100	Range: 12–36 mo
Gibson, 1979 <sup>100</sup>	R, Obs	% adults NR	Mean: 26	42	To describe the prevalence and treatment of cholelithiasis in patients with SCA	1	Inclusion: Patients with SCA attending the Medical University of South Carolina Hematology Clinic between 1968 and 1977	NR	HbSS	NA	100	NR
Hankins, 2005 <sup>101</sup>	R, Obs	Children	Median age: 7.6	27	Although not proven efficacious in secondary ACS prevention, it is believed CTX was an appropriate intervention because of its value in the management of acute ACS and in the primary prevention of ACS. To evaluate this approach, we retrospectively reviewed the charts of patients with recurrent or unusually severe ACS who were treated with CTX	1	Data were collected for patients who had experienced 2 or more episodes of ACS within a 2-yr period or who had experienced a "severe" episode of ACS (defined as an episode that required intensive care unit (ICU) admission with or without intubation) and who had been treated with CTX for at least 4 mo	66.7	HbSS	NR	100	Median of 1.8 yr
Hassell, 1994 <sup>102</sup>	R, Obs	93% adults	33	14	To describe the clinical course of acute multiorgan failure complicating an acute pain crisis in patients with SCD	1, patients with SCD with acute multiorgan failure	Inclusion: Patients with SCD, presenting with acute multiorgan failure as a complication to an acute pain crisis	43	HbSS (71%), HbSC (29%)	0	100	Range: 2–6 mo

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Hernigou, 2003 <sup>103</sup>	R, Obs	Adults	29	64	To evaluate the natural history of the hip after the development of symptomatic osteonecrosis in skeletally mature patients with SCD	1	Inclusion: 128 patients who were followed by our SCD center and who became adults (>18 yr) during 1980 and 1981 were eligible for the study after radiographs of both hips demonstrated no evidence of deformity of the hip secondary to osteonecrosis. Of the 128 patients, 64 subsequently were evaluated with radiographs or magnetic resonance imaging within 3 mo after the onset of pain in 1 or both hips	52	HbSS (64%), HbSC (19%), HbSβ-thal (17%)	0	100	167 mo
Hernigou, 2008 <sup>104</sup>	R, Obs	% adults NR	29 (range: 16–41)	38	To describe postop course for patients with SCD and osteonecrotic hips who underwent autologous bone marrow grafting	NA	Inclusion: Patients with SCD who underwent autologous bone marrow grafting in the Henri Mondor Hospital (Créteil, France)	NR	NR	0	100	Range: 10–17 yr
Hijazi, 2005 <sup>105</sup>	R, Obs	Children	6–18	55	To describe pulmonary function studies in Kuwaiti children with SCD and elevated HbF	4	Inclusion: Patients with SCD and in steady state (i.e., no acute illness within the preceding 6 w) and they were aged ≥6 yr and able to cooperate in conducting pulmonary function studies	NR	HbSS (75%), HbSβ-thal (25%)	NR	51%	NR
Holbrook, 1990 <sup>106</sup>	R, Obs	% adults NR	Range: 10 mo to 20 yr	20	To describe the experience of using PCA management of painful episodes in children with SCD	2	Inclusion: Children with severe or intolerable pain admitted to Children's Hospital of Eastern North Carolina from Nov. 1988 through Apr. 1990 and treated with analgesics	NR	HbSS, HbSβ <sup>0</sup> -thal	NA	100	Mean: 0.1 mo
Hulbert, 2006 <sup>107</sup>	R, Obs	Children	6.3	137	To test the hypothesis that exchange transfusion therapy is a more effective initial treatment for stroke than simple transfusion	2, exchange vs. simple transfusion	Inclusion: Patients who had therapy after stroke. Exclusion: Lack of documentation of stroke, lack of at least 5 yr of transfusion therapy documented in medical records, transfusion therapy that did not occur primarily at the participating institution, and transfusion therapy occurring at >6-week intervals at any time during followup	46	HbSS (100%)	0	100	3.6–10 yr
Isakoff, 2008 <sup>108</sup>	R, Obs	Children	8.46	31	To examine the use of corticosteroids for the treatment of ACS in patients with SCD	NA	Inclusion: Patients were between the ages of 1 and 21 yr with a diagnosis of SCD (HbSS, HbSC, HbSβ <sup>0</sup> -thal, or HbSβ <sup>+</sup> -thal) and developed severe ACS at or during admission to Connecticut Children's Medical Center during a 5.5-yr period from Jan. 1, 2001, to June 30, 2006. Exclusion: Patients who received corticosteroid treatment alone or transfusion therapy without corticosteroids were excluded from the series because they did not have a severe episode of ACS, as defined in the treatment guidelines at the institution	NR	HbSS (97%), HbSC (3%)	NR	100	66 mo

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Kalff, 2010 <sup>109</sup>	R, Obs	Adults	Median: 30	13	Endpoints retrospectively evaluated included the incidence of SCD-related acute events requiring hospitalization following and prior to regular emergency contraceptive pills (ECP), the development of new and progression of preexisting related end-organ damage, the effectiveness in reducing HbS levels acutely and prior to the next exchange and the transfusion-related complications	1	Inclusion: Recurrent painful crises, ACS, silent cortical ischemia, PHTN, multiorgan crises, and pregnancy	77	HbSS (61.5%), HbSβ <sup>+</sup> -thal (38.5%)	0	100	Median 70 mo
King, 1996 <sup>110</sup>	R, Obs	Children	Mean: 10.4	16	To describe patients with SCA and ACS who required admission to the pediatric critical care unit (PCCU) and compare the effects of simple versus exchange transfusion	2	Inclusion: Patients admitted to the PCCU for ACS between 1989 and 1994	44	HbSS	NA	100	NR
Kinney, 1990 <sup>111</sup>	R, Obs	Children	2.7	23	To assess the long-term management and outcomes of pediatric patients with SCD	3, observation vs. splenectomy vs. transfusion	Inclusion: Patients with SCD, children, history of splenic sequestration. Exclusion: Anemic events secondary to aplastic crisis, immune-mediated hemolysis, iron deficiency, or other causes were excluded	61	HbSS (91%), HbSC (9%)	Unclear	100	Range: 3.6–85.2
Kumar, 2010 <sup>112</sup>	R, Obs	Children	10.7	63	To assess the frequency of early (within 2 weeks) readmission among children who were treated with prednisone and those who were not	1	Inclusion: Children with ACS on admission and those who developed ACS during hospitalization for some other complication, usually for pain or fever	54	HbSS (76%), HbSC (14%), HbSβ <sup>+</sup> -thal (11%)	NR	100	NR
Lawrence, 1980 <sup>113</sup>	R, Obs	% adults NR	Range: 11 mo to 26 yr	12	To describe the outcomes of treating patient in sickle cell crisis with IV distilled water over the course of 12 mo	1	Inclusion: Patients treated over the past 12 mo who exhibited pain crisis and were treated in hospital	NR	HbSS	NA	100	Fixed: 12 mo
Leandros, 2000 <sup>114</sup>	R, Obs	Adults	23	82	To compare laparoscopic with open cholecystectomy in patients with SCD	2	Inclusion: Patients with SCD who had LC at the University of Athens Hospital during a 7 yr period (Sept. 1991–June 1998). Each patient was matched for age, sex, year of operation, and number of preoperative transfusions with a patient with SCD who had an open cholecystectomy during the same 7 yr	54	NR	NA	100	Mean: 11.7 mo
Leshner, 2009 <sup>115</sup>	R, Obs	Children	Median age at operation: 2	53	To review our experience with splenectomy in children with acute ASSC younger than 4 yr	1	Inclusion: Patients who had a history of ASSC and underwent splenectomy before their 4th birthday. Exclusion: Patients who underwent splenectomy for reasons other than splenic sequestration and patients who were older than 4 yr	52.3	HbSS (98.1%), HbSC (1.8%)	13.5	100	5.3 yr

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Little, 2006 <sup>116</sup>	R, Obs	Adults 100%	National Institutes of Health (NIH): median 51 Published reports: NR	NIH: 13 Published reports: 39	To summarize published data on erythropoietin (EPO) use in 39 patients with SCD, and on EPO or darbopoeitin use in 13 patients with sickle syndromes treated since 2002 at the NIH	1	Inclusion: Clinical reports on EPO and SCD, including homozygous HbS and compound heterozygous HbS $\beta^0$ -thal	NIH: 53.8% Published reports: NR	NIH: HbSS 12 (92.3%), HbSC 1 (7.7%) Published report: HbSS 30 (76.9%), HbS $\beta^0$ -thal, 9 (23.1%)	NR	100	NIH: median 16 moths. Published reports: NR
McCarthy, 2000 <sup>117</sup>	R, Obs	86% adults	26	7	To assess the efficacy of automated red cell exchange (RCE) transfusion in relieving priapism in patients with SCD	1, patients with SCD with priapism	Inclusion: Patients with SCD with priapism who received automated RCE transfusions	100	NR	0	100	During acute hospitalization
Meshikhes, 1998 <sup>118</sup>	R, Obs	% adults NR	25	71	Describe experience and demonstrate safety of LC in sickle cell patients with gallstones	NA	Inclusion: All patients with SCD who underwent LC between Oct. 1992 and Dec. 1996 at Qatif Central Hospital	59	NR	0	100	NR
Minniti, 2009 <sup>119</sup>	R, Obs	Adults	Range: 36–62	14	To assess the safety and efficacy of endothelin receptor blocker therapy in patients with SCD and PHTN	NA	Inclusion: Patients with SCD treated at the Clinical Center of NIH from 2005 to 2008 who had received clinically indicated bosentan or ambrisentan therapy for PHTN	29	HbSS (86%), HbSC (14%)	NR	100	8.5 mo
Mukisi-Mukaza, 2009 <sup>120</sup>	R, Obs	Adult	25	42	To investigate whether core decompression offers good relief from pain and delays the use of total arthroplasty in comparison to a conservatively treated control group by a simple non-weight-bearing protocol	2	Inclusion: Drepanocytic adults seen at the Caribbean drepanocytosis center between 1994 and 2008	25	HbSS (52%); HbSC (48%)	NR	100	Nonoperated group: 160.8; operated: 135.6
Muneer, 2009 <sup>121</sup>	R, Obs	% adults NR	42	60	To report the most efficacious treatment options for SP	1	Inclusion: Patients with a history of at least 1 episode of priapism requiring intervention followed by further episodes of priapism or prolonged painful erections (lasting <6 h) or if they gave a good history of prolonged erections (lasting <6 h) occurring spontaneously and on a regular basis that were deemed painful	100	NR	0	15 (9 out of 60)	25 yr
Ojo, 1999 <sup>122</sup>	R, Obs	% adults NR	Range: 13–55	82	To assess the efficacy of renal transplantation in end-stage sickle cell nephropathy	1, patients with SCD with end-stage renal disease who received renal transplant	Inclusion: kidney transplant recipients with ESRD as a result of sickle cell nephropathy	63	HbSS (98.7%), HbSC (1.3%)	0	100	36 mo

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Plummer, 2006 <sup>123</sup>	R, Obs	81% adults	28.5	16	To indicate that patients with SCD remain a high-risk group with the potential for significant morbidity even when subjected to minimal access surgery	1	Data were collected from the case files of patients with known SCD who underwent LC at the University Hospital of the West Indies (UHWI) between 1999 and 2004. All patients were subjected to endoscopic retrograde cholangiopancreatography (ERCP) preoperatively to assess for common bile duct (CBD) stones	25	HbSS (87.5%), HbSβ-thal (12.5%)	NR	100	NR
Powell, 1992 <sup>124</sup>	R, Obs	Children	26.8 mo	12	To analyze the hypothesis that with early detection of SCD by neonatal screening and an educational program developed by the Comprehensive Sickle Cell Center, morbidity and mortality from ASSC can be reduced	1	Inclusion: Patients with a discharge diagnosis of ASSC	42	HbSS (92%), HbSβ-thal (8%)	0	100	33mo
Rachid-Filho, 2009 <sup>125</sup>	R, Obs	% adults NR	16	35	To determine whether the use of finasteride controls recurrent priapism in patients with SCA	5	From Mar. 2001 to Jan. 2007, 56 patients with recurrent priapism because of SCD had been using finasteride. 35 patients used finasteride alone, and the remaining 21 used it as adjuvant therapy. Only these 35 patients, without any previous treatment, were analyzed according to the number of recurrences registered in a priapism record	100	NR	0	100	Mean 11 mo
Rambo, 1986 <sup>126</sup>	R, Obs	27% adults	Mean: 23.1	11	To review the experience at the Medical University of South Carolina with cholecystectomy in patients with SCD during the previous 10 yr	1	Inclusion: Patients with SCD or sickle-thalassemia at the Charleston Memorial Hospital and the Medical University Hospital who had cholecystectomy from 1977 to 1984 Exclusion: Patients with sickle cell trait or anemia due to other hemoglobinopathies	54	HbSS (90%), HbSβ-thal (10%)	NA	100	NR
Rao, 1985 <sup>127</sup>	R, Obs	Children	Range: 11–41 mo	13	To describe the clinical presentation and management of acute and sub-ASSC in pediatric patients with SCD at the University of Illinois Hospital	1	Inclusion: Patients with HbSS presenting who developed splenic sequestration and were seen at the University of Illinois Hospital between July 1976 and June 1982	NR	HbSS (100%)	NA	100	NR
Raphael, 2008 <sup>128</sup>	R, Obs	Children	Mean for day hospital group: 10.3; mean for inpatient group: 13.6	70	To determine whether day hospital management results in shorter length of stay (LOS) compared to inpatient care	2	Inclusion: Patients with SCD were defined as those having a diagnosis of HbSS, HbSC, HbSβ <sup>+</sup> -thal, or HbSβ <sup>0</sup> -thal. Exclusion: Patients who had secondary acute diagnoses including ACS, new onset headache, or changes in neurological status at the time of initial presentation	51.4	HbSS (84.2%), HbSC (10%), HbSβ <sup>+</sup> -thal (2.8%), HbSβ <sup>0</sup> -thal (2.8%)	NA	100	NA
Rezende, 2009 <sup>129</sup>	R, Obs	Children	Median: 16.6 mo	255	To analyze ASSC in children with SCA diagnosed through a newborn screening program in the state of Minas Gerais, Brazil, and followed up at the hematology center in the city of Belo Horizonte, Minas Gerais, Brazil	2	Inclusion: The study population included 89 case patients who had 1 or more episodes of ASSC. The control group was composed of 166 children with no record of ASSC, reaching a total of 255 patients analyzed	48.2	Hemoglobin FS electrophoretic profile at birth (HbSS/HbSβ <sup>0</sup> -thal)	NA	34.9	At least 24 mo

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Rudolph, 1992 <sup>130</sup>	R, Obs	% adults NR	Mean: 17.9	14	To assess the experience of cholecystectomy in patients with symptomatic SCD at Memorial Medical Center, a SCD referral center in Savannah, Georgia	1	Inclusion: Patients with a discharge diagnosis of both SCD and cholecystectomy at Memorial Medical Center from Jan. 1985 through Dec. 1989. Exclusion: Patients who had an HbS on electrophoresis that was <40% of total hemoglobin before transfusion 21	NR	NR	NA	100	NR
Salamah, 1989 <sup>131</sup>	R, Obs	Children	4.75	17	To describe the experience of treating ASSC in patients with SCD at Dhahran Health Center	1	Inclusion: All children admitted to Dhahran Health Center between Sept. 1981 and Sept. 1985 with the sickle cell hemoglobinopathy and ASSC	65	HbSS (82%), HbSβ <sup>0</sup> -thal (18%)	NA	100	NR
Sandoval, 2002 <sup>132</sup>	R, Obs	Children	Median: 7.8	13	To assess the safety and efficacy of laparoscopic surgery in treating hepatobiliary and splenic complications of SCD in children	2, patients undergoing splenectomy vs. patients undergoing cholecystectomy	Inclusion: HbSS	54	HbSS (100%)	0	100	19 mo
Sanjay, 1996 <sup>133</sup>	R, Obs	Adults	27	21 (26 hips)	To report the results and the problems encountered during 26 uncemented bipolar hip replacements for AVN of the femoral head due to SCD	1	Inclusion: Patients with avascular necrosis of femoral head due to SCD and had uncemented bipolar hip replacements	43	HbSS (95%), HbSβ-thal (5%)	0	100	55.2 mo
Sartori, 1990 <sup>134</sup>	R, Obs	Children	Range: 1.7–14.3	24	To describe the experience of using continuous papaveretum infusions to control pain in 24 children admitted on 45 occasions with painful sickling crisis	1	Inclusion: Children with severe sickling crisis Exclusion: Preexisting respiratory depression secondary to pulmonary or neurological problems; active cholecystitis and biliary colic	NR	HbSS (75%), HbSC (8%), HbSβ <sup>0</sup> -thal (8%)	NA	100	Range: 0.03–0.3 mo
Scothorn, 2002 <sup>135</sup>	R, Obs	Children	The average age at the initial stroke was 6.3 (1.4–14)	137	To test the hypothesis that children with SCD who have an initial stroke temporally unrelated to another medical event are at higher risk for recurrent stroke than are children who had strokes temporally related to medical events after receiving at least 5 yr of continued blood transfusion therapy	2	Inclusion: Patients with SCD with a history of at least 5 yr of documented regular blood transfusion therapy for stroke with a confirmed neuroimaging study documenting a stroke and a clinical history revealing a focal neurologic deficit (infarctive or hemorrhagic) were eligible for the study. Exclusion: Patients (1) did not have documentation of stroke; (2) were not transfused primarily at the participating institution; (3) did not have documentation of a minimum of a 5-yr transfusion history by medical record review; (4) had incomplete medical records; or (5) did not receive regular blood transfusion therapy consisting of a minimum interval of 6 weeks. TIAs, defined as neurologic symptoms and signs that resolved within 24 h, were not included	46	HbSS	NA	100	121 mo
Seguier-Lipszyc, 2001 <sup>136</sup>	R, Obs	Children	Mean: 9.75	29	To assess whether SCA pediatric patients can benefit from elective LC	1	Inclusion: All patients with SCA who underwent a LC between July 1991 and Apr. 1998 at our hospital in France between 1991 and 1998	72	HbSS	NA	100	NR

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Shapiro, 1993 <sup>137</sup>	R, Obs	% adults NR	Mean: 15	46	To delineate dose ranges, utilization patterns, and the frequency and types of problems encountered of patients with SCD who used PCA for the management of VOC pain	1	Inclusion: Patients hospitalized with VOC pain who received PCA between Apr. 1988 and July 30, 1990	NR	NR	NA	100	NR
Sobota, 2010 <sup>138</sup>	R, Obs	Children	10.3 (5.5)	3090	To examine the variation between hospitals in their use of corticosteroids for ACS, describe characteristics associated with corticosteroids, and investigate the association between corticosteroids, LOS, and readmission	2 (corticosteroids and no corticosteroids)	Inclusion: All pediatric hospitalizations for ACS between Jan. 1, 2004, and June 30, 2008, at the 32 hospitals in the Pediatric Health Information System database	55	NR	NA	100	4.5 yr
Sprinkle, 1986 <sup>139</sup>	R, Obs	Children	Median: 8.5	57	To describe 100 hospitalizations for ACS in pediatric patients with SCD over a period of 5 yr	1	Inclusion: All pediatric patients hospitalized with ACS between Jan. 1979 to Dec. 1983. Exclusion: Cases of mild pulmonary disease managed entirely in outpatient areas were not included	NR	HbSS (77%), HbSC (17%), HbSβ <sup>+</sup> -thal (1.7%), HbSβ <sup>0</sup> -thal (3.5%)	NA	100	NR
Strouse, 2006 <sup>140</sup>	R, Obs	Children	Cases: 10.4±1.3; controls: 5.2±0.4	44	To evaluate risk and prognostic factors for primary hemorrhagic stroke among children with SCD	2	Inclusion: Age <19 yr at Johns Hopkins Children's Center from Jan. 1979 and St. Louis Children Hospital from Jan. 1990 to Dec. 2004. Cases had SCD and intraparenchymal, subarachnoid, or intraventricular hemorrhage confirmed by neuroimaging, autopsy, or analysis of cerebrospinal fluid. Exclusion: Traumatic hemorrhages, isolated subdural or epidural hemorrhages or hemorrhagic conversion of ischemic stroke or cerebral venous sinus thrombosis. Control subjects had SCD and ischemic stroke (focal neurologic deficit lasting >24 h with medical documentation or deficit lasting <24 h and evidence of acute infarction by neuroimaging)	43	HbSS proportion NR, HbSβ <sup>0</sup> -thal 13 of cases, HbSβ <sup>+</sup> -thal 3 of controls	20	100	0.5 mo
Styles, 1996 <sup>141</sup>	R, Obs	Children	Mean: 15	10 patients (13 hips)	To report the results of core decompression in children with SCD afflicted with AVN of the hip	1	Inclusion: Patients followed regularly at the Northern California Comprehensive Sickle Cell Center and had their diagnosis of SCD confirmed by standard electrophoretic techniques. Patients were eligible for core decompression if they met the following criteria: (1) severe pain localized to the hip or inguinal area requiring hospitalization with IV narcotics, (2) physical examination findings of pain and limitation on movement of the affected hip, and (3) radiographic or MRI findings diagnostic of AVN. Patients had not received any other treatment for AVN (e.g., HU or CTX) prior to the core decompression procedure	50	HbSS (80%); HbSC (10%); HbSβ <sup>+</sup> -thal (10%)	NA	100	Range=8–108 mo

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Subbannan, 2009 <sup>142</sup>	R, Obs	Adults	26.5	124	To evaluate the need for splenectomy and its outcome in adult patients with HbSC	2	Inclusion: Patients with HbSC followed in the Sickle Cell Center at the Medical College of Georgia between 1975 and 2006	52	HbSC (99%), HbSC $\alpha$ -thal (1%)	NR	100	Nonsplenectomy group: 42 mo; Splenectomy group: 91 mo
Svarch, 1996 <sup>143</sup>	R, Obs	Children	Median: 3	25	To describe the clinical course of children with SCD and repeated episodes of splenic sequestration who underwent partial splenectomy	1	Inclusion: Patients with SCD and acute and repeated splenic sequestration treated with partial splenectomy	NR	HbSS (80%), HbS $\beta^0$ -thal (20%)	NR	100	Median: 48 mo
Svrach, 2003 <sup>144</sup>	R, Obs	Children	Median: 3	50	To describe the experience of pediatric patients with SCD who underwent partial splenectomy for ASSC in Cuba	1	Inclusion: Children with SCD who underwent partial splenectomy following >1 episode of ASSC	NR	HbSS (86%), HbS $\beta$ -thal (14%)	NR	100	Mean: 108 mo
Tagge, 1994 <sup>145</sup>	R, Obs	Children	13.3	32	To continue investigations relating to therapy for cholelithiasis in patients with SCD by reviewing experience at MUSC with cholecystectomy in children with SCD comparing open versus LC	2	Inclusion: Patients with SCD and underwent cholecystectomy	NR	NR	0	100	Unclear
Taylor, 2004 <sup>146</sup>	R, Obs	% adults NR	15.6	45	To evaluate the clinical presentation and describe clinical course	1, patients with SCD admitted with ACS	1: Lower respiratory tract symptoms 2: New pulmonary infiltrates on the chest radiograph	38	NR	0	100	10 d
Trentadue, 1998 <sup>147</sup>	R, Obs	Children	15.16	26 (60 episodes)	To compare the efficacy of high-dose patient-controlled analgesia/ low basal infusion (HPCA/LBI) vs. low-dose patient-controlled analgesia/high basal infusion (left posterior cerebral artery (LPCA)/HBI) in treating children with SCD and VOC pain	2, HPCA/LBI vs. LPCA/HBI	Inclusion: SCD pediatric patients, who presented with VOC pain and received PCA	42	NR	0	100	Acutely, during hospitalization
Turner, 2009 <sup>148</sup>	R, Obs	Adults	30.9	40	To evaluate the relative efficacy of exchange transfusion versus simple transfusion for treatment of SCA ACS	2	The first 20 individual adult were selected (age >21 yr) patients who were HbSS or HbS $\beta^0$ (HbSC were excluded) that had undergone an exchange transfusion for treatment of ACS in reverse chronological order from Dec. 31, 2006. The comparison group was similarly the first 20 individual age-matched adult HbSS or HbS $\beta^0$ patients, also in reverse chronological order from Dec. 31, 2006, who had received only simple transfusion for treatment of ACS	67.5	HbSS (92.5%), HbS $\beta$ -thal (7.5%)	0	100	NR

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Van Agtmael, 1994 <sup>149</sup>	R, Obs	% adults NR	Range: 15–59	53	To evaluate the frequency, presentation, and course of the ACS in adult Afro-Caribbean patients with SCD	1	Records of all patients 14 yr of age and older with SCD (demonstrated by hemoglobin electrophoresis) discharged from our hospital with a diagnosis of ACS (International Classification of Diseases, Ninth Revision, Clinical Modification code 282.62, with sub-specification of pulmonary sickling, chest crisis, lung crisis, or HbSS pneumonia) in the period between Jan. 1980 and Dec. 1991 were evaluated	41	HbSS (64%), HbSC (36%)	NA	100	NR
Velasquez, 2009 <sup>150</sup>	R, Obs	Children	Median: 10	44	RCE is part of the management of ACS in patients with SCD. The study describes the indications and outcome of the procedure	NA	Inclusion: Patients with ACS who received RCE transfusion between Jan. 2003 and Oct. 2006	55	HbSS (93%), HbSC (5%), HbSβ <sup>0</sup> -thal (2%)	0	100	NR
Wales, 2001 <sup>151</sup>	R, Obs	Children	8.6	35	To determine the incidence of postoperative ACS and assess for predisposing factors in all sickle cell patients undergoing abdominal surgery	2	A retrospective analysis of all sickle cell patients undergoing surgery between Jan. 1994 and Dec. 1998 was completed	37.1	HbSS (77.1%), HbSC (22.9%)	0	100	NR
Warady, 1998 <sup>152</sup>	R, Obs	Children	16±1.6	9	To examine the outcomes of renal transplantation in pediatric patients with SCD	1, pediatric patients with SCD who received renal transplantation	Inclusion: Patients who were enrolled in the transplant arm with a diagnosis of sickle cell nephropathy	56	NR	0	100	Range: 9–60 mo
Ware, 1988 <sup>153</sup>	R, Obs	Children	12.6	27	To assess the efficacy of elective cholecystectomy in children with sickle cell hemoglobinopathies	1, pediatric patients with SCD who underwent elective cholecystectomy	Inclusion: Pediatric patients with SCD	70	HbSS (82%), HbSC (7%), HbSβ-thal (11%)	0	100	Mean: 47 mo
Ware, 1992 <sup>154</sup>	R, Obs	Children	15	9	To report the diagnosis and management of CBD stones in 9 patients with sickle hemoglobinopathies	1	Patients with sickle hemoglobinopathies and cholelithiasis and with CBD stones	66.9	HbSS (88.9%), HbSβ-thal (11.1%)	NR	100	Mean 57 mo
Wilimas, 1980 <sup>155</sup>	R, Obs	Children	Range: 4–13	12	To evaluate the effectiveness of transfusion therapy for children with SCD who have already experienced a stroke	1	Inclusion: Pediatric patients with SCD who have already experienced a stroke and entered on a transfusion protocol for stroke prevention	NR	HbSS (92%), HbSC (8%)	NA	100	NR
Williamson, 2009 <sup>156</sup>	R, Obs	Adults	41	27	To describe the management of vitreoretinal complications of sickle cell retinopathy	2; surgery vs. observation	Retrospective review of the database and the clinical records of all patients with sickle cell retinopathy with vitreoretinal disorders presenting to the vitreoretinal service at St. Thomas' Hospital from Nov. 1997 to Nov. 2006	22.2	HbSS (7.4%), HbSC (92.6%)	0	100	15.5 mo

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Winter, 1994 <sup>157</sup>	R, Obs	Children	Group 1: 11.8; Group 2: 11.0	17	To provide evidence to support the recommendation that elective cholecystectomy should be performed on patients with gallbladder sludge as they eventually have gallstones	1	Inclusion: Children with SCD who underwent US from 1979 to present	76	HbSS 88, HbSC 6%	0	100	Group 1:4, Group 2:10
Winter, 1997 <sup>158</sup>	R, Obs	Children	10.7	24	To determine the appropriate evaluation and management of children with coronary artery disease (CAD) who have acute neurological symptoms	1	Inclusion: Patients with SCD with focal or nonfocal neurologic symptoms. Focal symptoms are unilateral weakness or numbness involving somatic or cranial nerve distributions for >24 h. Nonfocal symptoms are loss of consciousness, headache, visual disturbances, deterioration of penmanship, personality changes, nonfocal seizure	70.8	NR	0	100	17–76 mo
Woods, 1990 <sup>159</sup>	R, Obs	% adults NR	Range: 3–20	16	To study the effectiveness and feasibility of Nalbuphine compared to meperidine for the treatment of painful sickle episodes	2	Inclusion: Uncomplicated acute painful episodes. Exclusion: Painful sickle cell episodes associated with other acute events, such as fever >102°F on admission; documented infection (e.g., pneumonia, meningitis); ACS; acute exacerbation of asthma; pain possibly related to cholelithiasis; and transfusion therapy during hospitalization for painful episode	68.7	HbSS 81.25, HbS 18.75, HbSβ-thal 6.25	0	100	NR
Wu, 2005 <sup>160</sup>	R, Obs	% adults NR	Range: 11–22	12	To investigate the therapeutic effect of the vascularized iliac graft for ischemic necrosis in femoral head in young patients with SCD	1	Inclusion: Patients with SCD suffered from ischemic necrosis of the femoral head and received vascularized iliac bone graft	41.6	NR	0	100	24–30 mo
Yaster, 1994 <sup>161</sup>	R, Obs	Children	13±4	9	To determine whether continuous epidural analgesia could effectively decrease pain and thereby improve the management of severe VOC in children with SCD who were unresponsive to conventional analgesic therapy	1	Inclusion: All patients in this report had undergone exchange transfusion in the past for either ACS, hypoxemia unresponsive to oxygen therapy, or poor response to conventional analgesic therapy	55.6	HbSS (77.8%), HbSC (22.2%)	0	100	NR
Zemsky, 2008 <sup>162</sup>	R, Obs	Children	11.5 (4.9)	59	To characterize pain assessment and pain management practice for children and adolescents hospitalized with sickle-cell-related pain to get a better understanding of the natural history of patients hospitalized with this disorder	1	Inclusion: A diagnosis of SCD and hospitalization at an urban children's hospital for a VOC pain episode between Jan. 1, 2004, and Dec. 31, 2005. Exclusion: Patients were <3 yr of age, or they did not receive IV opiates during their hospitalization	50.8	HbSS (90%), HbSC (7%), HbSβ-thal (3%)	NA	100	24 mo
Al-Abkari, 2001 <sup>163</sup>	P, Obs	% adults NR	NR	147	To assess the efficacy and safety of LC in treating gallbladder stones in patients with SCD	2, patients with SCD vs. patients without SCD	Inclusion: Patients with and without SCD undergoing LC	78	NR	NR	25	72 mo

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Al-Dabbous, 2002 <sup>164</sup>	P, Obs	Children	6.9	132 (154 admissions)	To define the clinical features and outcome of ACS in patients with SCD in the Eastern Province of Saudi Arabia	1	Inclusion: All patients who were 12 yr or younger, admitted to Qatif Central Hospital with ACS (or developed ACS during hospitalization) between July 1992 and July 1997 were included	75	HbSS (96.2%), HbSβ <sup>0</sup> -thal (1.5%), HbSβ <sup>+</sup> -thal (2.3%)	0	100	0.22 mo
Al-Jam'a, 2002 <sup>165</sup>	P, Obs	% adults NR	22.3	36	To assess the safety and efficacy of HU in sickle cell VOC prevention	1, patients with SCD receiving with history of recurrent sickle cell VOC	Inclusion: Patients with SCD, age >5 yr, history of 4+ painful VOC requiring hospitalization annually. Exclusion: Pregnancy, lactation, contraceptive measures refusal, significant renal impairment (Cr >1.8 mg/dL), significant impairment of liver functions (ALT >150 U/L or albumin <3 g/dL), narcotic addiction, use of theophyllines, androgens, estrogens, progesterone (other than OCP) and infection with HIV, hepatitis C virus, or hepatitis B virus	64	HbSS, HbSβ-thal. Proportion not specified	25	100	Mean: 29 mo
Al-Mousawi, 2002 <sup>166</sup>	P, Obs	Adults	27.5	28	To present the experience, and the problems encountered, with total hip replacement in AVN of the femoral head in patients with SCD	1	Not clearly specified	53.5	HbSS (96%) HbAS (4%)	5	100	114 mo
Ataga, 2006 <sup>167</sup>	P, Obs	Adults	Patients with PHTN: 42.3; patients without PHTN: 38.4	93 (enrolled), 76 (included in analysis)	To evaluate the trends of development of PHTN, the association of PHTN with clinical and laboratory measures, and effect of PHTN on mortality in patients with SCD	2	The participants in this study represent a subset of all adults (age ≥18 yr) followed in the Sickle Cell Clinic at the University of North Carolina Hospitals, Chapel Hill. Patients were selected initially using a systematic sampling of those who presented to the clinic for a routine visit (i.e., every 4th patient who checked into the clinic was asked to enroll). To enhance accrual, recruitment procedures were adjusted after enrollment of the first 45 patients to target consecutive patients seen in the clinic. Each enrolled patient was in the non-crisis, steady state; had not experienced an episode of ACS in the preceding 4 weeks; and had no evidence of heart failure	39	HbSS (74%), HbSC (12%), HbSβ <sup>0</sup> -thal (5%), HbSβ <sup>+</sup> -thal (9%)	NR (17 patients of 60 patients were not available for repeat evaluations)	100	2.6 yr (for mortality)
Beiter, 2001 <sup>168</sup>	P, Obs	Children	Range: 6–18	51	To assess the efficacy of IV ketorolac tromethamine in treatment of children with SCD and VOC pain	1, pediatric patients with SCD with VOC pain	Inclusion: Children with SCD and VOC pain. Exclusion: Children with atypical pain, allergies to NSAIDs, or impaired vision or neurological function, and age under 6 yr	NR	HbSS, HbSC, HbSβ-thal. Proportions NR	0	100	During hospitalization
Bodhise, 2004 <sup>169</sup>	P, Obs	80% adults	Range: 12–44	5	To describe our experience in the utilization of a deep tissue or deep pressure massage therapy technique, including neuromuscular trigger point therapy with acupressure in patients with SCD	1	Inclusion: Patients with a diagnosis of SCD and painful AVN. The diagnosis of SCD was confirmed by hemoglobin electrophoresis in alkaline and acidic media, solubility testing, isoelectric focusing, and, in selected cases, by high-pressure liquid chromatography. The diagnosis of AVN was confirmed by radiography of the affected area and, in selected cases, by MRI	60	HbSS (40%), HbSC (40%), HbSβ-thal (20%)	0	100	NR

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Bond, 1987 <sup>170</sup>	P, Obs	Children	Range: 10–65	131	To report a prospective study of the incidence of gallbladder disease in patients aged 10–65 yr attending the sickle cell clinics at this hospital who were assessed by US examinations. The results of cholecystectomy were reviewed	1	Inclusion: All patients aged 10 yr or more attending sickle cell clinics from Mar. to Dec. 1985 who had not had a cholecystectomy	NR	HbSS (76%), HbSC (18%), HbSβ <sup>+</sup> -thal (9%)	NR (Long-term followup was possible in 14 of 29 patients who underwent cholecystectomy)	100	18–144 mo
Booz, 1999 <sup>171</sup>	P, Obs	% adults NR	Mean: 15.7	50	To conduct a prospective study to ascertain whether US might be useful in distinguishing between osteomyelitis and bone infarcts in patients with SCD and pain	1	Inclusion: Patients with SCD presenting with pain and swelling over a 2-yr period from May 1995 to Apr. 1997. All participating patients underwent a clinical evaluation, plain radiographs, and sonography	76	NR	NR	100	NR
Brousseau, 2004 <sup>172</sup>	P, Obs	Children	Median: 11	12	To determine the effect of IV magnesium sulfate on the LOS for children admitted with sickle cell pain crisis	1	Inclusion: Children with HbSS or HbSβ <sup>0</sup> (ages 4–18 yr) evaluated in a single urban pediatric ED and requiring admission to the hospital for sickle cell pain crisis were eligible. Exclusion: Children taking oral magnesium or having previously received IV magnesium, known elevated creatinine or liver disease, blood transfusion within 3 mo, pregnancy, temperature >39.08°C, evidence of bacterial infection, ACS, and hemodynamic instability or sepsis	8	HbSS	0	100	NR
Chaplin, 1989 <sup>173</sup>	P, Obs	Adults	37.5	4	To assess the efficacy of long-term mini-dose heparin prophylaxis for painful sickle cell crises	2, no heparin prophylaxis vs. heparin prophylaxis	Inclusion: A well-documented history of frequent severe pain crises requiring multiple ER and hospital admissions annually over several years, emotional stability and honesty in patients regarding communicating about their illness, demonstration of a high level of compliance by the patients' records	50	HbSS	0	100	24–72 mo
Christensen, 1996 <sup>174</sup>	P, Obs	Children	13.2±2.6	10	To determine the dose concentration relationship and clinical effect of transdermal fentanyl in patients with sickle cell pain crisis	1	Inclusion: Patients who had been admitted to the LeBonheur Children's Medical Center for management of acute sickle cell pain crisis requiring narcotic analgesics were eligible. Exclusion: Patients with a history of hypersensitivity to narcotic analgesics, acute respiratory distress or significant impairment of renal or hepatic function, or refused PCA morphine	30	HbSS (80%); HbSC (10%); HbSβ <sup>+</sup> -thal (10%)	0	100	0.1 mo

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Daltro, 2008 <sup>175</sup>	P, Obs	75% adults	Range: 15–48	8	To assess the efficacy and safety of autologous bone marrow mononuclear cells implantation in necrotic lesions of the femoral head in patients with SCD	1	Inclusion: Presence of femoral head collapse; presence of a sclerosis range on femoral head; crescent sign; double signal at T2 on MRI; cyst or sclerosis on femoral head; hip pain at motion; low-intensity focus on T1. Exclusion: Patients with Fiat's stage IV and Steinberg's C (or more) osteonecrosis of the femoral head showing bone infection at the limb affected by necrosis; history of previous surgery on the same injured limb; presence of neoplastic disease or any other pathology that could make therapy unfeasible; clinical conditions contraindicating the procedure	25	NR	0	100	8 mo
de Montalembert, 1997 <sup>176</sup>	P, Obs	Children	Median: 11	35	To observe the safety and efficacy of HU, a drug that stimulates HbF production, in previously severely ill children with SCD	1	Inclusion: Children were eligible for inclusion if they were affected with a major sickle cell syndrome, they had suffered at least 3 painful VOCs necessitating hospitalization in the year before entering the study, and they were aged 4–20 yr. Exclusion: Renal insufficiency (creatinine clearance <120 mL/min/1.73 m <sup>2</sup> ), hepatic insufficiency (alanine aminotransferase (ALAT) >5N or chronic hepatic disease), iron deficiency or current iron supplementation, hypersplenism, HIV infection, or past history of frequent and severe infections. Patients for whom a monthly followup seemed difficult to ensure were excluded	74	HbSS (94%), HbSβ <sup>0</sup> -thal (3%), HbSβ <sup>+</sup> -thal (3%)	NR (3 children undergoing long-term transfusion therapy in the prestudy period were excluded from this analysis)	100	32 mo
Dinges, 1997 <sup>177</sup>	P, Obs	% adults NR	Range: 5–51	37	To test the effectiveness of self-hypnosis in the management of sickle cell pain	2	Oral piroxicam was well-tolerated and effective in the management of the osteoarticular painful attack of SCA: a dose of 1 mg/kg/d it was superior to soluble aspirin (100 mg/kg/d) in achieving fast pain relief and restoring immediate sedation	43	HbSS (65%), HbSC (32%), HbSβ <sup>0</sup> -thal (3%)	NR (The diary compliance rate was 87% during conventional treatment and 83% during conventional + hypnosis)	100	22 mo
El-Beshlawy, 2006 <sup>178</sup>	P, Obs	Children	9.4±3.6	37	To assess the cardiac status and pulmonary blood pressure in pediatric patients with SCD in addition to evaluating the role of L-carnitine in treating cardiac complications	1	Inclusion: Randomly selected children with SCD who were attending the Hematology Clinic, Children's Hospital in Cairo, Egypt	57	NR	NR	100	NR
Emre, 1995 <sup>179</sup>	P, Obs	Children	Range: 2–17	36 patients (40 episodes of ACS)	To study the effects of transfusion on the clinical course and oxygenation indexes of children with SCD and ACS	1	Inclusion: Children with SCD who were admitted to Kings County or University Hospital at the Children's Medical Center of Brooklyn with a diagnosis of ACS were eligible. All patients were known to our sickle cell clinic, and the diagnosis of SCD had been confirmed by standard electrophoretic analysis	66	HbSS (92%), HbSβ-thal (5%), HbSC (3%)	0 (Post-transfusion arterial blood gas (ABG) only available for 24/27 patients transfused)	100	NR

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Gill, 1995 <sup>180</sup>	P, Obs	Children	3 mo	703	To describe complication rates in the Cooperative Study of SCD (CSSCD)	1	Infants with SCD at <6 mo of age	53	HbSS (62%), HbSC (32%), HbSβ <sup>+</sup> (5%), HbSβ <sup>0</sup> (2%)	23.2%	100	50 mo
Gil, 2000 <sup>181</sup>	P, Obs	Children	6–17	34	To analyze daily patterns of pain, medication use, health care use, and activity reduction during pain episodes in children and adolescents with SCD	1	Children with SCD	47	HbSS, HbSC, HbSβ-thal; respective proportions NR	0	100	14 d
Grover, 1990 <sup>182</sup>	P, Obs	Children	4.4±0.39	15	To describe the diagnosis, management, and course of 15 patients with ASSC followed at the St. Luke's–Roosevelt Hospital Center Comprehensive Sickle Cell Program and based on that experience recommend surgery after the 1st episode of ASSC in the child 5 yr of age and older and the choice of 1 yr or more of long-term transfusion therapy for the child under 3 yr	2	Not clearly specified	40	HbSS (87%), HbSβ-thal (13%)	0	100	100.8 mo
Hernigou, 1993 <sup>183</sup>	P, Obs	Adults	33	10 (16 hips)	To describe a new surgical treatment for hips at the stage of early collapse: necrotic bone and the articular cartilage overlying it are elevated by the injection of acrylic cement to restore the sphericity of the femoral head and to report the results in 16 hips in 10 patients who had severe pain due to collapse caused by SCD	1	Not clearly specified 20	HbSS (60%), HbSC (30%), HbSβ-thal (10%)	NR	0	100	60 mo
Ilyas, 2002 <sup>184</sup>	P, Obs	Adults	28	18	To address the issue of whether bilateral total hip arthroplasty in patients with SCD is safe, avoids the risk of 2 anesthetics, and the longer procedure increases risk	1	Not specified 45	HbSS (100%)	NR	0	100	68.4 mo
Jacob, 2003 <sup>185</sup>	P, Obs	Children	13.6 (4.3)	27	This study was conducted to evaluate the pain management strategies currently used for children with SCD and to determine the effectiveness of these strategies during hospitalization	1	Inclusion: Children 5–19 yr of age with SCD were recruited based on the following criteria: (1) admission to the hospital for VOC pain; (2) time of recruitment within 24 h of admission; and (3) no prior history of neurologic impairments (i.e., visual or hearing deficits, motor function deficit, and developmental delay)	59.3	HbSS (77.8%), HbSC (14.8%), HbSβ-thal (7.4%)	NR	100	Fixed: 9 mo

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Jayabose, 1996 <sup>186</sup>	P, Obs	Children	15.3	15	To determine the effect of HU on the hemoglobin level in children with SCA, evaluate the toxicity of HU, and assess any impact of HU on the frequency of VOCs	1	Inclusion: Patients with SCA and frequent VOCs (group 1) or severe anemia (group 2) were considered eligible for study	66	HbSS	NR (1 patient was excluded due to treatment discontinuation due to nausea)	100	Range: 14.4–54 mo
Khosla, 1984 <sup>187</sup>	P, Obs	% adults NR	Mean: 11.5	20	To evaluate the efficacy and safety of IV pentoxifylline in patients with SCA crises	1	Inclusion: Patients with HbSS, >5 yr of age, hospitalized with definite signs and symptoms of painful crisis between 4 and 48 h in duration, with no history of painful crisis in the last 30 d. Exclusion: Patients with Hg <5.5 mg/dL or with signs of overwhelming infection, renal or hepatic failure, severe heart disease, hypertension, or pulmonary edema	25	HbSS	NR	100	NR
Kimmel, 1986 <sup>188</sup>	P, Obs	% adults NR	33	44 (70 eyes)	To report data on 44 patients (70 eyes, 220 sea fans) with PSR receiving peripheral circumferential retinal scatter photocoagulation (PCRP) to the peripheral zones of retinal capillary nonperfusion and analyze the value of PCRP in reducing the risk of nonresolving vitreous hemorrhage and/or traction retinal detachment	1	Inclusion: Patients with PSR who were treated with PCRP from Sept. 1977 to May 1985	41	HbSS (16%), HbSC (50%), HbSβ-thal (4%) Established SCD but genotypes NA (30%)	0	100	39.6 mo
Koch, 2008 <sup>189</sup>	P, Obs	Children	14	18	To test the feasibility of administration, acceptability to patients, and potential ability to reduce pruritus of concomitant administration of naloxone and CIV infusion of morphine in children with SCD and painful crisis	1	Inclusion: Patients 5–21 yr of age, who were admitted to Children's Medical Center Dallas between Aug. 2003 and Jan. 2005 for uncomplicated painful crisis (without fever, ACS, recent surgery, or other problems) and who received a CIV infusion of morphine. Exclusion: Patients were excluded if they were receiving a program of chronic RBC transfusions, their pain was believed not to be due to SCD, they had known hepatic or renal disease that might alter the pharmacokinetics of naloxone, they were not developmentally able to rate the severity of their pain or pruritus, or they had previously been enrolled in this pilot study	38	HbSS (77%), HbSC (23%)	0 (However, 2 patients (11%) were not evaluable as they were removed from the protocol)	100	NR
Liem, 2004 <sup>190</sup>	P, Obs	Children	9.5	8	To assess RCE transfusion therapy for patients with SCD who have severe, progressive ACS	1	Inclusion: (1) diagnosis of SCD with HbSS confirmed by electrophoresis; (2) ACS defined by the presence of fever, chest pain, or any respiratory complaint, and new infiltrate on chest x ray; and (3) need for a double-volume exchange transfusion as determined by the treating physician. Exclusion: Patients were on HU at the time of enrollment, had been transfused within 6 weeks prior to entry, or had been treated with glucocorticoid therapy within 1 week prior to entry into the study	62.5	HbSS	0	100	24 h

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Machado, 2005 <sup>191</sup>	P, Obs	Adults	43±3	12	To evaluate the safety and efficacy of selective pulmonary vasodilators and antiproliferative agents in a population of patients with SCD	1	All patients had HbSS, determined by high-performance liquid chromatography of their hemoglobin. Sick cell subjects with PHTN were identified by a tricuspid regurgitant jet velocity of $\geq 2.5$ m/s (corresponding to an estimated pulmonary artery systolic pressure of $\geq 30$ – $35$ mmHg). Consenting patients with tricuspid regurgitant jet velocity of $\geq 2.9$ m/s also underwent right heart catheterization. To minimize the risk of priapism, male patients were allowed to participate only if they had erectile dysfunction or were on CTX. All patients had comprehensive ophthalmological evaluations prior to initiating sildenafil therapy and with each dose escalation; patients with active retinopathy or a history of retinal detachment or hemorrhage were excluded	25	HbSS	NR (1 patient could not tolerate sildenafil because of persistent headaches after initiation of the drug and was discontinued from the study)	100	Mean=6 mo
Mantadakis, 2000 <sup>192</sup>	P, Obs	Children	13.7	15	To assess the efficacy of outpatient penile aspiration and epinephrine irrigation for young patients with SCD and prolonged priapism	1, pediatric patients with SCD with priapism	Not clear	100	HbSS	0	100	Acutely, during hospitalization
McCurdy, 1971 <sup>193</sup>	P, Obs	Adults	NR	14	To examine the effectiveness of urea in the treatment of acute pain crisis in patients with SCD	1	Inclusion: Adult patients with SCD who had typical acute painful crises severe enough to require ER admission. No patient had clinically apparent infection	NR	HbSS (86%), HbSD (7%), HbSC (7%)	NR	100	NR
McKie, 2007 <sup>194</sup>	P, Obs	Children	12.1±4	191	To review data to explore the safety and utility of HU and angiotensin-converting enzyme inhibition (ACEI) in the prevention and treatment of sickle cell nephropathy	2, HU or ACEI	Inclusion: Patients were included from routine annual screening for microalbuminuria from Sept. 1996 to Dec. 2002	49.7	HbSS	1	100	Mean 2.1±2 yr
McPherson, 1990 <sup>195</sup>	P, Obs	Adults	Median: 27	16	To determine the effectiveness of PCA in treating VOC pain in patients with SCD	1	Inclusion: Patients 18 and older with SCD. Exclusion: Pregnancy, abnormal renal function, and a history of drug abuse	56	HbSS (94%), HbS $\beta$ -thal (6%)	NR (6 patients had discontinued treatment by d 3)	100	0.1 mo
Melzer-Lange, 2004 <sup>196</sup>	P, Obs	Children	NR	44 patients (69 patient episodes of sickle cell pain crises)	To determine whether a protocol to start PCA in the ED (ED-PCA) would shorten the length of time between narcotic bolus doses and PCA initiation as compared with standard inpatient initiation of PCA (IP-PCA)	2	Inclusion: Eligible patients were limited to children and adolescents with SCD and previous experience in the use of IP-PCA therapy who required hospital admission for moderate to severe VOC pain. Exclusion: Patients with headaches were excluded due to the possibility of stroke. Patients with abdominal pain were included only after a surgical etiology was excluded	NR	NR	NA	100	NR
Meshikhes, 1995 <sup>197</sup>	P, Obs	% adults NR	26	30	To recommend LC as an attractive, safe option in patients with SCD with gallstones	1	Not specified	77	NR	0	100	12 mo

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Moran, 1993 <sup>198</sup>	P, Obs	Adults	Primary group: 37; revision group: 39	14 (22 hips)	To evaluate the clinical and radiographic outcome and to assess failure mechanisms after primary and revision total hip arthroplasty in patients with sickle cell hemoglobinopathy	1	Not specified	35	HbSS (78.6%), HbSβ-thal (7.1%), HbAS (14.3%)	0	100	Primary group: 4.8 yr; revision group: 5.3 yr
Morris, 2003 <sup>199</sup>	P, Obs	% adults NR	SCD group: 32.7±15; control group: 20.6±10	20	To assess the efficacy of L-arginine therapy in treating PHTN in patients with SCD	2, patients with SCD with PHTN vs. ethnically matched healthy volunteers	Inclusion: Patients with SCD with documented PHTN at steady state. Exclusion: Renal or liver dysfunction	60	HbSS (80%), HbSC (10%), HbSβ-thal (10%)	10% of the SCD group	50	Unclear; >2 mo
Okany, 2004 <sup>200</sup>	Obs, P	Adults	22.5	20	To assess the efficacy of natural honey in healing SCD leg ulcers	2, natural honey vs. eusol solution	Inclusion: HbSS patients in a steady state with chronic lower leg ulcers. Exclusion: All patients whose ulcers have underlying chronic osteomyelitis certified by leg x rays	53	HbSS	25	100	30 d
Pashankar, 2008 <sup>201</sup>	P, Obs	Children	6–19	19	To report on the prospective longitudinal followup of elevated pulmonary artery pressures and the effect of HU on elevated pulmonary artery pressures in children with SCD	1	Of the 62 patients screened with echocardiography, 19 children were found to have elevated pulmonary artery pressures. These 19 children were recruited into this longitudinal followup observational study 50	NR	NR	5.3	100	Median of 23 mo
Pegelow, 2002 <sup>202</sup>	P, Obs	Children	6–19	266	To analyze the risk of developing initial silent infarcts in children with SCD with previously normal MRI results and the risk of developing new or more extensive lesions in children previously identified with silent infarcts	1	Inclusion: At least 1 acceptable, study-mandated MRI in child with SCD enrolled in the CSSCD. Exclusion: MRI performed in response to acute clinical events	Unclear	HbSS	14	100	120 mo
Poflee, 1991 <sup>203</sup>	P, Obs	% adults NR	20.75	18	To study the utility of IV pentoxifylline in sickle cell crises	2	Inclusion: 9 patients in acute painful VOCs and 9 age- and sex-matched controls	NR	NR	0	100	NR
Rombos, 2002 <sup>204</sup>	P, Obs	Adults	20–59	13	To identify the potential utility of iron load reduction in the management of painful crises in patients with SCD	1	Inclusion: Patients with SCD experiencing frequent painful crises, the frequency and duration of which was not improving with the conventional therapeutic modalities and suffering from severe sickle cell complications such as CNS involving bone necrosis or chronic pain	23	HbSS (15%), HbSβ-thal (77%), HbS/Hb Lepore (Pylos) (7%)	0	100	11–96 mo
Samal, 1997 <sup>205</sup>	P, Obs	Children	7.2±2.4	40	To evaluate the frequency, clinical presentations, and outcomes of ACS in hospitalized patients with SCD	1, patients with SCD presenting with ACS	Inclusion: Patients had at least 2 of the following: temperature >38°C, physical exam findings consistent with pulmonic inflammation and chest radiograph findings consistent with an acute pulmonic process	60	NR	0	100	Acute

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Sangare, 1990 <sup>206</sup>	P, Obs	Adults	24	100	To determine the efficacy of IM piroxicam treatment of painful articular attacks	2, piroxicam and lysine acetylsalicylate	Inclusion: Presence of painful osteoarticular attacks, and biologic findings such as the detection of sickle cell factors HbSS or HbSC Exclusion: Hypersensitivity to piroxicam or other NSAIDs; concomitant peptic ulcer; severe gastrointestinal disease; or renal hepatic, or cardiac impairment	61	HbSS (19%), HbSC (27%), HbSβ <sup>0</sup> -thal (25%), HbSβ <sup>+</sup> -thal (19%), HbSα-thal (8%), hemoglobin SO-Arab (HbSO-Arab) (2%)	0	100	3 d
Santos, 2002 <sup>207</sup>	P, Obs	5% adults	11.7	21	To evaluate the effects of long-term therapy with HU on recovery of splenic function using liver/spleen imaging	1	The inclusion criteria in the long-term HU treatment protocol were: HbSβ <sup>0</sup> or HbSS hemoglobinopathy, age between 3 and 22 yr, with a severe clinical course of the disease as defined by at least 1 of the following clinical features: (1) A minimum of 6 painful crises during the last 2 yr, (2) at least 2 episodes of ACS, and (3) 2 episodes of priapism	67	HbSS (67%), HbSβ <sup>0</sup> (33%)	0	100	12 mo
Sayag, 2008 <sup>208</sup>	P, Obs	Adults	Range: 18–63	73	To compare the clinical outcome of stage III PSR treated by peripheral retinal scatter photocoagulation to natural course disease	2, treated vs. untreated retinopathy	Inclusion: Patients with SCD with PSR stage III	53	HbSS (52%), HbSC (48%)	0	100	48 mo
Seleem, 2005 <sup>209</sup>	P, Obs	Children	7.8	12	To evaluate the safety and outcome of mini-laparoscopic cholecystectomy in young children under age of 10 yr with SCD	NA	Inclusion: Children with SCD under 10 years of age with recurrent abdominal pains	83	NR	0	100	13.4 mo
Serjeant, 1970 <sup>210</sup>	Obs, P	NR	NR	34	To assess the efficacy of oral zinc sulphate in treating SCD leg ulcers, compared to placebo	2, oral zinc sulphate vs. placebo	Inclusion: Patients with SCD with active leg ulcers, who lived close to the hospital and could attend at 2-week intervals	47	NR	15	100	6 mo
Serjeant, 1994 <sup>211</sup>	P, Obs	57% adults	Median age at crisis: 22.3	118 (183 episodes)	To report the details of onset, perceived precipitating factors, associated symptoms, and pain distribution in the painful crisis of HbSS; these have been prospectively recorded in 183 painful crises in 118 patients admitted to a daycare center in Kingston, Jamaica	1	Inclusion: Patients with SCD above 3.5 yr of age. All patients had episodic pain unaccounted for by other obvious pathology and of sufficient severity to require narcotic analgesia	39 (43% for episodes)	HbSS	0	100	Unclear

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Sporrer, 1994 <sup>212</sup>	P, Obs	Children	11.2	17	To characterize pain reporting among children with SCA experiencing painful VOCs and manage the pain according to a protocol based on self-reports	1	Inclusion: All patients 3–18 with HbSS admitted to the Medical University of South Carolina Children's Hospital from June–Aug. 1992 for VOCs were included in the pilot study. Exclusion: Patients with other primary admitting diagnosis related to SCD	67	HbSS	0	100	NR
Srair, 1995 <sup>213</sup>	P, Obs	Children	Mean: 7.1	50	To describe the clinical course of patients with SCD and ACS	1	All patients with SCD who had ACS and admitted to the Pediatric Medical Ward from Jan. 1993 to Dec. 1993 were studied	56	NR	NR	100	NR
Sumoza, 2002 <sup>214</sup>	P, Obs	Children	Range: 3–16	5	To determine the benefit of prophylactic HU in the prevention of recurring stroke in pediatric patients	1	Inclusion: Pediatric patients with SCA and previous stroke treated with HU and without CTxs	80	HbSS	NA	100	Median: 84 mo
Telfer, 2009 <sup>215</sup>	P, Obs	Children	10	22	To assess the efficacy of intranasal diamorphine in acute painful sickle cell crises and evaluate the safety profile	2	Inclusion: Children with SCD, aged 1–16 yr, presenting to the pediatric ED with acute painful crisis that had not responded to home analgesia. Exclusion: <1 yr, shock, airway compromise, respiratory depression, and diminished level of consciousness	NR	HbSS, HbSC, or HbSβ-thal (each percentage unclear)	0	100	0 mo (pain relief measured hours after medication administration)
Thomas, 1984 <sup>216</sup>	P, Obs	Adults	Range: 22–35	15	To examine the effects of biofeedback therapy in controlling pain in patients with SCD	2, adult patients with SCD on biofeedback management vs. no biofeedback	Patients with SCD program for yr or more and had frequent pain crisis	53	NR	0	100	12 mo
Topley, 1981 <sup>217</sup>	Observational prospective	Children	Newborn	216	To report the incidence of ASSC and hypersplenism in the first 5 yr of life in HbSS	1	Patients with homozygous SCD	Out of 216 children, only 52 develop the complication. Males are 25 (48%) out of 52	HbSS	NR	100	5 yr
Udezue, 2007 <sup>218</sup>	P, Obs	Adults	NR	1154	To present an acute pain management protocol for sickle cell pain crisis	2, on demand pain treatment vs. regular pain treatment	Inclusion: Patient aged ≥14 yr with SCD presenting with pain crisis	50	NR	Unclear	100	72 h

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Vichinsky, 2000 <sup>219</sup>	P, Obs	24% adults	13.8	537	We initiated a prospective, multicenter study of the ACS in order to determine the causes, incidence, and clinical outcome of the syndrome and factors that predict prognosis	1	To be eligible, patients had to have a phenotype of HbSS, HbSC, or HbSβ-thal on electrophoretic analysis of the hemoglobin chains and to have had an episode of the ACS. The ACS was defined on the basis of the finding of a new pulmonary infiltrate involving at least 1 complete lung segment that was consistent with the presence of alveolar consolidation but excluding atelectasis. In addition, the patients had to have chest pain, a temperature of >38.5°C, tachypnea, wheezing, or cough	58	HbSS (82%), HbSC, HbSβ-thal (18%, the latter two combined)	NR	100	NR (study=60 mo)
Ware, 1992 <sup>154</sup>	P, Obs	% adults NR	13.3	9	To describe the use of LC in 9 young patients with sickle hemoglobinopathies while also reviewing perioperative concerns for patients with SCD in light of this recent advance	1	Patients with sickle hemoglobinopathies and cholelithiasis and with CBD stones	67	HbSS (67%), HbSC (11%), HbSS with elevated fetal hemoglobin (11%), Hb S/O (Arab) (11%)	0	100	8 mo
Ware, 2004 <sup>220</sup>	P, Obs	Children	11.9±4	35	To assess the efficacy of HU in stroke prevention in previously transfused patients with SCD	1, pediatric patients with SCD, with history of stroke and of CTX for stroke prevention	Inclusion: Pediatric patients with SCD, with history of stroke and CTXs for stroke prevention	66	NR	0	100	NR
Ware, 1999 <sup>221</sup>	P, Obs	Children	Mean: 12.1±4.9	16	To determine if daily oral HU therapy (combined with an aggressive periodic phlebotomy regimen to reduce iron overload) pediatric patients with SCD helps prevent stroke recurrence	1	A total of 25 patients with SCD and stroke who were followed by the Duke University Pediatric Sickle Cell Program (Durham, NC) were considered for this protocol. 16 patients were identified who had clinical events or sequelae that suggested they would be unable to tolerate indefinite chronic erythrocyte transfusion therapy. Reasons to consider discontinuing transfusions included erythrocyte alloimmunization, erythrocyte autoantibody formation, recurrent stroke on transfusion therapy, iron overload (serum ferritin >2,000 ng/mL), and noncompliance with transfusion or chelation regimens. The remaining 9 patients were not offered enrollment, because they had received blood transfusions for <2 yr or had no clinical or laboratory contraindications to continuing CTX	69	HbSS (94%), HbSO-Arab (6%)	NR	100	Median: 22 mo

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Badaloo, 1996 <sup>222</sup>	R-P, Obs	Children	99 mo	6	To determine whether, in the same individual, an observed fall in whole body protein turnover following splenectomy in children with hypersplenism and homozygous SCD is associated with a measurable fall in resting metabolic rate (RMR) and an increase in rate of growth	1	Inclusion: Children with HbSS or HbSβ <sup>0</sup> -thal were eligible for the study if they had hypersplenism and were considered to for splenectomy	16	HbSS (84%), HbSβ <sup>0</sup> -thal (16%)	0	100	12 mo
Conti, 1996 <sup>223</sup>	R-P, Obs	Adults	29.8	12	To describe our experience using an oral morphine protocol for the treatment of sickle cell crisis pain and to suggest it as a useful tool for providing consistent oral analgesia to patients with sickle cell crisis pain	1	Not clearly specified	67	NR	0	100	12 mo
Duncan, 2000 <sup>224</sup>	R-P, Obs	Children	12.8	27	To report the Jamaican experience with cholecystectomy for symptomatic gallstones in a selectively transfused group of children with HbSS	1	Inclusion: Children aged 18 and under with HbSS who had open cholecystectomy for symptomatic gallstones at the University Hospital of the West Indies, Jamaica, between Sept. 1985 and Aug. 1997	41	HbSS	NR	100	NR
Koren, 1990 <sup>225</sup>	Case control	Children	Range: 7-14	22 (52 ACS admissions)	To describe the admissions and hospital course of children with SCD presenting with ACS, compared to healthy children presenting with pneumonia	2, patients with SCD vs. patients without SCD	NR	NR	HbSS, HbSβ-thal	NR	0	144 mo (during hospitalization)
Strouse, 2008 <sup>226</sup>	Case control	Children	12.5	65	To evaluate risk factors for readmission and prolonged hospitalization after different treatments for ACS	2, ischemic stroke vs. hemorrhagic stroke	Patients with prolonged hospitalization after ACS	NR	HbSS (86%), HbSC 13%) by episodes	NR	100	NR
Wright, 1999 <sup>227</sup>	Case control	Children	NR	260	To determine whether children with HbSS and splenectomy are at greater risk of death, overwhelming septicemia, or other complications compared to control nonsplenectomized patients with SCD	2	Inclusion: Patients attended the Sickle Cell Clinic of the University Hospital of the West Indies, Kingston, Jamaica. The study was confined to 130 patients with HbSS undergoing splenectomy in a 22.5-yr period (July 1, 1974, to Dec. 31, 1996). A nonsplenectomized control group was identified retrospectively by selecting for each index case the patient with HbSS of the same sex, closest in date of birth, and under followup at the date of splenectomy in the index case	64	HbSS	(30% of patients had <5-yr followup and were excluded from analysis of postsplenectomy events)	100	Median: 87 mo
Adekile, 1999 <sup>228</sup>	Case report/ case series	Children	2	1	To report a case of acute splenic infarction following air travel in a child with HbSD	NA	NA	0	HbSD	NA	100	NA

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Ahmed, 2003 <sup>229</sup>	Case report/case series	75% adults	17.75	4	To report 4 cases of acute pancreatitis during sickle cell VOC	NA	Inclusion: Patients with SCD with acute pancreatitis due to microvascular occlusion and ischemic injury to the pancreas	50	HbSS (75%), HbSC (25%)	NA	100	NA
Ahmed, 2006 <sup>230</sup>	Case report/case series	Children	6	1	To report a case of a 6-yr-old girl of Afro-Caribbean origin with SCD and recurrent history of jaundice and abdominal pain in which ERCP revealed diffuse cholangiopathy of both extrahepatic and intrahepatic bile ducts	NA	NA	0	HbSS	NA	100	63 mo
Ahmed, 2007 <sup>231</sup>	Case report/case series	Children	5	1	To present a case of a 5-yr-old boy with HbSβ-thalassemia and acute hepatic sequestration associated with <i>Streptococcus pneumoniae</i> sepsis	NA	NA	100	HbSβ-thal	0	100	NR
Aisiku, 2009 <sup>232</sup>	Case report/case series	Adults	36	1	To report a case of episodic pain in SCD	NA	NA	0	HbSβ-thal	NA	100	NA
Ariyan, 1976 <sup>233</sup>	Case report/case series	Children	14	1	To report a case of cholecystitis and cholelithiasis masking as abdominal crises in SCD	NA	NA	100	HbSS	NA	100	NA
Al Jam'a, 1998 <sup>234</sup>	Case report/case series	Adults	25	1	To describe a patient with major and SP who responded dramatically to treatment with HU after several other measures failed	NA	NA	100	NR	NA	100	22 mo
Al Jama, 2002 <sup>60</sup>	Case report/case series	Adults	22	8	To report 8 patients with massive splenic infarction in Saudi patients with SCA	NA	NA	50	HbSS	NA	100	Mean: 3.5 yr
Al-Abdulla, 2001 <sup>235</sup>	Case report/case series	Children	9	1	To report a dramatic occlusive event of the macula surrounding the foveal avascular zone, causing severe and permanent loss of vision in a child with SCD	NA	NA	100	HbSS	0	100	1 mo
Al-Afif, 2008 <sup>236</sup>	Case report/case series	Children	10	1	To report a case of epidural hematoma in a patient with SCD	NA	NA	0	NR	NA	100	NA

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Alam, 2004 <sup>237</sup>	Case report/ case series	Adults	24	1	To describe a case of SCD crisis in a Saudi patient at 28 weeks gestation	NA	NA	0	HbSS	0	100	NR
Al-Ansari, 2007 <sup>238</sup>	Case report/ case series	Adults	31.5	4	To report use of noninvasive positive pressure ventilation during pregnancy in 4 patients	NA	Inclusion: Pregnant patients with ACS and AFR admitted to the ICU	0	NR	NA	100	NR
Alebiosu, 2002 <sup>239</sup>	Case report/ case series	Adults	25	1	To report renal papillary necrosis as 1st presentation of a Nigerian sickle cell patient	NA	NA	0	HbSC	NA	100	NA
Al-Hawsawi, 2001 <sup>240</sup>	Case report/ case series	Children	2.5	8	To demonstrate the clinical experience with ASSC in children, followed in Madina Maternity and Children's Hospital, Madina Al-Munawara, Kingdom of Saudi Arabia (KSA)	NA case series	Inclusion: All children with SCD followed in the Pediatric Hematology unit at Madina Maternity and Children's Hospital (MMCH) from 1993 to 2000 known to have ASSC during this period	25	HbSS (87.5%), HbSβ-thal (12.5%)	0	100	12 mo
Al-Hawsawi, 2004 <sup>241</sup>	Case report/ case series	Children	Range: 2-13	12	To demonstrate the clinical experience of ACS in children with SCD in Madina Region, Northwestern Province of KSA	NA	Inclusion: All pediatric patients (12 or younger) with SCD and developed ACS within the study period at MMCH between Jan. 1996 and Jan. 2000 were included and case notes were reviewed	66	HbSS	NA	100	Fixed: 48 mo
Ali, 1978 <sup>242</sup>	Case report/ case series	Children	7.5	1	To report a case of choreiform activity in HbSC	NA	NA	100	HbSC	NA	100	NA
Alli, 2007 <sup>243</sup>	Case report/ case series	Children	8	1	To describe an 8-yr-old male child with HbSS who presented with left parietal skull bone infarction and, during his stay in hospital, developed a right femoral deep vein thrombosis	NA	NA	100	HbSS	0	100	5 mo
Al-Malki, 2004 <sup>244</sup>	Case report/ case series	Children	9	1	To describe a child with common hepatic duct perforation and SCD	NA	NA	100	NR	NA	100	NA
Al-Momen, 1997 <sup>245</sup>	Case report/ case series	Adults	19	1	To report a case of acute bone pain associated with painful sickle cell crisis treated with clodronate	NA	NA	0	NR	NA	100	NA

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Al-Mueilo, 2005 <sup>246</sup>	Case report/ case series	Adults	41.5	2	To describe the clinical course of 2 adult males with end-stage sickle cell nephropathy from Eastern Saudi Arabia	NA	NA	100	NR	NA	NR	Unclear
Al-Rashid, 1979 <sup>247</sup>	Case report/ case series	Children	11	1	To report a case of massive sequestration crisis in SCD following ocular evisceration	NA	NA	0	HbSC	NA	100	6 h
Al-Salem, 1994 <sup>248</sup>	Case report/ case series	Children	13	4	To report 4 cases of splenic abscess in children	NA	NA	75	HbSS	NA	100	NR
Al-Suleiman, 2006 <sup>249</sup>	Case report/ case series	33% adults	21	3	To report 3 cases of acute fulminant cholestatic jaundice in SCD	NA	NA	33.3	NR	NA	NA	NA
Al-Tawfiq, 2008 <sup>250</sup>	Case report/ case series	Adults	18	1	To describe a case that presents an unusual cause of splenic abscess due to <i>Bacteroides distasonis</i> with a subacute to chronic course	NA	NA	100	NR	0	100	NR
Alvarado, 1988 <sup>251</sup>	Case report/ case series	Children	15	1	To describe a child who developed splenic infarction	NA	NA	100	HbSC	0	100	1 mo
Annobil, 1990 <sup>252</sup>	Case report/ case series	Children	7.5	8	To present the comparative clinical and radiologic manifestations of CVA in patients with SCD permanently residing at high and low altitudes of the southwestern region of the Kingdom of Saudi Arabia	NA	Patients with SCD and had cerebrovascular accidents	62.5	Unclear	0	100	Variable; 1 week to 45 mo
Aslam, 2005 <sup>253</sup>	Case report/ case series	Adults	34	1	To describe a case of splenic sequestration crisis together with fatal multiorgan failure in a 34-yr-old African American woman with HbSβ <sup>+</sup> -thal	NA	NA	0	HbSβ <sup>+</sup> -thal	NA	100	<1 mo
Ataga, 2000 <sup>254</sup>	Case report/ case series	Adults	38	3	To heighten awareness of the clinical syndrome of generalized bone marrow necrosis in the setting of SCD	NA	NA	67	Cases 1 and 3: HbSβ <sup>-</sup> -thal. Case 2: NR	0	100	Range: 0.25–1

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Atz, 1997 <sup>255</sup>	Case report/ case series	Children	4.5 and 9	2	To examine the hypothesis that patients with ACS may represent a particular type of acute lung injury in which iNO may improve oxygenation, cause specific pulmonary vasodilation, and potentially ameliorate the underlying VOC process	NA	NA	NA	NR	NA	100	0.1 mo
Baichi, 2005 <sup>256</sup>	Case report/ case series	Adults	2 cases: 27 and 26	2	To report cases of liver transplantation in acute sickle cell intrahepatic cholestasis (SCIC) and in another patient with SCD and sclerosing cholangitis	NA	NA	0	NR	0	(2 cases reported only)	Case 1: 2.5 mo Case 2: 4.8 mo
Baird, 1994 <sup>257</sup>	Case report/ case series	Children	3.8	1	To report a case of combined pressure control/high frequency ventilation in adult respiratory distress syndrome and SCD	NA	NA	100	NR	NA	100	1 mo
Ballas, 1998 <sup>258</sup>	Case report/ case series	Adults	52	1	To report a case of postmortem diagnosis of HbSC disease complicated by fat embolism	NA	NA	100	HbSC	NA	100	NA
Ballas, 2004 <sup>259</sup>	Case report/ case series	Adults	25	1	To describe the utilization of nebulized morphine in the management of severe chest pain in 2 young adult African American patients who suffered from generalized acute sickle cell painful episodes	NA	NA	0	HbSS	NA	100	<1 mo
Ballester, 1979 <sup>260</sup>	Case report/ case series	Adults	29	1	To report a case of recurrent splenic pain relieved by splenectomy	NA	NA	0	HbSS	NA	100	6 mo
Bandyopadhyay, 2008 <sup>261</sup>	Case report/ case series	Adults	26	1	To describe the unique hepatic presentation in a male with SCD	NA	NA	100	HbSS	NA	100	NR
Baruchel, 1993 <sup>262</sup>	Case report/ case series	Children	16	1	To report a case of sickle cell priapism treated with hydralazine	NA	NA	100	HbSS	NA	100	1 mo
Baykul, 2004 <sup>263</sup>	Case report/ case series	Adults	23	1	To describe a case of AVN of the mandibular condyle in a patient with SCD	NA	NA	0	NR	NA	100	7 mo

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Bell, 2005 <sup>264</sup>	Case report/ case series	Children	17	1	To describe a case of a ceftriaxone-induced hemolytic anemia and hepatitis leading to multiple organ failure and death in an adolescent with HbSC	NA	NA	0	HbSC	0	100	Acute
Benner, 2000 <sup>265</sup>	Case report/ case series	67% adults	17.3	3	To study 3 patients with glaucoma caused by sickle cell hyphema who were successfully treated with transcorneal oxygen therapy	NA	NA	100	NR	0	100	1–36 mo
Berry, 1991 <sup>266</sup>	Case report/ case series	Adults	25.5	2	To describe the clinical course and treatment of ASSC in patients with SCD	NA	NA	100	HbSC (50%), HbSβ <sup>-</sup> -thal (50%)	NA	100	NR
Betrosian, 1996 <sup>267</sup>	Case report/ case series	Adults	36	1	To describe the clinical course of a patient with HbSβ <sup>-</sup> -thal and reversible acute liver failure	NA	NA	100	HbSβ <sup>-</sup> -thal	NA	100	NR
Blank, 1981 <sup>268</sup>	Case report/ case series	Children	10.3	3	To report 3 cases of orbital infarction in SCD	NA	NA	33.3	NR	NA	100	Patients 1, 2, and 3: 1 yr, 5 yr, and 16 mo, respectively
Bonatsos, 2001 <sup>269</sup>	Case report/ case series	Adults	34.7	13	To study the impact of laparoscopic cholecystectomy for patients with SCD and cholelithiasis	1	Inclusion: Patients with SCD operated on at Hippokraton, Ygeias Melathron and Evgenidion hospitals between Apr. 1991 and Dec. 1999. All of the patients had experience symptoms (biliary colic and/or extrahepatic obstruction) attributable to cholelithiasis, which was demonstrated by preoperative US examination	38	HbSS (61.5%), HbSβ <sup>-</sup> -thal (23.1%), HbSβ <sup>0</sup> -thal (15.4%)	NA	100	Fixed: 105 mo
Boulmay, 2009 <sup>270</sup>	Case report/ case series	Adults	38.3	3	To present 3 sickle cell patients with recent cocaine abuse who presented to the emergency department with symptoms of typical VOs and rapid onset of life-threatening complications	NA	NA	66.6	HbSS (33.3%), HbSC (66.6%)	NA	100	NR
Brando, 2009 <sup>271</sup>	Case report/ case series	Adults	37.5	2	To demonstrate the association of SCD and the occurrence of cerebral aneurysms, by presenting 2 cases and further reviewing the English literature	NA	NA	100	HbSS	NA	100	NR (periodic followup examination)
Burnett, 2006 <sup>272</sup>	Case report/ case series	Adults	28	3	To assess the efficacy of phosphodiesterase 5 (PDE5) inhibitors in prevention of recurrent sickle cell associated priapism	1, patients with SCD with recurrent priapism	NA	100	HbSS (33%), HbSC (67%)	NA	100	Range: 5–14 mo

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Cacciola, 1989 <sup>273</sup>	Case series	Adults	29.7	10	To report on the efficacy of a combination of subcutaneous calcium heparin and human antithrombin concentrate in treating leg ulcers refractory conventional therapy	1, patients with SCD	Inclusion: HbSβ-thal adult patients with refractory to conventional therapy	30	HbSβ-thal	NA	100	6 weeks
Campbell, 2008 <sup>274</sup>	Case report/ case series	Adults	24	1	To describe the clinical course of a woman 36 weeks pregnant and ACS	NA	NA	0	NR	NA	100	<1 mo
Carey 1990 <sup>275</sup>	Case report/ case series	Children	13	1	To report a case of subarachnoid hemorrhage in SCD	NA	NA	0	NR	NA	100	NA
Casey, 1994 <sup>276</sup>	Case report/ case series	Children	3	1	To report a case of ASSC in the absence of palpable splenomegaly	NA	NA	0	HbSC	NA	100	48 mo
Cavenagh, 1994 <sup>277</sup>	Case report/ case series	Adults	Mean: (18.5)	2	To report 2 cases of splenic sepsis in SCD	NA	NA	100	HbSS (50%), HbSβ <sup>0</sup> -thal (50%)	NA	100	NR
Chang, 2008 <sup>278</sup>	Case report/ case series	Adults	27	1	To present a case report of patient with sequelae from both pathways (namely ACS, bone pain, and hemolysis), who for religious reasons would not accept many of the standard treatments for her disease	NA	NA	0	HbSS	0	100	NR
Chaplin, 1980 <sup>279</sup>	Case report/ case series	% adults NR	NR	3	To describe the clinical course of 3 patients who were treated with daily aspirin-dipyridamole for the prevention of pain crisis	NA	NA	NR	NR	NA	100	48 mo
Chehal, 2002 <sup>280</sup>	Case report/ case series	Adults	40	1	To report a case of SCD with multiorgan failure syndrome and thrombotic thrombocytopenic purpura	NA	NA	100	HbSβ-thal	NA	100	NA
Chuang, 1997 <sup>281</sup>	Case report/ case series	Children	12	3	To alert clinicians to the possible association between SCA and autoimmune liver disease (AILD)	NA	NA	NA	NR	0	100	NR

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Ciurea, 2006 <sup>282</sup>	Case report/ case series	Adults	22	1	To report a case of dural venous sinus thrombosis (DVST) in a patient who developed seizures following exchange transfusion for treatment of ACS associated with SCD	NA	NA	0	HbSS	0	100	3 weeks
Clarke, 2001 <sup>283</sup>	Case report/ case series	Children	5	1	To report a case of bilateral, retinal infarction in a young patient	NA	NA	100	HbSS	0	100	4 mo
Colombani, 2000 <sup>284</sup>	Case report/ case series	Children	8.3	6	To report on patients with SCD between 1985 and 1995 admitted to the authors dept. for a 24-h, persisting priapism	NA	NA	100	HbSS	0	100	2–12 yr
Conrad, 1988 <sup>285</sup>	Case report/ case series	Adults	19	2	To report 2 cases of aplastic crisis with SCD	NA	NA	50	NR	NA	100	NA
Costa, 2006 <sup>286</sup>	Case report/ case series	Adults	48	1	To describe a 48-yr-old African American man with HbS $\beta$ -thal and previously treated hepatitis C with compensated cirrhosis, who presented with a total bilirubin of 59.7 mg/dL and direct bilirubin of 43.6 mg/dL in the absence of choledocholithiasis	NA	NA	100	HbS $\beta$ -thal	0	100	Unclear
Costabile, 1998 <sup>287</sup>	Case report/ case series	Adults	30	1	To present a patient who was treated successfully with daily administration of an antiandrogen for stutter priapism	NA	NA	100	NR	0	100	18 mo
Cross, 2007 <sup>288</sup>	Case report/ case series	Adults	38	1	To describe an unusual case in which a patient was asymptomatic for >35 yr, representing a novel instance of SCD, which should be considered in appropriate patients when unusual presentations of liver disease arise	NA	NA	100	HbSC	0	100	NR
Curran, 1997 <sup>289</sup>	Case report/ case series	Children	8	1	To report a case of orbital compression syndrome in SCD	NA	NA	100	HbS $\beta^0$ -thal	NA	100	14 mo

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Dahdaleh, 2009 <sup>290</sup>	Case report/ case series	Adults	18	1	To report a case of a patient with SCA who presented with a sickle cell crisis that was complicated by the development of multiple acute epidural and subgaleal hematomas requiring surgical evacuation	NA	NA	100	NR	0	100	6 weeks
Dahm, 2002 <sup>291</sup>	Case report/ case series	Adults	20.5	2	To suggest the role for anti-androgens in the treatment of men with refractory priapism that should be evaluated in the setting of a controlled study	NA	NA	100	NR	0	100	Unclear
Darbari, 2008 <sup>292</sup>	Case report/ case series	50% adults	23	4	A case series of 4 patients describing severe VOEs associated with use of systemic corticosteroids with SCD	NA	NA	75	HbSS (75%), HbSβ-thal (25%)	NA	100	NA
Davenport, 2008 <sup>293</sup>	Case report/ case series	Adults	47	1	To report a case of acute kidney injury, where dynamic renal imaging established a diagnosis of intrarenal sickling	NA	NA	100	HbS <sup>+</sup> F	0	100	NR
Davila, 2008 <sup>294</sup>	Case report/ case series	Adults	23	1	To describe a case of subarachnoid hemorrhage following phenylephrine therapy for priapism in a patient with SCD	NA	NA	100	NR	NA	100	2 d (acutely)
Delis, 2006 <sup>295</sup>	Case report/ case series	Adults	43	1	To report on SCIC in a patient with SCA and metastatic liver disease who was subjected to right hepaticectomy	NA	NA	0	HbSS	0	100	NR
Deymann, 2003 <sup>296</sup>	Case report/ case series	Children	16	1	To describe the case of an adolescent who had SCD and previous evidence of myocardial damage and presented with abdominal pain and rapid progression to cardiogenic shock and subsequent development of myocardial infarction	NA	NA	100	HbSS	NA	100	<1 mo
Disch, 2004 <sup>297</sup>	Case report/ case series	Adults	42	1	To present a patient with a severe skeletal manifestation of SCD and bone marrow oedema with a regimen of a 5 d course of IV iloprost	NA	NA	100	NR	0	100	12 weeks
Dixit, 2004 <sup>298</sup>	Case report/ case series	Children	17	1	Our case was unique for presenting as orbital compression syndrome without any history of VOC	NA	NA	100	NR	0	100	12 mo

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Doodnath, 2010 <sup>299</sup>	Case report/case series	Children	20-mo-old male	1	To review the anesthetic implications and outcome of the 1st pediatric patient with SCD to have a laparoscopic splenectomy due to repeated splenic infarcts in the Republic of Ireland	NA	NA	100	NR	0	100	3 weeks after discharge
Douglas, 1990 <sup>300</sup>	Case report/case series	Adults	Range: 20–24	5	To present a review of experience with priapism and management of impotence in SCD with penile prosthesis	NA	NA	100	NR	NA	100	24–120 mo
Dowling, 2010 <sup>301</sup>	Case report/case series	Children	Range: 3–11	7	To report 7 cases of acute silent cerebral infarction in children with SCA	NA	NA	57.1 (4 out of 7)	HbSS	NA	100	NR
Dumarey, 2000 <sup>302</sup>	Case report/case series	Adults	19	1	To describe severe multijoint osteonecrosis and ankylosis	1	NA	100	HbSS	NA	100	Unclear
Durand, 2009 <sup>303</sup>	Case report/case series	Adults	34	1	To report on a women with HbSS presenting to the ED with pain, jaundice, and anorexia	NA	NA	0	HbSS	0	100	8 mo
Durant, 1982 <sup>304</sup>	Case report/case series	Adults	21	1	To report a case of exudative retinal detachment in HbSC	NA	NA	100	HbSS	NA	100	NA
el Mauhoub, 1991 <sup>305</sup>	Case report/case series	Children	11	1	To describe a case of priapism in a male pediatric patient with SCA managed successfully with blood transfusion	NA	NA	100	HbSS	NA	100	<1 mo
El Morsi, 1973 <sup>306</sup>	Case report/case series	Adults	Range: 21–56	5	To report 5 cases of priapism	NA	NA	100	Sickle hemoglobin A disease (HbSA) (40%), HbSC (40%), NR (20%)	NA	100	NA

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Elsayegh, 2007 <sup>307</sup>	Case report/case series	Adults	22	1	To report a pregnant woman with respiratory failure due to acute hemolytic crisis and ACS, requiring critical care management with emergency exchange transfusion, intubation, and cesarean delivery	NA	NA	0	HbSβ-thal	0	100	NR
Emre, 2000 <sup>308</sup>	Case report/case series	Children	6	1	To report a case of SCIC undergoing liver transplantation for therapy	NA	NA	100	NR	NA	100	6 mo
Engelhardt, 1989 <sup>309</sup>	Case report/case series	Adults	36	1	To review the rare complication, ischemic intestinal necrosis, and discuss the clinical problems of diagnosing typical and atypical abdominal pain in patients with SCD with and without concomitant crisis	NA	NA	100	NR	NA	100	24
Enwerem, 1992 <sup>310</sup>	Case report/case series	Children	9 and 8	2	To report 2 pediatric cases of secondary priapism due to hematological disorder of SCD leading to slugging of blood within the corpora cavernosa, which were treated successfully with conservative measures	NA	NA	100	HbSS	0	100	0.25
Erhan, 2007 <sup>311</sup>	Case report/case series	Children	4	1	To present the analgesic management of a 4-yr-old child who suffered from severe abdominal and leg pain during his 1st VOC with SCD	NA	NA	100	HbSβ-thal	0	100	NR
Feldman, 2003 <sup>312</sup>	Case report/case series	Adults	25	1	To report the clinical course of a patient with SCA who ultimately was found to have ACS despite having no infiltrate on chest x ray. His ventilation-perfusion scan (V/Q) showed abnormalities that were suggestive of the diagnosis of ACS and thereby demonstrates the potential utility of this test in promptly making the diagnosis	NA	NA	100	NR	NA	100	2 mo
Ferster, 1993 <sup>313</sup>	Case report/case series	Children	11.6	3	To report 3 cases of splenic reticuloendothelial dysfunction in SCA that were treated with BMT	NA	NA	NR	NR	NA	100	Range: 8–43 mo

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Fich, 1981 <sup>314</sup>	Case report/ case series	Adults	23	1	To report a case of priapism in a non-Black with SCA associated with HbS $\alpha$ -thal	NA	NA	100	HbS $\alpha$ -thal	NA	100	24 mo
Filipek, 2000 <sup>315</sup>	Case report/ case series	Adults	30	1	To present at patient with aortic thrombus and SCD	NA	NA	0	NR	0	100	3 mo
Freilich, 1972 <sup>316</sup>	Case report/ case series	Adults	29.5	2	To describe a technique of scleral buckling in patients with sickle cell retinopathy and retinal detachment, using the hyperbaric oxygen chamber	NA	NA	50	HbSC (50%), HbSS (50%)	0	100	NR
Freilich, 1973 <sup>317</sup>	Case report/ case series	Adults	30	3	To report 3 cases of retinal detachment with SCD	NA	NA	33.3	NR	NA	100	NA
Freilich, 1975 <sup>318</sup>	Case report/ case series	% adults NR	NR	8	To describe the development of scleral buckling technique in patients with sickle cell retinopathy and retinal detachment using the hyperbaric oxygen chamber	NA	NA	NR	HbSS; HbSC, proportions NR	NA	100	NR
Freischlag, 1991 <sup>319</sup>	Case report/ case series	Adults	42	1	To describe the unusual case of an adult patient with SCD presenting with TIAs	NA	NA	100	HbSS	NA	100	40 mo
Gabrovsky, 2010 <sup>320</sup>	Case report/ case series	Adults	18	1	To report a patient with HbSC and prolonged, life-threatening hemorrhage from papillary necrosis successfully treated with oral, low-dose epsilon aminocaproic acid (EACA)	NA	NA	100	HbSC	0	100	1 mo
Gbadoe, 2001 <sup>321</sup>	Case report/ case series	Children	Range: 2.5–15	11	To assess the results of intracavernous injections of etilefrine treatment in 11 children with SCA suffering from priapism	1	Inclusion: 11 children with SCA, and admitted from 1996 to 1999, were treated for acute priapism (AP, $n=6$ ), SP ( $n=4$ ), or AP complicating SP ( $n=1$ )	100	NR	0	100	3 mo–4 yr
Gentile, 1999 <sup>322</sup>	Case report/ case series	Children	6.7	3	To treat ACS with high-frequency oscillatory ventilation (HFOV) in 3 pediatric patients	NA	NA	NR	NR	0	100	NR

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Geola, 1978 <sup>323</sup>	Case report/ case series	Adults	24	1	To report a case of splenic sequestration with HbSC	NA	NA	100	HbSC	NA	NA	NA
Gerber, 1993 <sup>324</sup>	Case report/ case series	Children	15	1	To report a death from morphine infusion during a sickle cell crisis	NA	NA	100	HbSS	0	100	NA; patient died in hospital
Gillett, 1987 <sup>325</sup>	Case report/ case series	Adults	20	1	To report a case of life-threatening sickle ACS treated with extracorporeal membrane oxygenation	NE	NA	0	NR	NA	100	6 mo
Gilli, 2002 <sup>326</sup>	Case report/ case series	Adults	22	1	To report a case of liver transplantation in a patient with HbS $\beta^0$ -thal	NA	NA	100	HbS $\beta^0$ -thal	NA	100	NA
Girard, 1979 <sup>327</sup>	Case report/ case series	Adults	19	1	To report a case of postoperative pulmonary edema and sickle cell crisis	NA	NA	100	NR	NA	100	NA
Goldbaum, 1976 <sup>328</sup>	Case report/ case series	Adults	33	5	To discuss vitrectomy to treat retinal detachment in patients with sickle hemoglobinopathy and to treat vitreous hemorrhage in stage IV PSR	NA	NA	40	HbSC (80%) HbSA (25%)	NA	100	NR
Goldberg, 1978 <sup>329</sup>	Case report/ case series	50% adults	28	4	To report the diagnosis and treatment of sickled erythrocytes in 4 cases of human hyphemas	NA	NA	75	HbSC (25%), HbSA (75%)	NA	100	1.5–10 mo
Goodwin, 2008 <sup>330</sup>	Case report/ case series	Adults	15	1	To report a case of bilateral central retinal artery occlusion associated with moyamoya syndrome	NA	NA	100	HbSS	NA	100	NA
Gradisek, 1983 <sup>331</sup>	Case report/ case series	Adults	18	1	To report a case of priapism in SCD	NA	NA	100	HbSS	NA	100	NA
Green, 1975 <sup>332</sup>	Case report/ case series	Adults	23.5	2	To report sickle cell crisis treated by exchange transfusion; treatment of 2 patients with heterozygous sickle cell syndrome	NA	NA	100	HbSC	NA	100	NA

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Greenbaum, 1988 <sup>333</sup>	Case report/ case series	Children	24, 39 mo	2	To describe 2 cases of recurrent strokes in 2 siblings with SCD and von Willebrand's disease	NA	NA	50	HbSS	NA	100	Unclear (years)
Gupta, 2008 <sup>334</sup>	Case report/ case series	Adults	43	1	To describe the clinical course of a woman with SCD who was admitted for sickle cell crisis and found to have an intracerebral hemorrhage at presentation and subsequently developed an arterial infarct	NA	NA	0	HbSS	NA	100	7 mo
Hamilton, 1978 <sup>335</sup>	Case report/ case series	Children	7	1	To report a case of angina pectoris in a child with SCA	NA	NA	100	HbSS	NA	100	NA
Hammersley, 1984 <sup>336</sup>	Case report/ case series	Adults	29	1	To report a case of mandibular infarction occurring during a sickle cell crisis	NA	NA	0	HbSS	NA	NA	NA
Hamre, 1991 <sup>337</sup>	Case report/ case series	Children and adults	Range: Reviewed: 2–55, Treated: 2–18	Reviewed: 305, Personal cases: 11	To review all available reported cases and add experience of 11 cases of priapism in SCD in pediatric patients at Sickle Cell Center of South Louisiana	NA	Inclusion for review: all adult and pediatric cases of priapism reported in the literature since 1934 with clear definition of genotypes Inclusion for personal cases: All children presenting for scheduled appointments at the Tulane Clinic of the Sickle Cell Center of Southern Louisiana in 1988 with reports of priapism	100	Personal cases: HbSS (45.5%), HbSC (45.5%), HbSO Arab (10%) Reviewed group: % NR	0	100	NR
Hasan, 2004 <sup>338</sup>	Case report/ case series	Adults	31	1	To describe the case of a 31-yr-old man with SCA who developed the complication of central retinal vein occlusion, which has not been reported previously in patients with SCA	NA	NA	100	HbSS	0	100	4 mo
Helton, 2002 <sup>339</sup>	Case report/ case series	Children	7	1	To report serial CNS findings in a girl with SCD and stroke. Religious considerations precluded transfusion and BMT; therefore, she received single-agent HU therapy for almost 6 yr	NA	NA	0	HbSS	NA	100	60 mo

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Henderson, 2003 <sup>340</sup>	Case report/case series	Children	Range: 3–9	5	To describe 5 cases of reversible posterior leukoencephalopathy syndrome and silent cerebral infarcts associated with severe ACS in children with SCD	NA	NA	80	HbSS	NA	100	4–60
Henry, 2004 <sup>341</sup>	Case report/case series	Children	11.3	3	To report 3 cases with SCD and pseudotumor cerebri	NA	NA	0	HbSS (66.6%), HbSC (33.3%)	NA	100	NA
Hillaire, 2000 <sup>342</sup>	Case report/case series	Adults	23	1	To report a case of cholangiopathy and intrahepatic stones in SCD	NA	NA	0	HbSS	NA	100	NA
Hillyer, 1991 <sup>343</sup>	Case report/case series	Adults	26	1	To describe the experience of a patient with sickle cell treated with incompatible blood transfusion for sickle cell crisis and resulting alloimmunization and delayed hemolytic transfusion reaction	NA	NA	0	HbSβ-thal	NA	100	14 d
Hitchcock, 1983 <sup>344</sup>	Case report/case series	Adults	41	1	To report a case of subarachnoid hemorrhage in SCA	NA	NA	0	HbSS	NA	100	NA
Hochberger, 1983 <sup>345</sup>	Case report/case series	Children	7	1	To report a case of cholelithiasis in a child with SCA	NA	NA	100	HbSS	NA	100	NA
Honore, 1993 <sup>346</sup>	Case report/case series	Adults	24	1	To describe the clinical course of a patients with SCA who presented with ACS	NA	NA	100	HbSS	NA	100	<1 mo
Horn, 1987 <sup>347</sup>	Case report/case series	Adults	20	1	To report a case of sickle cell hepatopathy	NA	NA	100	NR	NA	100	NR
Horton, 1995 <sup>348</sup>	Case report/case series	Children	14	1	To suggest that that fat embolism syndrome must be considered as a possible cause of acute neurologic deterioration in patients with SCA	NA	NA	0	NR	0	100	3 mo

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Hsiao, 2005 <sup>349</sup>	Case report/ case series	Adults	28	1	To present an unusual case of a man with SCD with chief complaints of jaundice, abdominal distension, constipation, and back and hip pain	NA	NA	100	NR	0	100	NR
Huang, 2003 <sup>350</sup>	Case report/ case series	Adults	32	1	To describe the clinical course of an adult patient with severe HbSC who developed symptomatic splenomegaly requiring splenectomy while being treated with HU	NA	NA	0	HbSC	NA	100	NR
Huffman, 2000 <sup>351</sup>	Case report/ case series	Adults	19	1	To report the complex case of recurring priapism in a patient with SCA	NA	NA	100	NR	NA	100	NR
Idowu, 1998 <sup>352</sup>	Case report/ case series	Children	1.7	6	To attempt to assess the outcome of pediatric patients <4 yr of age undergoing partial splenectomy using the argon beam	NA	6 patients underwent partial splenectomy by the same surgeon from May 1993 to Sept. 1995. The need for splenectomy in these cases was determined by the increasing need for blood transfusions, specifically, sequestration crisis, and hypersplenism	NR	HbSS (66.7%), HbSβ-thal (16.7%)	0	83.3	6 mo–2 yr
Irizarry, 2006 <sup>353</sup>	Case report/ case series	Children	10 and 17	2	To describe the clinical course of 2 patients with SCIC and cholelithiasis; the clinical picture of 1 is complicated by choledocholithiasis	NA	NA	100	NR	NA	100	NR
Islam, 2005 <sup>354</sup>	Case report/ case series	Adults	19 (case report)	1	To present a case of a 19-yr-old African American male with ACS	NA	NA	100	NR	NA	100	NR; "was moved out of ICU after 2 d, and remained stable until discharge"
Ives, 1987 <sup>355</sup>	Case report/ case series	Adults	42	1	To report a case of CIV morphine infusion for severe sickle cell crisis pain	NA	NA	100	NR	NA	100	6 d
Jayabose, 1983 <sup>356</sup>	Case report/ case series	Children	5	1	To report a case of CNS crisis in SCD treated with exchange transfusion	NA	NA	100	HbSS	NA	100	NA
Jeng, 2003 <sup>357</sup>	Case report/ case series	Children	18	1	To describe the clinical course of a 17-yr-old male patient with HbSS and chronic hepatic sequestration who was treated with long-term (60 mo) HU	NA	NA	100	HbSS	NA	100	60 mo

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Kar, 2008 <sup>358</sup>	Case report/ case series	Adults	20	1	To report a case of HbSβ <sup>+</sup> -thal with splenic calcification and bone marrow infarction	NA	NA	100	HbSβ <sup>+</sup> -thal	NA	100	NA
Karaunatilake, 2009 <sup>359</sup>	Case report/ case series	Adults	34	1	To describe a patient with HbSβ-thal with SCIC successfully treated by partial exchange blood-plasma transfusion	NA	NA	100	HbSβ-thal	NA	100	1 mo
Karayalcin, 1972 <sup>360</sup>	Case report/ case series	Adults	Mean: 28.6	5	To describe 5 cases and treatment of priapism associated with SCD	NA	NA	100	HbSS (80%), HbSC (20%)	20	100	NR
Karim, 2002 <sup>361</sup>	Case report/ case series	Adults	35	1	To report a case of fulminant ischemic colitis with atypical clinical features complicating SCD	NA	NA	100	HbSS	NA	100	NA
Kato, 2006 <sup>362</sup>	Case report/ case series	Adults	20–47	6	To describe the association of cerebrovascular disease and PHTN in SCD	NA	NA	50	HbSS	0	100	Unclear
Keller, 1979 <sup>363</sup>	Case report/ case series	Adults	18	1	To present a case of a patient with SCD suffering from painful hemolytic crises since childhood	NA	NA	0	HbSS	0	100	NR
Kelly, 1986 <sup>364</sup>	Case report/ case series	Adults	33	2	To report 2 cases of acute renal failure in SCD	NA	NA	50	NR	NA	100	NR
Khattab, 2001 <sup>365</sup>	Case report/ case series	Children	6	1	To describe a report of a patient with an unusual complication of sickle cell crisis	NA	NA	100	NR	0	100	NR
Khurshid, 2002 <sup>366</sup>	Case report/ case series	Adults	37	1	To report a patient who presented with SCIC, a rare and potentially lethal complication of SCD	NA	NA	100	HbSS	NA	100	12 mo
Kinney, 1975 <sup>367</sup>	Case report/ case series	Children	10	4	To describe 4 cases of priapism in children with sickling disorders and suggest a rational therapeutic approach	NA	NA	100	NR	NA	100	NR

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Kleinman, 1980 <sup>368</sup>	Case report/case series	Children	Mean: 22	3	To describe the clinical course of patients with SCA complications (priapism and ACS) treated with exchange transfusion	NA	NA	66	HbSS	NA	100	NR
Kleinman, 1984 <sup>369</sup>	Case report/case series	% adults NR	Range: 11–42	9	To examine the effects of erythrocytapheresis on patients with SCD with acute and/or chronic complications	2, acute vs. chronic complications	NR	67	NR	0	100	Varied (acute; 18 mo)
Kleinman, 1981 <sup>370</sup>	Case report/case series	Children	13	1	To report a case of exchange RBC pheresis in a pediatric patient with severe complications of SCA	NA	NA	100	NR	NA	100	8 d
Knight-Perry, 2009 <sup>371</sup>	Case report/case series	Children	14	1	To describe an adolescent with SCD who underwent a methacholine challenge as part of a clinical research study and was subsequently hospitalized for an acute painful episode	NA	NA	10	HbSS	NA	100	Unclear
Koduri, 2006 <sup>372</sup>	Case report/case series	Adults	34	9	To describe the clinicopathological features of ASSC in 9 adults with HbSC	NA	Inclusion: Patients seen in consultation at Cook County Hospital and followed in the hematology clinics by the senior author during 1972–2000 with a diagnosis of HbSC. The diagnosis of ASSC required the findings of an acute illness characterized by left-sided abdominal pain, splenomegaly, and an otherwise unexplained drop in the hemoglobin of $\geq 3$ g/dL from the steady state value with active erythropoiesis	33	HbSC	NA	100	Range: 0–252 mo; mean=108 mo
Koduri, 2006 <sup>373</sup>	Case report/case series	Adults	22	1	To report a 22-yr-old man with HbS $\beta$ -thal who developed ASSC 1 d after suffering multiple blunt trauma	NA	NA	100	HbS $\beta$ -thal	NA	100	<1 mo
Koirala, 2009 <sup>374</sup>	Case report/case series	Children	14	1	To describe Risperidone-induced priapism and treatment	NA	NA	100	NR	NA	100	NR
Kotb, 2006 <sup>375</sup>	Case report/case series	% adults NR	19	36	To describe brain MRI and computerized tomography (CT) findings in patients with SCD presenting with stroke, headache, or seizure	1	NA	47	HbSS	NA	100	NR
Kreindler, 2000 <sup>376</sup>	Case report/case series	Children	8	1	To review the clinical presentation and management of a patient with SCD who presents with ACS	NA	NA	100	HbSS	NA	100	NR

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Kruse, 1983 <sup>377</sup>	Case report/ case series	Children	21	1	To report a case of sickle cell crisis after discontinuation of periodic transfusion therapy	NA	NA	0	NR	NR	100	NA
Kumar, 2007 <sup>378</sup>	Case report/ case series	Children	12	1	To report a 12-yr-old girl with SCD who presented with pain in abdomen, fever, joint pain, and hematemesis	NA	NA	0	HbSS	0	100	4 weeks
Labat, 2001 <sup>379</sup>	Case report/ case series	Children	9	1	To present a case of a child with severe abdominal VOC and priapism was successfully treated with a combination of epidural local anesthetics and morphine	NA	NA	1	NR	0	100	NR
Lacaille, 2004 <sup>380</sup>	Case report/ case series	Children	Median age: 11.5	6	To describe 6 children with acute hepatic sickle crisis to emphasize the importance of early diagnosis and management of this rare complication of SCD in childhood	NA	NA	66.7	HbSS (100%)	0	100	1–10 yr
Lakkireddy, 2002 <sup>381</sup>	Case report/ case series	Adults	20	1	To report a case of fatal pulmonary artery embolism in a patient with SCD	NA	NA	100	NR	NA	100	NA
Lama, 1993 <sup>382</sup>	Case report/ case series	Children	10	1	To report a case of hepatic abscess in SCA	NA	NA	0	NR	NA	100	1.5 mo
Lang, 1995 <sup>383</sup>	Case report/ case series	Children	11.5	1	To report experience of what appears to be the first case of liver transplantation in a child with SCA describing steps taken for prevention of sickling during the perioperative period	NA	NA	100	HbSS	0	100	24 mo
Lanzkron, 2002 <sup>384</sup>	Case report/ case series	Adults	26	1	To report a patient with a VOC who refused transfusion on a religious basis	NA	NA	0	NR	0	100	8 d
Lanzkron, 2002 <sup>384</sup>	Case report/ case series	Adults	26	1	To present a patient with ACS and several high-risk features	NA	NA	0	NR	0	100	8 d

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Lau, 2007 <sup>385</sup>	Case report/ case series	Adults	37	8	To evaluate the results of shoulder arthroplasty for the treatment of AVN in patients with SCD	NA	Inclusion: Adult patients seen at the sickle cell clinic of Washington University, St. Louis, MO, who underwent shoulder arthroplasty between 1994 and 2005 and had at least 2 yr of followup	62.5	HbSS (75%), HbSC (25%), HbSβ <sup>+</sup> -thal (25%)	0	100	Mean: 51 mo
Laurie, 2010 <sup>386</sup>	Case report/ case series	Adults	33	1	To describe the efficacy of iNO and exchange transfusion in the treatment of ACS	NA	NA	100	HbSS	NA	100	5 weeks
Lebensburger, 2008 <sup>387</sup>	Case report/ case series	Children	17	1	To report on biloma and pneumobilia in a young patient with hepatobiliary complications, which are common in SCD,	NA	NA	100	HbSS	0	100	2 weeks
Lee, 1996 <sup>388</sup>	Case report/ case series	Adults	33	1	To present a case of a patient who had an unusual clinical course after developing a sickle cell crisis with hepatic and pulmonary sequestration	NA	NA	0	HbSS	0	100	NA; she died in hospital
Lee, 2002 <sup>389</sup>	Case report/ case series	Children	12 and 6	2	To provide evidence supporting that patients with acute neurologic deterioration in conjunction with ACS should be evaluated thoroughly for other causes of CNS disease, including infectious/parainfectious processes as well as stroke	NA	NA	50	HbSS	0	100	1–2 mo
Leen, 2002 <sup>390</sup>	Case report/ case series	Adults	40	1	To report a case of anterior segment ischemia after vitrectomy in SCD	NA	NA	0	HbSC	NA	100	NA
Lerut, 1999 <sup>391</sup>	Case report/ case series	Adults	42	1	To report a case of liver transplantation in a patient with HbSβ-thal complicated by liver sickling, indicating that intrahepatic sickling must be considered in case of allograft dysfunction	NA	NA	0	HbSβ-thal	NA	100	39 mo
Levine, 1993 <sup>392</sup>	Case report/ case series	Adults	18	1	To report a case of SCA-associated priapism treated with gonadotropin releasing hormone analogues	NA	NA	100	NR	NA	100	12 mo

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Liaquat, 2010 <sup>393</sup>	Case report/case series	67% adults	28	6	To assess possible intracranial vascular sequelae of SCD and identify risk factors and management strategies	1, patients with SCD with subarachnoid hemorrhage requiring neurosurgical intervention	NR	83	HbSS	NA	100	NR
Liberman, 1997 <sup>394</sup>	Case report/case series	Children	12	1	To report a case of laparoscopic management of CBD stones in the pediatric patient with SCD	NA	NA	100	NR	NA	100	NA
Liem, 2008 <sup>395</sup>	Case report/case series	67% adults	13.6	3	To present 3 patients with SCD and retinal artery occlusion	NA	NR	33.3	HbSS	NR	100	NR
Liu, 2003 <sup>396</sup>	Case report/case series	Children	12.3	3	To report 3 cases of priapism in patients with SCD in Yemenis	NA	NA	100	HbSS	0	100	NR
Lombardo, 2003 <sup>397</sup>	Case report/case series	Adults	38.2	21	To evaluate the therapeutic efficacy of RCE during ACS	NA	NA	33	HbSS (19%), HbSβ <sup>+</sup> (62%), HbSβ <sup>0</sup> (19%)	0	100	34
Loutfy, 1997 <sup>398</sup>	Case report/case series	Adults	25	1	To describe the clinical course of a patients with homozygous sickle cell disease who developed an acute lateral myocardial infarction	NA	NA	100	HbSS	NA	100	6 mo
Love, 1985 <sup>399</sup>	Case report/case series	50% adults	20.5	2	To report 2 cases of ruptured intracranial aneurysms in cases of SCA	NA	NA	50	NR	NA	100	Case 1: 5 yr, Case 2: 6 mo
Lowenthal, 1996 <sup>400</sup>	Case report/case series	Adults	23	3	To describe 3 cases of ACS in patients with HbSC in association with acute parvovirus B19 infection	1	Patients with HbSC and were admitted for acute respiratory illness associated with a declining hematocrit	100	HbSC	0	100	Acute
Ludmerer, 1982 <sup>401</sup>	Case report/case series	Adults	27	1	To report a case of a woman with painful crisis and persistent left elbow effusion	NA	NA	0	NR	0	100	NA; patient died

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Maconochie, 1988 <sup>402</sup>	Case report/ case series	Children	6.5	1	To report a case of priapism in a 6 1/2-yr-old boy with SCD	NA	NA	100	HbSS	NA	100	8 d
Mak, 2003 <sup>403</sup>	Case report/ case series	Adults	21	1	To describe the clinical course of a patient with ACS treated with a multidisciplinary approach	NA	NA	100	NR	NA	100	<1 mo
Makhoul, 2010 <sup>404</sup>	Case report/ case series	Children	15	1	To present a case report of pseudouveitis in the setting of severe sickle cell retinopathy complicated by macular infarction.	NA	NA	100	HbSS	NA	100	2 d (from hospital admission to diagnosis)
Malone, 1988 <sup>405</sup>	Case report/ case series	Children	11.2	12	To report 12 cases of cholecystectomy and cholelithiasis in SCA	NA	NA	66.6	NR	0	100	Hospitalization average 6.3 d, total followup NR
Manna, 2003 <sup>406</sup>	Case report/ case series	Children	7 (1 patient)	1	To report a case of plastic bronchitis in ACS of SCD	NA	NA	100	HbSS	NA	NA	NA
Markowitz, 1980 <sup>407</sup>	Case report/ case series	Children	8	1	To present a case of focal nodular hyperplasia of the liver in a child with SCA	NA	NA	0	NR	0	100	NA; patient died in hospital
McHardy, 2007 <sup>408</sup>	Case report/ case series	Children	7	1	To describe the successful management of priapism	Secondary to SCA in a child using neuraxial analgesia provided via an epidural catheter	NA	NA	NR	0	100	NR
Medoff, 2005 <sup>409</sup>	Case report/ case series	Adults	22	1	To describe the clinical course of a patient with SCD who developed ACS	NA	NA	0	HbSS	NA	100	<1 mo
Mekeel, 2007 <sup>410</sup>	Case report/ case series	Children	14	3	To examine the outcomes of liver transplantation in treating children with SCD-related hepatopathies	1, SCD pediatric patients who received a liver transplantation	NR	NR	NR	0	100	50
Merritt, 1982 <sup>411</sup>	Case report/ case series	Children	10	1	To report a case of bilateral macular infarction in HbSS	NA	NA	0	HbSS	NA	100	6 mo

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Meshikhes, 1996 <sup>412</sup>	Case report/ case series	Adults	25	1	To report a case of successful combined LC and appendectomy in a patient with SCD	NA	NA	100	NR	NA	100	NA
Middleton, 1984 <sup>413</sup>	Case report/ case series	Adults	29	1	To report a case of hepatic biloma complicating SCD	NA	NA	0	NR	NA	100	6 mo
Miner, 1987 <sup>414</sup>	Case report/ case series	Adults	34	1	To present a case of a patient with SCA with a decline in renal function 3.5 yr following transplant	NA	NA	100	NR	0	100	18 mo
Mishra, 1992 <sup>415</sup>	Case report/ case series	Children	7	3	To report experience with 3 previously undiagnosed children with SCD who primarily presented with hepatic manifestations	NA	NA	100	HbSS (100%)	0	100	1.5–6 mo
Modrykamien, 2007 <sup>416</sup>	Case report/ case series	Adults	21	1	To report a case of a 21-yr-old man with HbSC and acute shortness of breath with left upper abdominal pain	NA	NA	100	HbSC	NA	100	NA
Moll, 1996 <sup>417</sup>	Case report/ case series	Adults	25	1	To report a case of splenomegaly and splenic sequestration in an adult with SCA	NA	NA	100	HbSS	NA	100	NA
Monga, 1996 <sup>418</sup>	Case report/ case series	% adults NR	26	7	To describe 7 cases of early penile prosthesis implantation in treating recurrent ischemic priapism in patients with SCD	1, patients with SCD with recurrent ischemic priapism	NA	100	HbSS (100%)	NA	100	NR
Montero-Huerta, 2006 <sup>419</sup>	Case report/ case series	Children	13	1	To report the case of a 13-yr-old African American boy diagnosed at the age of 6 mo with HbSS, who had a nonhemorrhagic stroke after a routine anesthetic and was treated with iNO	NA	NA	100	HbSS	0	100	NR
Montgomery, 1994 <sup>420</sup>	Case report/ case series	Adults	35.2	5	To illustrate that excellent 1-yr results can be achieved following renal transplantation in patients with sickle cell nephropathy (SCN)	NA	Renal transplant cases from patients with SCN	60	HbSS (60%), HbSC (20%), HbSA (20%)	0	100	Variable for all 5 cases

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Morgan, 1987 <sup>421</sup>	Case report/case series	Adults	40.75	4	To examine patients with longstanding vitreous hemorrhages or retinal detachments that were treated successfully with standard vitrectomy surgery techniques or scleral buckling procedures without serious complications	NA	NA	25	NR	NA	100	Variable
Moukarzel, 2000 <sup>422</sup>	Case report/case series	Children	5	1	To present a child with SCA and a painful crisis secondary to a massive ischemia of her colon	NA	NA	0	NR	0	100	1 yr
Mueller, 2009 <sup>423</sup>	Case report/case series	Children	9	1	To report on a 9-yr-old boy with HbSS, who developed unilateral exophthalmia due to a VOC event in his orbital bones	NA	NA	100	HbSS	0	100	NR
Mukisi Mukaza, 2009 <sup>424</sup>	Case report/case series	Adults	25	4	To report the onset of osteonecrosis of the elbow in 4 SCA patients	NA	Inclusion: Patients with SCA seen between 1985 and 2005 at the Henri-Mondor Hospital for adult nontraumatic osteonecrosis of the elbow	25	NR	NA	100	NR
Murtuza, 2009 <sup>425</sup>	Case report/case series	Adults	59	1	To describe the clinical course of ACS in an adult undergoing aortic valve replacement despite instituting established perioperative optimization measures to prevent sickling	NA	NA	0	HbSS	NA	100	NR
Nachmann, 2003 <sup>426</sup>	Case report/case series	Adults	47	1	To report a case of superficial thrombophlebitis of the penis in a patient with SCD	NA	NA	100	NR	NA	100	1.5 mo
Nasr, 2006 <sup>427</sup>	Case report/case series	Children	15	1	To report a case of SCD, nephrotic syndrome, and renal failure	NA	NA	100	HbSS	NA	100	NA
Navaid, 2010 <sup>428</sup>	Case report/case series	Adults	27	1	To describe the efficacy of chronic exchange transfusion in treating recurrent sickle cell pain	NA	NA	0	NR	NA	100	12 mo
Noe, 1981 <sup>429</sup>	Case report/case series	Children	NR	5	To present the successful management of 5 children with SCA and priapism	NA	NA	100	NR	40	100	NR

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Noto, 1999 <sup>430</sup>	Case report/ case series	Adults	41	1	To describe a male patient with an acute pulmonary process associated with HbSC that was clinically similar to acute pulmonary thromboembolism	NA	NA	100	HbSC	NA	100	NR
Nouri, 1991 <sup>431</sup>	Case report/ case series		7	12	To examine the benefit of partial splenectomy to treat ASSC or hypersplenism in pediatric patients with SCD	NA	NA	NR	HbSS (33%), HbSβ-thal (66%)	NA	100	50.4 mo
O'Callaghan, 1995 <sup>432</sup>	Case report/ case series	Children	15	1	To describe the clinical course of a patient with SCD and cholestasis treated for >1 yr with exchange transfusion	NA	NA	100	NR	NA	100	36 mo
Okoro, 1989 <sup>433</sup>	Case report/ case series	Children	8.25	4	To describe the experience of splenectomy for patients SCD and hypersplenism treated at the University of Nigeria Teaching Hospital	NA	NA	50	HbSS	NA	100	Range: 12–72 mo
O'Neil, 2001 <sup>434</sup>	Case report/ case series	Children	3, 15	2	To describe nursing care in SCD exacerbations	NA	NA	50	HbSS	NA	100	Unclear
Oppert, 2004 <sup>435</sup>	Case report/ case series	Adults	36	1	To report on a 36-yr-old male with a known history of SCD and ACS who was treated in our hospital	NA	NA	100	NR	0	100	NR
Orringer, 1991 <sup>436</sup>	Case report/ case series	Adults	31.5	2	To report 2 cases of splenic infarction and ASSC in adults with HbSC	NA	NA	100	HbSC	NA	100	NA
Ouyang, 2008 <sup>437</sup>	Case report/ case series	Adults	20	1	To report a case of massive splenic infarct in a collegiate football player with HbSC	NA	NA	100	HbSC	NA	100	NA
Padman, 2004 <sup>438</sup>	Case report/ case series	Children	11.8	9	To assess the outcome of bilevel positive airway pressure (BPAP) use for pediatric patients with SCD and ACS	NA	Not specified	78	NR	0	100	Unclear
Pappo, 1989 <sup>439</sup>	Case report/ case series	Children	2 mo	1	To report an infant with ASSC and SCD	NA	NA	100	HbS and HbF	NA	100	NA

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Pashankar, 2008 <sup>201</sup>	Case report/ case series	Children	10	1	To present a patient with intracranial hemorrhage complicating reversible posterior leucoencephalopathy syndrome and discuss the management	NA	NA	100	HbSS	0	100	12 mo
Patel, 2006 <sup>440</sup>	Case report/ case series	Children	13	1	To present the case of a 13-yr-old girl with stage III osteonecrosis of the femoral head caused by SCD that has been successfully treated with a valgus-flexion osteotomy of the proximal femur, with 42-mo postoperative followup	NA	NA	0	Hemoglobin AS (HbAS)	NA	0	42 mo
Pelidis, 1997 <sup>441</sup>	Case report/ case series	Children	8	1	To report a case of life-threatening ACS of SCD that was successfully treated with venovenous extra-corporeal membrane oxygenation	NA	NA	100	HbSS	NA	100	60 mo
Periman, 1994 <sup>442</sup>	Case report/ case series	Adults	52	1	To report a case of retrobulbar ischemic optic neuropathy associated with SCD	NA	NA	100	HbSS	NA	100	NA
Pollack, 1991 <sup>443</sup>	Case report/ case series	Adults	29–38	4	To report 4 representative cases and review the salient points of the management of pain crisis in adult patients in the ED	NA	NA	50	HbSS	0	100	0.5 mo
Powers, 2002 <sup>444</sup>	Case report/ case series	Children	10	3	To describe 3 cases of patients with SCD who received along with their parents a program of intensive pain management skills training	1	Children who received intensive pain management skills training in nonpharmacological and pharmacological pain management strategies	66	HbSS 100%	1	100	3 mo
Pruzansky, 1980 <sup>445</sup>	Case report/ case series	Adults	21	1	To report a case of sickle cell osteonecrosis simulating osteomyelitis	NA	NA	100	NR	NA	100	NA
Qureshi, 2006 <sup>446</sup>	Case report/ case series	Adults	27	1	To describe a case of sickle cell pain crisis (girdle syndrome) progressing to ischemic colitis and colonic perforation	NA	NA	100	NR	NA	100	12 mo
Rada, 1987 <sup>447</sup>	Case report/ case series	50% adults	22	2	To report 2 cases of sickle cell crisis precipitated by periodontal infection and review considerations for crisis and noncrisis patients with SCD	NA	NA	NA	NR	NA	100	Unclear

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Ramos, 1995 <sup>448</sup>	Case report/ case series	50% adults	18	2	To report 2 cases of high-flow priapism associated with SCD	NA	NA	100	NR	50	100	Case 1: 4 mo
Rand, 1987 <sup>449</sup>	Case report/ case series	Adults	28	5	To report 5 cases of hip arthroplasty in patients with SCD suffering from AVN of the femoral head in an attempt to describe challenges faced in achieving success in the same	1	Not specified	40	HbSS (60%), HbSC (20%), HbSβ-thal (20%)	0	100	Unclear
Rao, 1979 <sup>450</sup>	Case report/ case series	Children	13	1	To report a case of ASSC in an adolescent with HbSC hemoglobinopathy	NA	NA	0	HbSC	NA	100	3 d
Resar, 1996 <sup>451</sup>	Case report/ case series	Children	14	1	To report the case of a patient with SCA and multiple skull infarctions associated with epidural hematomas	NA	NA	100	HbSS	NA	100	NR
Rifkind, 1979 <sup>452</sup>	Case report/ case series	Adults	27	1	To report a case of RBC exchange pheresis for priapism in SCD	NA	NA	100	NR	NA	100	6 mo
Rijke, 1990 <sup>453</sup>	Case report/ case series	Adults	49	1	To report a case of bilateral protrusio acetabuli in SCA	NA	NA	0	NR	NA	100	NA
Ris, 1996 <sup>454</sup>	Case report/ case series	Children	12	1	To describe MRI and neuropsych testing in a patient with SCD and a stroke	1	NA	0	HbSS	NA	100	Unclear
Rivera-Ruiz, 2008 <sup>455</sup>	Case report/ case series	Adults	44	1	To describe a case of ASSC in an adult male with HbSC	NA	NA	100	HbSC	NA	100	6 mo
Robertson, 1997 <sup>456</sup>	Case report/ case series	Children	2	1	To describe and discuss the clinical course of a pediatric patient with ACS	NA	NA	100	HbSS	NA	100	<1 mo

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Roohi, 2001 <sup>457</sup>	Case report/ case series	Adults	30	2	To describe the clinical course, electrophysiological findings, diagnosis, and management of 2 patients with SCD with mononeuropathy multiplex	NA	NA	50	HbSS	NA	100	Case 1: 24 mo, Case 2: 36 mo
Roshkow, 1990 <sup>458</sup>	Case report/ case series	Adults	31 and 36	2	To describe clinical course of 2 adult patients with heterozygous SCD and ASSC	NA	NA	100	HbSC (50%), HbSβ-thal (50%)	NA	100	4 mo
Ross, 2002 <sup>459</sup>	Case report/ case series	Adults	49	1	To describe a patient who underwent combined liver and kidney transplantation for multiple end-organ damage caused by SCA	NA	NA	100	NR	0	100	NA; patient died in hospital
Rossof, 1981 <sup>460</sup>	Case report/ case series	Adults	38	1	To report a case of intrahepatic sickling crisis in HbSC	NA	NA	0	HbSC	NA	100	NA
Rouxel, 2008 <sup>461</sup>	Case report/ case series	Adults	25	1	To report a case of pulmonary infarction without fat or thromboembolism in SCA	NA	NA	100	HbSC	NA	100	NR
Roy, 1987 <sup>462</sup>	Case report/ case series	Adults	27.5	2	To report 2 cases of retroequatorial red retinal lesions	NA	NA	100	HbSS	NA	100	10 d for both
Russell, 1976 <sup>463</sup>	Case report/ case series	Children	7.2	5	To report 5 cases of cerebrovascular abnormalities in SCD treated with transfusion therapy	NA	NA	NR	NR	NA	100	NR
Saad, 2004 <sup>464</sup>	Case report/ case series	60% adults	20.2	5	To report our clinic's experience during the last 10 yr in using hydroxyurea to prevent priapism in patients who have had stuttering or major attacks of priapism but who are still capable of intercourse on demand	1	Inclusion: We treated 5 patients suffering from priapism with HU, seen at the University of Campinas Hospital, aging from age 13–35 yr at the time of the 1st episode	100	HbSS (80%), HbSβ-thal (20%)	0	100	3–10 yr (range)
Sacerdote, 1999 <sup>465</sup>	Case report/ case series	Adults	21	1	To describe the sustained symptomatic and hematologic improvement in a 21-yr-old woman with HbSS disease during treatment with pentoxifylline, 400 mg 3 times daily after meals	NA	NA	0	HbSS	NA	100	108 mo

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Saleem, 2007 <sup>466</sup>	Case report/ case series	Adults	31	1	To present a 31-yr-old man with HbSC disease was admitted with ACS, treated with antibiotics and ventilator support	NA	NA	100	HbSC	0	100	NR
Sarma, 1989 <sup>467</sup>	Case report/ case series	Adults	20	1	To report a case of ASSC with SCD	NA	NA	0	HbSS	NA	100	12 mo
Savafi, 2006 <sup>468</sup>	Case report/ case series	Adults	21	1	To describe chronic liver disease in a patient with SCA	NA	NA	100	HbSS	0	100	NR
Sawke, 2009 <sup>469</sup>	Case report/ case series	Children	11	1	To report a case of cholelithiasis and splenomegaly in a patient with SCD	NA	NA	0	HbSS	NA	100	NA
Schechter, 1988 <sup>470</sup>	Case report/ case series	Children	10	3	To analyze the hypothesis that adolescents in sickle-cell pain crisis using PCA would report better pain control and require less narcotic than those given standard care	NA	Inclusion: Patients who had pain caused by a sickle cell VOC were evaluated in clinic and given analgesics and hydration. If they did not improve in 2 h, they were admitted for further hydration and analgesic therapy	100	NR	NA	100	Unclear
Schmugge, 2001 <sup>471</sup>	Case report/ case series	Children	11	1	To report on the 28-mo followup of a patient with HbSD and moyamoya syndrome	NA	NA	100	HbSD	0	100	28 mo
Schubert, 2005 <sup>472</sup>	Case report/ case series	Adults	44	1	To report a case of retinal schisis in patient with SCD	NA	NA	0	HbSS	0	100	60 mo
Seiberth, 1999 <sup>473</sup>	Case report/ case series	Adults	30	1	To demonstrate the feasibility of transscleral diode laser photocoagulation for the treatment of PSR	NA	NA	100	NR	0	100	22 mo
Shah, 1993 <sup>474</sup>	Case report/ case series	Adults	23 (range: 17–29)	5	To report 5 cases of knee arthroplasties for SCD	NA	NA	60	NR	NA	100	Mean: 5 yr Range: 1–11 yr
Shah, 2004 <sup>475</sup>	Case report/ case series	Children	14	1	To report a 14-yr-old boy with SCD who presented with priapism of 72-h duration and who was successfully treated by bilateral saphenocorporal shunts	NA	NA	100	NR	0	100	4 mo

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Shaiova, 2004 <sup>476</sup>	Case report/ case series	Adults	35	3	To report 3 cases of SCD pain managed with chronic opioid pharmacotherapy	NA	NA	33.3	NR	NA	100	NA
Shao, 1995 <sup>477</sup>	Case report/ case series	50% adults	23	2	To describe the clinical course of 2 patients with SCIC treated with exchange transfusion and supportive care aimed at correction of coagulopathy, stabilization of the acute liver disease	NA	NA	100	HbSS	NA	100	2 mo
Shao, 1996 <sup>478</sup>	Case report/ case series	Adults	21	1	To describe the clinical course of a woman with previously undiagnosed HbSC whose initial presentation was that of severe ASSC	NA	NA	0	HbSC	NA	100	<1 mo
Sharma, 2009 <sup>479</sup>	Case report/ case series	Adults	50	1	To describe a case of delayed spontaneous splenic rupture in a case of SCA, which was treated with subcapsular splenectomy	NA	NA	100	HbSS	0	100	Unclear
Shash, 2003 <sup>480</sup>	Case report/ case series	Adults	37	1	To report the diagnosis of bilateral AVN of the hip with autoinfarction of the spleen via various radiological modalities and confirmed by blood investigation in a patient with SCD	NA	NA	100	NR	NA	100	NA
Sheehy, 1980 <sup>481</sup>	Case report/ case series	Adults	21	1	To report a case of SCIC	NA	NA	100	HbSS	NA	NA	NA
Shelat, 2010 <sup>482</sup>	Case report/ case series	Children	16	1	To discuss the diagnosis and therapeutic management issues and the challenges of differentiating the VOC and hemolytic complications of sickling RBCs from the thrombotic microangiopathy of thrombotic thrombocytopenic purpura	NA	NA	0	HbSS	NA	100	During hospitalization
Sherman, 2004 <sup>483</sup>	Case report/ case series	Adults	29	1	To present a case of a 29-yr-old man with SCD who presented with an acute non-ST segment myocardial infarction	NA	NA	100	HbSS	0	100	NR
Shoemaker, 2004 <sup>484</sup>	Case report/ case series	Adults	19	1	To describe a 19-yr-old patient with HbSS who experienced an acute splenic rupture crisis requiring emergent splenectomy	NA	NA	100	HbSS	0	100	10 mo

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Shulman, 1971 <sup>485</sup>	Case report/ case series	Adults	4	1	To report a case of pyogenic hepatic abscess in a patient with SCD	NA	NA	100	HbSS	NA	100	NA
Shulman, 1995 <sup>486</sup>	Case report/ case series	Adults	35	1	To report a case of chronic pain with SCD	NA	NA	0	NR	NA	100	9.5 mo
Sidani, 2008 <sup>487</sup>	Case report/ case series	Adults	21	1	To describe an adult patient with SCD who presented with venous infarct secondary to dural sinus thrombosis	NA	NA	100	HbSS	NA	100	12 mo
Sidman, 1990 <sup>488</sup>	Case report/ case series	Children	10	1	To report a case of orbital complications with SCD	NA	NA	0	HbSS	NA	100	Hospitalization 10 d
Siegel, 1988 <sup>489</sup>	Case report/ case series	Adults	49	1	To report a case of sickle cell retinopathy	NA	NA	0	NR	NA	100	NR
Singh, 2008 <sup>490</sup>	Case report/ case series	Children	8.6	3	To describe 3 patients with SCD with chronic hypoxemia treated with HU	NA	NA	33.3	HbSS	NA	100	NR
Slayton, 1995 <sup>491</sup>	Case report/ case series	Children	13.5	2	To report 2 cases of testosterone-induced priapism in 2 adolescents with SCD	NA	NA	100	NR	NA	NA	NA
Smith, 2005 <sup>492</sup>	Case report/ case series	Adults	52	1	To report recent treatment of a patient with refractory chronic SCA bone pain with implantable drug delivery systems (IDDS), because many patients with SCA pain are treated in the same manner as patients with chronic cancer pain	NA	NA	0	HbSC	0	100	8 mo
Sodipo, 1986 <sup>493</sup>	Case report/ case series	Children	15	1	To report a case of SCD crises treated with acupuncture	NA	NA	0	NR	NA	100	16 d

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Sokol, 2008 <sup>494</sup>	Case report/ case series	33% adults	16	3	To present 3 cases of orbital compression syndrome caused by infarction of the greater wing of the sphenoid in patients with SCD	NA	NA	66.6	HbSS	NA	100	NA
Solanki, 1979 <sup>495</sup>	Case report/ case series	90% adults	22.7	10	To report and review 10 patients with SCA older than age 10 who had cholecystectomy in order to analyze the recommendation for routine cholecystograms in all adolescent and adult patients with SCD with elective cholecystectomy for those who have stones	NA	Patients with SCA over the age of 10 and had cholecystectomy	60	HbSS	0	100	NR
Sorrells, 1998 <sup>496</sup>	Case report/ case series	Children	2.5	16	To evaluate septic complications after splenectomy for sickle cell sequestration crisis	1	Patients with SCD who underwent splenectomy for splenic sequestration	62.5	Not specified	45	100	40 mo
Spector, 1978 <sup>497</sup>	Case report/ case series	Adults	34	1	To present a case of painful crises following renal transplantation in SCA	NA	NA	0	HbSS	0	100	8 mo
Spinapolice, 1982 <sup>498</sup>	Case report/ case series	Adults	29	1	To report a case of HbSD in pregnancy and review her management	NA	NA	0	HbSD	NA	100	3 mo
Staser, 2006 <sup>499</sup>	Case report/ case series	Children	15	1	To report a case of a calcified pulmonary thromboembolism in a child with SCD	NA	NA	100	NR	0	100	NR
Steinberg, 1991 <sup>500</sup>	Case series	Adults	55	2	To test the effectiveness of recombinant human EPO in the treatment of anemia of renal failure in SCD	NA	NA	50	HbSS	NA	100	8 mo
Steinberg, 2003 <sup>501</sup>	P, Obs	Adults	NR	299	To determine whether HU attenuates mortality in patients with SCA	1	Inclusion: Patients were at least 18, had HbSS (patients with HbS $\alpha$ -thal were not excluded). If patients had received transfusions, hemolysates of their red cells could not contain >15% Hg A at treatment initiation; patients had to have at least 3 crises reported to study physician in the year before study entry. Exclusion: Pregnancy; known narcotic addiction; participation in a long-term program of transfusion; concurrent treatment with another potential antisickling agent	NR	HbSS	(9% of patients had unknown vital status)	100	Up to 108 mo

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Stephan, 1995 <sup>502</sup>	Case report/ case series	Children	12	1	To report a case of fulminant liver failure with SCD	NA	NA	0	HbSS	NA	100	7 d
Stewart, 2009 <sup>503</sup>	Case report/ case series	Adults	29	1	To report a case that highlights the importance of differentiating simple pain crisis from more serious and life-threatening ischemic bowel	NA	NA	0	NR	0	100	7 d
Suara, 2001 <sup>504</sup>	Case report/ case series	Children	15	1	To describe an ACS event and otitis media due to Group A b-hemolytic <i>Streptococcus</i> in a 15-yr-old African American girl with HbSS	NA	NA	0	HbSS	0	100	NR
Sullivan, 1999 <sup>505</sup>	Case report/ case series	Children	15	1	To report a case of ACS of SCD treated successfully with nitric oxide	NA	NA	100	NR	NA	100	<1 mo
Svarch, 1986 <sup>506</sup>	Case report/ case series	Children	9	1	To report a case of plasma exchange for acute cholestasis in homozygous SCD	NA	NA	100	HbSS	NA	100	25 mo
Taksande, 2009 <sup>507</sup>	Case report/ case series	Children	5	1	To describe the clinical course of a child with SCA who developed a renal abscess	NA	NA	100	HbSS	NA	100	Unclear
Taylor, 2008 <sup>508</sup>	Case report/ case series	Children	15	1	To present the diagnosis of severe pulmonary hypertension in an adolescent with SCD	NA	NA	0	HbSS	NA	100	NR
Tiftik, 2004 <sup>509</sup>	Case report/ case series	Adults	21	1	To present a 21-yr-old Mediterranean female with a lifelong history of SCD resulting in multiple hospital admissions for painful crises	NA	NA	0	NR	0	100	NR
Tinti, 2010 <sup>510</sup>	Case report/ case series	Adults	32	1	To examine the effects of kinesiotherapy and aquatic rehabilitation on pain levels and lung capacity in an adult woman with SCA levels and lung capacity in an adult woman with SCA	NA	NA	0	HbSS	NA	100	NR
Trant, 1996 <sup>511</sup>	Case report/ case series	Children	4	1	To describe the successful use of extracorporeal membrane oxygenation (ECMO) in a child with severe SCA and ACS	NA	NA	100	HbSS	0	100	NR

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Upadhyay, 1998 <sup>512</sup>	Case report/case series	Adults	19	1	To report a case of penile implant for intractable priapism associated with SCD	NA	NA	100	NR	NA	100	6 mo
Van de Pette, 1982 <sup>513</sup>	Case report/case series	Adults	29.4	5	To report the experience of 5 adult patients in whom more extensive exchange transfusion was carried out as an emergency procedure in life-threatening sickle crises	NA	NA	80	HbSS (20%), HbS-thal (20%), HbSC (60%)	NA	100	NR
Van Hoff, 1985 <sup>514</sup>	Case report/case series	Children	6.58	2	To report 2 cases of intracranial hemorrhage in children with SCD	NA	NA	50	NR	NA	100	Case 1: 16 mo Case 2: 22 mo
Van Mierlo, 2003 <sup>515</sup>	Case report/case series	Children	12 (1 patient)	1	To report a case of SCD with cortical hemorrhagic infarction in her right frontal lobe	NA	NA	0	HbSS	NA	100	NA
Vecchio, 2001 <sup>516</sup>	Case report/case series	Adults	Range: 18–47	7	To report cases of patients affected by SCD who underwent elective LC for symptomatic gallbladder lithiasis	NA	Patients with SCD who underwent elective LC	43	HbSS (29%), HbSβ-thal (71%)	NA	100	<1 mo
Vicari, 2008 <sup>517</sup>	Case report/case series	Adults	27	1	To describe a case of multiple primary choledocholithiasis, associated with pancreatitis, in a patient with SCD, 14 yr after cholecystectomy	NA	NA	100	HbSS	NA	100	<1 mo
Villavicencio, 2008 <sup>518</sup>	Case report/case series	Children	7	1	To present a case that demonstrates not only how occult elevation of tricuspid regurgitant jet velocity occurs but also that symptomatic HbSS-associated PHTN may occur during childhood, masquerading as ACS, and can be difficult to treat	NA	NA	100	HbSS	0	100	29 mo
Virag, 1996 <sup>519</sup>	Case report/case series	Adults	26.8	6	To present 6 patients with SCD receiving a new therapeutic regimen to prevent the occurrence and recurrence of priapism	NA	NA	100	HbSS (83.3%), HbSC (16.7%)	0	100	13 mo
Vishwanathan, 1984 <sup>520</sup>	Case report/case series	Adults	19	1	To report a case of salmonella splenic abscess with SCD	1	NA	0	NR	NA	100	NA

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Wali, 2000 <sup>521</sup>	Case report/ case series	Children	13	1	To report a case of adenotonsillar hypertrophy as precipitating factor of CVA in a child with SCA	NA	NA	0	NR	NA	100	24 mo
Walker, 1983 <sup>522</sup>	Case report/ case series	40% adults	17.6	5	To describe the use of automated erythrocytapheresis in relieving priapism in sickle cell hemoglobinopathies	NA	NA	100	HbSS (80%), HbSC (20%)	NA	100	Acute (during hospitalization)
Wang, 2004 <sup>523</sup>	Case report/ case series	Adults	42	1	To describe the presentation and clinical course of a patient with HbSC who suffered an AMI	NA	NA	0	HbSC	NA	100	NR
Wang-Gillam, 2004 <sup>524</sup>	Case report/ case series	Adults	36	1	To present a case of ASSC in an adult with SCA who suddenly developed tender splenomegaly, high fever, acute anemia, thrombocytopenia, leukocytosis, jaundice, hypoxia, and tachycardia	NA	NA	100	HbSC	0	100	NR
Washington, 1985 <sup>525</sup>	Case report/ case series	Children	Range: 11–16	3	To describe conservative treatment of sickle cell AVN of the femoral head in 3 pediatric patients	NA	NA	66	HbSS	NA	100	NR
Wethers, 1987 <sup>526</sup>	Case report/ case series	50% adults	19	2	To report 2 cases of patients with SCD whose spleen function was restored to normal range after transfusion	NA	NA	0	HbSS	NA	100	Range: 2–4 mo
Wetton, 1995 <sup>527</sup>	Case report/ case series	Adults	35	1	To report a case of splenic infarction	NA	NA	100	HbSS	NA	100	2 weeks
Williams, 2007 <sup>528</sup>	Case report/ case series	Adults	48	1	To evaluate whether the activation of ACE may be an early step in the arterial VOC typical of SCD	NA	NA	0	NR	0	100	12 mo
Winter, 1979 <sup>529</sup>	Case report/ case series	90% adults	NR	5	To report a series of 5 patients with priapism that was treated by modification of creation of fistulas between glans penis and corpora cavernosa	NA	NA	100	NR	NA	80	NR

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Wolf, 2008 <sup>530</sup>	Case report/ case series	Children	12	1	To present a case of a 12-yr-old female suffering a catastrophic intracranial hemorrhage thought to be the result of a CVA secondary to her underlying SCD	NA	NA	0	HbSS	NA	100	<1 mo
Wolff, 1985 <sup>531</sup>	Case report/ case series	Adults	19	1	To report a case of orbital infarction in SCD	NA	NA	100	NR	NA	100	6 mo
Wratney, 2004 <sup>532</sup>	Case report/ case series	Children	6.83	6	To report the 1st successful HFOV management of pediatric patients suffering from severe ACS and hypoxic respiratory failure	NA	NA	67	HbSS (84%), HbSO-Arab (16%)	0	100	0.3 mo
Wu, 1999 <sup>533</sup>	Case report/ case series	Adults	50	1	To report a case of purpura as a cutaneous association of SCD	NA	NA	0	HbSS	NA	100	NA
Yang, 1990 <sup>534</sup>	Case report/ case series	Adults	20	1	To describe a case of corporectomy procedure used to treat intractable sickle-associated priapism	NA	NA	100	NA	NA	100	13 mo
Yates, 2009 <sup>535</sup>	Case report/ case series	Children	Range: 3–15	5	To report 5 cases of simultaneous ASSC and transient aplastic crisis in children with SCD	NA	NA	40	HbSS (20%), HbSC (80%)	NA	100	Patient 1: 24 mo; patient 3: 12 mo; patient 5: 1 mo; patient 2, 4: NR
Yeghen, 1995 <sup>536</sup>	Case report/ case series	Adults	21	1	To report a case of right atrial thrombosis and antiphospholipid antibody	NA	NA	100	HbSS	NA	100	8 mo
Zeltzer, 1979 <sup>537</sup>	Case report/ case series	Adults	20	2	To report 2 cases of hypnotically induced pain control in SCA	NA	NA	100	NR	NA	100	Case 1: 8 mo, case 2: 4 mo
Zempsky, 2010 <sup>538</sup>	Case report/ case series	Children	13.4	5	To review the experience of low-dose ketamine for children hospitalized with VOE	NA	Inclusion: Patients with SCD who were hospitalized for VOC pain and received ketamine at our institution between June 22, 2006, and Oct. 20, 2007	20	HbSS (80%), HbSβ-thal (20%)	0	100	NR
Ziegler, 2006 <sup>539</sup>	Case report/ case series	Children	9	1	To the clinical course of a 9-yr-old boy with necrosis of the femoral head treated with triple pelvic osteotomy	NA	NA	0	HbSS	NA	100	54

Study label	Design	Patient age group	Total population age in yr (mean)	Total number of patients in the study	What is the objective of this study?	Number and description of study arms	Describe the inclusion/exclusion criteria*	% males	Genotypes	% of patients lost to followup	% of patients with SCD in study	Followup
Zinn, 1981 <sup>540</sup>	Case report/ case series	Adults	31	1	To report a case of vitreoretinal surgery in a patient with sickle cell retinopathy	NA	NA	0	HbSC	NA	100	3 mo
Zolezzi, 2001 <sup>541</sup>	Case report/ case series	Children	7	1	To describe an adverse effect with IV codeine in a child diagnosed with SCA	NA	NA	100	NR	NA	100	<1 mo

**Table 2. Quality of Included Randomized Controlled Trials**

Study label	Blinding	Allocation concealment	Reported baseline imbalances	% of patients lost to followup	What is the source of study funding?
Adams, 1998 (Stroke Prevention Trial in Sickle Cell Anemia (STOP) <sup>1</sup>	Outcome assessors	Unclear/NR	Baseline hemoglobin and hematocrit values were slightly lower in the transfusion group	0.8	A not-for-profit organization
Miller, 2001 (STOP) <sup>31</sup>	Outcome assessors	NR	None	NR	A not-for-profit organization
Vichinsky, 2001(STOP) <sup>48</sup>	Outcome assessors	NR	None	NR	A not-for-profit organization
Lezcano, 2006 (STOP) <sup>29</sup>	Outcome assessors	NR	None	NR	A not-for-profit organization
Pegelow, 2001 (STOP) <sup>37</sup>	None/NR	No	None	NR	A not-for-profit organization
Adams, 2005 (STOP 2) <sup>2</sup>	Outcome assessors	Unclear/NR	None	(13% of continued transfusion group)	A not-for-profit organization
Adams-Graves, 1997 <sup>3</sup>	Caregivers, patients	Unclear/NR	Body weight and baseline pain scores	0	A for-profit organization
Al-Jam'a, 1999 <sup>4</sup>	Caregivers, patients	Remote randomization	None	NR	Unclear/NR
Alvim, 2005 <sup>5</sup>	Caregivers, patients	Unclear/NR	None	0	A not-for-profit organization
Barst, 2010 <sup>6</sup>	Caregivers, patients	Unclear/NR	None	NR (4 patients (2 each in ASSET 1 and 2 bosentan arms) discontinued medication)	Combined for-profit/not-for-profit organizations
Bartolucci, 2009 <sup>7</sup>	Caregivers, patients	Unclear/NR	None	NR (But 14 patients of 54 patients were excluded from analysis because of treatment failures)	A not-for-profit organization
Baum, 1987 <sup>8</sup>	NR	NR	None	7	A for-profit organization
Bellet, 1995 <sup>9</sup>	Outcome assessors, data analysts	Forced-randomization procedure of Taves	None	6.9	A not-for-profit organization
Benjamin, 1986 <sup>10</sup>	Caregivers, patients	Coded ampules	None	6 (4 patients of the original 67 patients)	Combined for-profit/not-for-profit organizations
Bernini, 1998 <sup>11</sup>	Outcome assessors, patients, caregivers	Computer-generated random assignment only accessible to pharmacist who was not involved directly in patient care	None	37 (lost to followup after discharge)	A not-for-profit organization
Cabannes, 1983 <sup>12</sup>	Caregivers, patients	Test ampoules were dispensed by the hospital pharmacist	None	NR	A for-profit organization
Charache, 1995 <sup>13</sup>	Caregivers, patients	Unclear/NR	None	NR (But at study analysis time, only 134 patients of 299 patients had finished 24-mo followup)	Combined for-profit/not-for-profit organizations

Study label	Blinding	Allocation concealment	Reported baseline imbalances	% of patients lost to followup	What is the source of study funding?
Co, 1979 <sup>14</sup>	Caregivers, outcome assessors, data collectors, patients	Sealed envelopes	None	NR	Unclear/NR
Cooperative Urea Trials Group, 1974 <sup>15</sup>	Caregivers, outcome assessors, data collectors, patients	Using sham IV canulas, administering the invert sugar solution at a rate approximating that planned for urea	None	NR	Unclear/NR
de Abood, 1997 <sup>16</sup>	None/NR	Unclear/NR	None	0	A not-for-profit organization
Eke, 2000 <sup>17</sup>	None/NR	Yes	None	NR	Combined for-profit/not-for-profit organizations
Farber, 1991 <sup>18</sup>	None/NR	Unclear/NR	None	9.5	A not-for-profit organization
Foucan, 1998 <sup>19</sup>	Patients, caregivers	Likely yes	None	4.5	Not-for-profit organizations
Fox, 1993 <sup>20</sup>	None/NR	No	None	NR	Unclear/NR
Gonzalez, 1988 <sup>21</sup>	Caregivers, patients	Unclear/NR	None	0	A for-profit organization
Gonzalez, 1991 <sup>22</sup>	None/NR	Unclear/NR	None	0	Unclear/NR
Griffin, 1994 <sup>23</sup>	Caregivers, outcome assessors, patients	Sealed opaque envelopes in computer-generated random order	Larger proportion of younger patients randomly assigned to receive methylprednisolone ( $p=.016$ )	0	A not-for-profit organization
Grisham, 1996 <sup>24</sup>	Caregivers, patients	Unclear/NR	None	0	A not-for-profit organization
Hardwick, 1999 <sup>25</sup>	Patients	Yes	None	0	Unclear/NR
Jacobson, 1991 <sup>26</sup>	None/NR	Unclear/NR	None	34.1	A not-for-profit organization
Jacobson, 1997 <sup>27</sup>	Caregivers, outcome assessors, data collectors, patients	Computer-generated blocks	Characteristics of patients were similar in the 2 groups except that 16 patients assigned oral morphine and 7 patients assigned IV morphine had findings suggestive of chest involvement or chest crisis	0	A not-for-profit organization
La Grenade, 1993 <sup>28</sup>	None	No	None	NA	A for-profit organization
McMahon, 2010 <sup>30</sup>	Data analysts	NR	NR	0	A not-for-profit organization
Myers, 1999 <sup>32</sup>	None/NR	Unclear/NR	None	25	A not-for-profit organization
Neumayr, 2006 <sup>33</sup>	None	Unclear/NR	None	0	A not-for-profit organization
Odebiyi, 2007 <sup>34</sup>	None/NR	Unclear/NR	None	NR	Unclear/NR
Opio, 1972 <sup>35</sup>	Caregivers, patients	Sealed envelopes	None	NR (1 patient was excluded)	Combined for-profit/not-for-profit organizations
Orringer, 2001 <sup>36</sup>	Caregivers, patients	Unclear/NR	None	0	A for-profit organization
Perlin, 1993 <sup>38</sup>	None/NR	Unclear/NR	None	NR (7 of 20 patients quit the study by d 3)	Combined for-profit/not-for-profit organizations
Perlin, 1994 <sup>39</sup>	Caregivers, patients	Unclear/NR	None	14	A for-profit organization
Qari, 2007 <sup>40</sup>	Caregivers, patients	Unclear/NR	None	NR	A not-for-profit organization

Study label	Blinding	Allocation concealment	Reported baseline imbalances	% of patients lost to followup	What is the source of study funding?
Robieux, 1992 <sup>55</sup>	Caregivers, patients	No	None	NR	A not-for-profit organization
Sangare, 1993 <sup>41</sup>	None/NR	Unclear/NR	None	0	A for-profit organization
Schnog, 2001 <sup>42</sup>	Caregivers, patients	Computer algorithm and use of central telephone service	None	24	A not-for-profit organization
Serjeant, 1985 <sup>43</sup>	Caregivers, patients	Allocation of tablet A or B with no information about what was in either of the tablets until the study was over	None	0	A not-for-profit organization
Serjeant, 1997 <sup>44</sup>	Patients, caregivers	NR	None	13	Combined for-profit/not-for-profit organizations
Teuscher, 1989 <sup>45</sup>	Caregivers, patients	Unclear/NR	None	5	Unclear/NR
Uzun, 2010 <sup>46</sup>	None/NR	Unclear/NR	None	NR	Unclear/NR
van Beers, 2007 <sup>47</sup>	Caregivers, outcome assessors, patients	Performed in blocks of 6 with closed envelopes	None	8	Unclear/NR
Wade, 1996 <sup>49</sup>	Patients	No	NA	0	Unclear/NR
Wang, 1988 <sup>50</sup>	Outcome assessors, patients	Assistant managed randomization and was not involved in outcome measurement	None	0	A not-for-profit organization
Weiner, 2003 <sup>51</sup>	Caregivers, patients	Unclear/NR	None	0	A not-for-profit organization
Wethers, 1994 <sup>52</sup>	Patients, caregivers, outcome assessors	NR	Randomization was performed with a 2:1 target ratio of treatment to placebo. Otherwise no significant differences	13	A for-profit organization
Wright, 1992 <sup>53</sup>	Caregivers, patients	Computer-generated randomization schedule	None	0	A not-for-profit organization
Zipursky, 1992 <sup>54</sup>	Caregivers, patients	Unclear/NR	None	NR (3 patients did not have sickle cell counts available)	A not-for-profit organization

**Table 3. Quality of Included Observational Studies (selected components of the Ottawa Newcastle scale)**

Study label	Baseline imbalances between groups	Was outcome assessment blinded?	Outcome ascertainment similar in 2 groups?	Analysis adjustment for confounding
Acurio, 1992 <sup>56</sup>	Unclear/NA	NA	NA	Unclear/NR
Adetayo, 2009 <sup>57</sup>	Unclear/NA	NR	Similar	Unclear/NR
Adeyokunnu, 1981 <sup>58</sup>	NA, single cohort	NR	NA	No
Al Hawsawi, 1998 <sup>59</sup>	Unclear/NA	No	NA	No
Al Jama, 2002 <sup>60</sup>	Unclear/NA	No	NA	Unclear/NR
Al Salem, 1996 <sup>61</sup>	Unclear/NA	NR	NA	No
Al-Abkari, 2001 <sup>163</sup>	Patients with SCD vs. non-SCD patients. Bigger sample in non-SCD group	No	Yes, similar, clinically	No
Al-Dabbous, 2002 <sup>164</sup>	Unclear/NA	NA	NA	Unclear/NR
Al-Jam'a, 2002 <sup>165</sup>	Unclear/NA	No	NA	Unclear/NR
Al-Mousawi, 2002 <sup>166</sup>	Unclear/NA	NA	NA	Unclear/NR
Al-Mulhim, 2002 <sup>62</sup>	Unclear/NA	NR	NA	No
Al-Salem, 1995 <sup>63</sup>	Unclear/NA	NR	NA	No
Al-Salem, 1996 <sup>64</sup>	Unclear/NA	NA	NA	Unclear/NR
Al-Salem, 1998 <sup>65</sup>	Unclear/NA	NR	NA	No
Al-Salem, 1999 <sup>66</sup>	Unclear/NA	NR	NA	No
Al-Salem, 1999 <sup>67</sup>	Unclear/NA	No	NA	No
Al-Salem, 2000 <sup>68</sup>	Unclear/NA	No	NA	No
Al-Suleiman, 2005 <sup>69</sup>	Unclear/NA	NR	NA	No
Alvarez, 2006 <sup>70</sup>	NR	NR	NR	NR
Ataga, 2006 <sup>167</sup>	Unclear/NA	NR	NA	No
Badaloo, 1996 <sup>222</sup>	Unclear/NA	NA	NA	Unclear/NR
Bader-Meunier, 2009 <sup>71</sup>	Unclear/NA	No	NA	No
Beiter, 2001 <sup>168</sup>	Unclear/NA	No	NA	Unclear/NR
Bernaudin, 1997 <sup>72</sup>	Unclear/NA	No	NA	No
Bhattacharya, 1993 <sup>73</sup>	Unclear/NA	NA	NA	Unclear/NR
Bishop, 1988 <sup>74</sup>	Unclear/NA	NA	NA	Unclear/NR
Bodhise, 2004 <sup>169</sup>	Unclear/NA	NR	NA	No
Bond, 1987 <sup>170</sup>	Unclear/NA	NR	NA	Age and African and Caribbean origin
Booz, 1999 <sup>171</sup>	Unclear/NA	NR	NA	No

Study label	Baseline imbalances between groups	Was outcome assessment blinded?	Outcome ascertainment similar in 2 groups?	Analysis adjustment for confounding
Brookoff, 1992 <sup>75</sup>	Unclear/NA	NR	Similar	Unclear/NR
Brousse, 2009 <sup>76</sup>	Primary prevention group had no history of stroke and were followed up for 14.3 mo, while secondary prevention group had history of stroke and were followed up for 59.6 mo	No	Yes, similar, clinically	Unclear/NR
Brousseau, 2004 <sup>172</sup>	Unclear/NA	Not blinded	NA	No
Buchanan, 1989 <sup>77</sup>	No, quite similar	No	Yes, similar, clinically	No
Buchann, 2005 <sup>78</sup>	Patients receiving morphine were more likely to have higher white cell counts on admission ( $p<.05$ ), and to use continuous intravenous (CIV) infusion for medication administration (49% vs. 3%), $p<.001$ . They also had longer hospital stays than patients who received nalbuphine (median stay 3 d vs. 4 d, morphine), $p<.001$ . Although the mean presenting pulse oximetry readings were not significantly different, more patients receiving nalbuphine had pulse oximetry levels $<95\%$ . Patients receiving nubain upon admission had more medication changes during the hospital stay (12% vs. 3% for the morphine group, $p=.04$ )	NR	Similar	Use of CIV, increased pain scores, elevated white cell count, lower hemoglobin level, and younger age
Cackovic, 1998 <sup>79</sup>	NA	No	NA	NR
Castro, 2003 <sup>80</sup>	Unclear/NA	No	NA	No
Chaplin, 1989 <sup>173</sup>	No, quite similar	No	Yes, similar, patient-reported+clinically	No
Charache, 1979 <sup>81</sup>	Unclear/NA	NR	NA	No
Christensen, 1996 <sup>174</sup>	Unclear/NA	NR	NA	Body weight
Clarke, 1989 <sup>82</sup>	Unclear/NA	NA	NA	Unclear/NR
Cole, 1986 <sup>83</sup>	Unclear/NA	NR	NA	No
Conti, 1996 <sup>223</sup>	Unclear/NA	NA	NA	Unclear/NR
Couillard, 2007 <sup>84</sup>	Unclear/NA	NR	NA	No
Crawford, 2004 <sup>85</sup>	NA	NR	NA	No
Crawford, 2006 <sup>86</sup>	No, quite similar	NR	Similar	No
Curro, 2006 <sup>87</sup>	No, quite similar	No	Yes, similar, clinical	No
Curro, 2007 <sup>88</sup>	No, quite similar	NR	Similar	No
Daltro, 2008 <sup>175</sup>	Unclear/NA	NR	NA	No
de Montalembert, 1997 <sup>176</sup>	Unclear/NA	NR	NA	To limit the influence of age, results were expressed as standard deviation
de Montalembert, 2004 <sup>89</sup>	Unclear/NA	NR	NA	No
Delatte, 1999 <sup>90</sup>	Unclear/NA	NA	NA	Unclear/NR

Study label	Baseline imbalances between groups	Was outcome assessment blinded?	Outcome ascertainment similar in 2 groups?	Analysis adjustment for confounding
Dinges, 1997 <sup>177</sup>	Unclear/NA	NR	NA	No
Duncan, 1992 <sup>91</sup>	Unclear/NA	NR	NA	No
Duncan, 2000 <sup>224</sup>	Unclear/NA	NR	NA	No
Dunn, 1995 <sup>92</sup>	Unclear/NA	No	NA	Unclear/NR
Ebong, 1977 <sup>93</sup>	Unclear/NA	NR	NA	Unclear/NR
Ebong, 1986 <sup>94</sup>	Unclear/NA	NR	NA	Unclear/NR
El-Beshlawy, 2006 <sup>178</sup>	Unclear/NA	NR	NA	No
Emre, 1993 <sup>95</sup>	Unclear/NA	Unclear/NA	No	Multivariate analysis used but unclear adjustment
Emre, 1995 <sup>179</sup>	Unclear/NA	NR	NA	No
Enniful-Eghan, 2010 <sup>96</sup>	Unclear/NA	No	Yes	No
Finkelstein, 2007 <sup>97</sup>	Unclear/NA	NR	Similar	No
Frei-Jones, 2008 <sup>98</sup>	Unclear/NA	NR	NA	No
Gholson, 1995 <sup>99</sup>	Unclear/NA	No	NA	Unclear/NR
Gibson, 1979 <sup>100</sup>	Unclear/NA	NR	NA	No
Gill, 1995 <sup>180</sup>	Unclear/NA	No	NA	Unclear/NR
Gill, 2000 <sup>181</sup>	Unclear/NA	No	NA	Multivariable regression used but unclear adjustment
Grover, 1990 <sup>182</sup>	Unclear/NA	NA	NA	Unclear/NR
Hankins, 2005 <sup>101</sup>	Unclear/NA	NR	NA	No
Hassel, 1994 <sup>102</sup>	Unclear/NA	No	NA	Unclear/NR
Hernigou, 1993 <sup>183</sup>	Unclear/NA	NA	NA	Unclear/NR
Hernigou, 2003 <sup>103</sup>	Unclear/NA	NR	NA	Unclear/NR
Hernigou, 2008 <sup>104</sup>	Unclear/NA	NR	NA	No
Hijazi, 2005 <sup>105</sup>	No, quite similar	No	Yes	No
Holbrook, 1990 <sup>106</sup>	Unclear/NA	NR	Similar	No
Hulbert, 2006 <sup>107</sup>	Unclear/NA	NR	Similar	Unclear/NR
Ilyas, 2002 <sup>184</sup>	Unclear/NA	NA	NA	Unclear/NR
Isakoff, 2008 <sup>108</sup>	Unclear/NA	NR	NA	No
Jacob, 2003 <sup>185</sup>	Unclear/NA	NR	NA	NR
Jayabose, 1996 <sup>186</sup>	Unclear/NA	NR	NA	No
Kalff, 2010 <sup>109</sup>	NA	No	1 cohort	No
Khosla, 1984 <sup>187</sup>	Unclear/NA	NR	NA	No

Study label	Baseline imbalances between groups	Was outcome assessment blinded?	Outcome ascertainment similar in 2 groups?	Analysis adjustment for confounding
Kimmel, 1986 <sup>188</sup>	Unclear/NA	NA	NA	Unclear/NR
King, 1996 <sup>110</sup>	No, quite similar	NR	NR	Unclear/NR
Kinney, 1990 <sup>111</sup>	Unclear/NA	No	Yes, similar, clinically	No
Koch, 2008 <sup>189</sup>	Unclear/NA	NR	NA	No
Koren, 1990 <sup>225</sup>	Patients with SCD vs. non-SCD (healthy) controls	No	Yes, similar, clinically	Unclear/NR
Kumar, 2010 <sup>112</sup>	Prednisone was used more frequently in patients with moderate or severe acute chest syndrome (ACS) at diagnosis. Oxygen saturation was significantly lower in patients treated with prednisone and slightly lower in those transfused	NR	Similar	Use of hydroxyurea (HU)
Lawrence, 1980 <sup>113</sup>	Unclear/NA	Not blinded	NA	No
Leandros, 2000 <sup>114</sup>	No, quite similar	NR	NR	Unclear/NR
Leshner, 2009 <sup>115</sup>	Unclear/NA	NR	NA	No
Liem, 2004 <sup>190</sup>	Unclear/NA	NR	NA	No
Little, 2006 <sup>116</sup>	NR	NR	NR	NR
Machado, 2005 <sup>191</sup>	Unclear/NA	NR	NA	No
Mantadakis, 2000 <sup>192</sup>	Unclear/NA	No	NA	Unclear/NR
McCarthy, 2000 <sup>117</sup>	Unclear/NA	No	NA	No
McCurdy, 1971 <sup>193</sup>	Unclear/NA	NR	NA	No
McKie, 2007 <sup>194</sup>	No	NR	Yes	No
McPherson, 1990 <sup>195</sup>	Unclear/NA	NR	NA	No
Melzer-Lange, 2004 <sup>196</sup>	Unclear/NA	NR	NA	No
Meshikhes, 1995 <sup>197</sup>	Unclear/NA	NA	NA	Unclear/NR
Meshikhes, 1998 <sup>118</sup>	Unclear/NA	NR	NA	No
Minniti, 2009 <sup>119</sup>	Unclear/NA	NR	NA	No
Moran, 1993 <sup>198</sup>	Unclear/NA	NA	NA	Unclear/NR
Morris, 2003 <sup>199</sup>	Control group was healthy volunteers	Yes	No, control group was made of healthy volunteers, who did not undergo as much testing	Unclear/NR
Mukisi-Mukaza, 2009 <sup>120</sup>	No, quite similar	Not blinded	NA; no comparison group	No
Muneer, 2009 <sup>121</sup>	Unclear/NA	NR	NA	Unclear/NR
Ojo, 1999 <sup>122</sup>	Unclear/NA	No	NA	Human leukocyte antigen mismatch, sex of donor, sex of recipient, race of donor
Okany, 2004 <sup>200</sup>	NR	No	Yes, clinical	NR

Study label	Baseline imbalances between groups	Was outcome assessment blinded?	Outcome ascertainment similar in 2 groups?	Analysis adjustment for confounding
Pashankar, 2009 <sup>542</sup>	NA	NR	NA	No
Pegelow, 2002 <sup>202</sup>	Unclear/NA	NA	NA	Unclear/NR
Plummer, 2006 <sup>123</sup>	Unclear/NA	NR	NA	No
Poflee, 1991 <sup>203</sup>	No, quite similar	NR	NR	No
Powell, 1992 <sup>124</sup>	Unclear/NA	NA	NA	Unclear/NR
Rachid-Filho, 2009 <sup>125</sup>	No, quite similar	NR	NR	No
Rambo, 1986 <sup>126</sup>	Unclear/NA	NR	NA	No
Rao, 1985 <sup>127</sup>	Unclear/NA	NR	NA	No
Raphael, 2008 <sup>128</sup>	Unclear/NA	Unclear	Unclear	Sickle cell type, pain score, and age
Rezende, 2009 <sup>129</sup>	No, quite similar	No	Similar	No
Robieux, 1992 <sup>55</sup>	Unclear/NA	No (except for the randomized control trial (RCT) portion)	Yes, similar, clinical	No
Rombos, 2002 <sup>204</sup>	Unclear/NA	NA	NA	Unclear/NR
Rudolph, 1992 <sup>130</sup>	Unclear/NA	NR	NA	No
Salamah, 1989 <sup>131</sup>	Unclear/NA	NR	NA	No
Samal, 1997 <sup>205</sup>	NA	No	NA	NR
Sandoval, 2002 <sup>132</sup>	Patients undergoing splenectomy only were younger than those undergoing cholecystectomy (median age, 3.6 yr vs. 11.5 yr, respectively)	No	Yes, similar, clinically	No
Sangare, 1990 <sup>206</sup>	Unclear/NA	No	NA	No
Sanjay, 1996 <sup>133</sup>	Unclear/NA	NA	NA	Unclear/NR
Santos, 2002 <sup>207</sup>	Unclear/NA	NA	NA	Unclear/NR
Sartori, 1990 <sup>134</sup>	Unclear/NA	NR	NA	No
Sayag, 2008 <sup>208</sup>	No, quite similar	No	Yes, similar, clinical	No
Scothorn, 2002 <sup>135</sup>	Unclear/NA	NR	Similar	Unclear/NR
Seguier-Lipszyc, 2001 <sup>136</sup>	Unclear/NA	NR	NA	No
Seleem, 2005 <sup>209</sup>	Unclear/NA	NR	NA	No
Serjeant, 1970 <sup>210</sup>	NR	No	Yes, clinical	NR
Serjeant, 1994 <sup>211</sup>	Unclear/NA	NA	NA	Unclear/NR
Shapiro, 1993 <sup>137</sup>	Unclear/NA	NR	NA	No
Sobota, 2009 <sup>138</sup>	Unclear/NA	NR	Similar	Yes
Sporrer, 1994 <sup>212</sup>	Unclear/NA	NR	NA	Multiple comparisons

Study label	Baseline imbalances between groups	Was outcome assessment blinded?	Outcome ascertainment similar in 2 groups?	Analysis adjustment for confounding
Sprinkle, 1986 <sup>139</sup>	Unclear/NA	NR	NA	No
Srair, 1995 <sup>213</sup>	Unclear/NA	NR	NA	No
Steinberg, 2003 <sup>501</sup>	Unclear/NA	NR	NA	Unclear/NR
Strouse, 2006 <sup>140</sup>	Cases were significantly older than controls (10.4±1.3 vs. 5.2±0.4; $p<.0001$ ). History of hypertension more common in cases (20%) than controls (0%, $p<.05$ ) and frequency of hospitalization for painful crisis over last year was greater for cases than for controls, $p<.05$	Not blinded	Yes, similar, medical record extraction	No
Strouse, 2008 <sup>226</sup>	Unclear/NA	NA	NA	Patient characteristics and the duration of hospitalization
Styles, 1996 <sup>141</sup>	Unclear/NA	NR	NA	No
Subbannan, 2009 <sup>142</sup>	Patients in the splenectomy group were more likely to have splenomegaly, lower median hemoglobin levels and platelet counts, develop ACS, require cholecystectomy, and receive HU treatment	NR	Similar	Patients in the splenectomy group were more likely to have splenomegaly, lower median hemoglobin levels and platelet counts, and develop ACS
Sumoza, 2002 <sup>214</sup>	Unclear/NA	NR	NA	No
Svarch, 1996 <sup>143</sup>	Unclear/NA	NR	NA	No
Svrach, 2003 <sup>144</sup>	Unclear/NA	NR	NA	No
Tagge, 1994 <sup>145</sup>	The patients undergoing open cholecystectomy were fewer (8) than those undergoing laparoscopic procedure	Not blinded	Yes, similarly	Unclear/NR
Taylor, 2004 <sup>146</sup>	NA	No	NA	No
Telfer, 2009 <sup>215</sup>	Unclear/NA	NR	Similar	Unclear/NR
Thomas, 1984 <sup>216</sup>	Unclear/NA	No	Yes, similar, clinical	No
Topley, 1981 <sup>217</sup>	NR	NR	NR	NR
Trentadue, 1998 <sup>147</sup>	No, quite similar	No	Yes, similar, clinically	Unclear/NR
Turner, 2009 <sup>148</sup>	No, quite similar	NR	Similar	No
Udezue, 2007 <sup>218</sup>	Unclear/NA	No	Yes, similar, clinical	No
Van Agtmael, 1994 <sup>149</sup>	Unclear/NA	NR	NA	No
Velasquez, 2009 <sup>150</sup>	Unclear/NA	NR	NR	No
Vichinsky, 2000 <sup>48</sup>	Unclear/NA	NR	NA	Multivariate analysis used but unclear all adjustments
Wales, 2001 <sup>151</sup>	No, quite similar	NR	Similar	No
Warady, 1998 <sup>152</sup>	Unclear/NA	No	NA	No
Ware, 1988 <sup>153</sup>	Unclear/NA	No	NA	Unclear/NR
Ware, 1992 <sup>154</sup>	Unclear/NA	NR	NA	Unclear/NR

Study label	Baseline imbalances between groups	Was outcome assessment blinded?	Outcome ascertainment similar in 2 groups?	Analysis adjustment for confounding
Ware, 1992 <sup>543</sup>	Unclear/NA	NA	NA	Unclear/NR
Ware, 1999 <sup>221</sup>	Unclear/NA	NR	NA	No
Ware, 2004 <sup>220</sup>	Unclear/NA	No	NA	No
Wilimas, 1980 <sup>155</sup>	Unclear/NA	NR	NA	No
Williamson, 2009 <sup>156</sup>	Some had type 2 diabetes, pregnant, all with varying duration of symptoms and disorders	No	No	No
Winter, 1994 <sup>157</sup>	Unclear/NA	NA	NA	Unclear/NR
Winter, 1997 <sup>158</sup>	Unclear/NA	NR	NA	Unclear/NR
Woods, 1990 <sup>159</sup>	No, quite similar	NR	Similar	No
Wright, 1999 <sup>227</sup>	Prophylaxis against infection continued for longer in the splenectomy group compared to control	NR	Yes	Age at event and patient sex
Wu, 2005 <sup>160</sup>	Unclear/NA	NR	NA	No
Yaster, 1994 <sup>161</sup>	NA	NR	NA	No
Zempsky, 2008 <sup>162</sup>	Unclear/NA	NR	NA	Age

**Table 4. Acute Chest Syndrome Incidence and Outcomes**

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Bernini, 1998 <sup>11</sup>	RCT	Acute chest syndrome (ACS) is defined as the presence of a new pulmonary infiltrate and 2 or more of the following: fever, tachypnea, dyspnea, retractions, nasal flaring, grunting, or chest pain	Clinical examination/investigations	Corticosteroid, dexamethasone	22	100	Dexamethasone, 0.3 mg/kg of body weight intravenously (IV) in 20 mL in of normal saline on admission and 12, 24, and 36 h after the 1st dose. Drug was infused over 30 min	4 doses of the drug or resolution of symptoms, whichever came first	Placebo controlled	21	100	Patients received an equivalent volume of normal saline (as dexamethasone) on the same schedule. All syringes were labeled "steroid study drug" and it was infused over 30 min	Mean hospital stay was shorter in the dexamethasone-treated group (47 h vs. 80 h; $p=.005$ ). Dexamethasone therapy prevented clinical deterioration and reduced the need for blood transfusions ( $p<.001$ and $=.013$ , respectively). Mean duration of oxygen and analgesic therapy, number of opioid doses, and the duration of fever were also significantly reduced in the dexamethasone-treated patients. Of 7 patients readmitted within 72 h after discharge (6 after dexamethasone; $p=.095$ ), only 1 had respiratory complications ( $p=1.00$ ). No side effects clearly related to dexamethasone were observed. In a stepwise multiple linear regression analysis, gender and previous episodes of ACS were the only variables that appeared to predict response to dexamethasone, as measured by length of hospital stay
Al-Suleiman, 2005 <sup>69</sup>	R, Obs	A spectrum of pulmonary pathology, which can include common chest pain, fever, cough, and dyspnea with abnormal clinical and radiological chest signs	Clinical presentation, a significant increase in leukocytes, and a significant decrease in hemoglobin	Transfusion, admission to intensive care unit (ICU) (19%), and mechanical ventilator (12%)	135	100	Simple blood transfusion was required in 44% and exchange transfusion in 5%	The mean duration of admission was $8.5\pm 5$ d	No	NA	NA	NA	ACS was associated with painful crisis of varying intensity in >90% of the patients. Bacteremia was found only in 4.2%. 13 patients died during an attack of ACS (9.6%)

\* When the exact time in hospital was not clear in the articles and the treatment was short or one-time, "acute" or "acutely" were used as the "Duration of treatment."

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Buchanan, 2005 <sup>78</sup>	R, Obs	The final discharge diagnosis of ACS for the purpose of this study was defined as a new pulmonary infiltrate on chest radiograph after admission and before discharge	ACS status was recorded in the medical records but if the chest x-ray report was not available in the chart, radiology records were reviewed for confirmation. All chest x rays were reviewed and the final report signed by an attending radiologist	Nubain for pain relief	86	Nubain (12.7%)	NR	Mean hospital stay was 4.1 d, range: 1–15 d	Morphine for pain relief	89	Morphine group (29%)	NA	There were a total of 37 (21%) episodes of ACS. Of these, 26 (29%) were in the morphine group and 11 (12%) were in the Nubain group ( $p<.01$ ). Patients receiving morphine were more likely to have higher white cell counts on admission ( $p<.05$ ), and to use continuous intravenous (CIV) infusion for medication administration (49% vs. 3%), $p<.001$ . They also had longer hospital stays than patients who received Nubain (median stay 3 d vs. 4 d, morphine), $p<.001$
Charache, 1979 <sup>81</sup>	R, Obs	ACS describes the combination of chest pain, fever, increased leukocytosis, and appearance of a new shadow on chest x-ray films	Chest roentgenograms showed no infiltrate at illness onset in 13/52 episodes. In 29 episodes, patients had 1 lobe involved; in 19 episodes 2 lobes were involved; and in 4 episodes, 3–4 lobes were involved. No patient had an infiltrate confined to an upper lobe of the lung. Arterial pO <sub>2</sub> ranged from 46 to 73 mmHg	Antibiotics	28	100	NR	NR	No	NA	NA	NA	1 patient died. Bacterial pathogens were identified in sputum cultures from less than half of the episodes; no pneumococci were found, and only Staphylococcus aureus was associated with a longer illness (duration of fever and hospital stay) compared to patients with normal flora. Excluding 1 patient with intermittent fever in each group, duration of fever did not differ between patients who did or did not receive antibiotics (5.2 vs. 4.3 d)

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Crawford, 2004 <sup>85</sup>	R, Obs	The diagnosis of ACS was based on the following criteria: (1) radiographic evidence of a new pulmonary infiltrate that involved at least 1 complete lung segment and was consistent with the presence of alveolar consolidation but excluding atelectasis; (2) a temperature >38.0°C; and (3) respiratory symptoms	Chest radiographs	Therapy for ACS included the administration of supplemental oxygen, IV antibiotics, opioid analgesics, chest physiotherapy, and incentive spirometry in all cases. The onset of ACS was associated with a reduction in hemoglobin concentration (mean reduction, 15.1±8.9 g·L <sup>-1</sup> ; <i>p</i> <.05). This was treated with simple transfusion in 2 patients and exchange transfusion in 1	16	100	Supplemental oxygen, IV antibiotics, opioid analgesics, chest physiotherapy, and incentive spirometry	The duration of oxygen therapy was 5±1 d	No	NA	NA	NA	1 patient with unilateral involvement who was transfused preoperatively required nasal bilevel positive airway pressure for 48 h in the ICU. The overall mean length of postoperative hospitalization was 9 d (range: 5–13 d). No positive sputum, blood, or urine cultures were documented. There were no vaso-occlusive crises (VOCs) or other postoperative complications of sickle cell disease (SCD) and no deaths attributed to ACS
Delatte, 1999 <sup>90</sup>	R, Obs	Defined as the presence of a new pulmonary infiltrate, confirmation of ACS is by radiographic investigation in a patient with clinical suspicion of ACS	Clinical exam/investigations	Prophylactic antimicrobial treatment, transfusions, incentive spirometry, additional pulmonary therapy	19	100	Cefotaxime, erythromycin: dose not specified	Mean: 6.1 d, range: 3–11 d	No	NA	NA	NA	Preoperatively, all 6 patients received oxygen saturation monitoring and intravenous fluid (IVF) hydration. 3 patients required transfusion to achieve hemoglobin levels of >10 mg/dL. All patients received postoperative oxygen supplementation and IVF hydration. Onset of ACS ranged from 1 to 7 h postoperatively. 1 of 6 was of microbial etiology, but all 6 received antimicrobial therapy and aggressive pulmonary therapy. Overall length of hospitalization was increased with average stay of 6.1 d. There were no postoperative ACS deaths

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Emre, 1993 <sup>35</sup>	R, Obs	Defined as the presence of fever and either clinical symptoms and signs of lung disease, new abnormalities on chest radiographs, or both	Electrophoretic analysis	NA	37	100%	NA	NA	No	NA	NA	NA	Conclusion: Alveolar-arterial (A-a) oxygen partial pressure (PO <sub>2</sub> ) gradient was the strongest predictor of ACS clinical course and for the need of transfusion
Finkelstein, 2007 <sup>97</sup>	R, Obs	ACS is defined by the appearance of new pulmonary infiltrates, hypoxemia, fever ( $\geq 38^{\circ}\text{C}$ ), and respiratory symptoms such as cough, tachypnea, and chest pain	Clinical or radiographic manifestations	Morphine for pain associated with VOC	17	100	Morphine was administered as a CIV drip, with a typical initial rate of 10 $\mu\text{g}/\text{kg}/\text{h}$ , and dose escalation and the need for additional rescue doses are determined following assessment of patient response	Length of pain while hospitalized	Same patients, when hospitalized and didn't develop ACS (reference)	100	17	Morphine was administered as a continuous drip, with a typical initial rate of 10 $\mu\text{g}/\text{kg}/\text{h}$ , and dose escalation and the need for additional rescue doses are determined following assessment of patient response	As expected, index hospitalizations (hospitalization in which the patient developed ACS) were longer than reference hospitalizations (hospitalization in which the patient did not develop ACS). Site of pain included chest ( $n=3$ for both hospitalizations), back ( $n=4$ for both hospitalizations), abdomen ( $n=5$ in index hospitalization and $n=3$ in reference hospitalization), and limbs ( $n=5$ in index hospitalization and $n=7$ in reference hospitalization). The index hospitalization occurred after the reference hospitalization for 10 patients; for 7 patients, the index hospitalization preceded the reference hospitalization, and of these 7 patients, 3 were treated with oral hydroxyurea (HU) (20–30 mg/kg/d) at the time of reference hospitalization, and none had received blood transfusion in the 3 preceding mo. The median time interval between index and reference hospitalizations was 2 mo (interquartile range: -0.8 to +0.7 yr). Mean (standard deviation (SD)) index interval was 46 (20) h (range: 12–78 h). The mean (SD) cumulative dose of morphine during the index interval was 1.24 (0.60) and 1.44 (0.84) mg/kg during the reference interval. The mean (SD) morphine infusion rate was 28.6 (10.0) $\mu\text{g}/\text{kg}/\text{h}$ during index hospitalizations, as compared with 31.4 (12.8) $\mu\text{g}/\text{kg}/\text{h}$ during reference hospitalizations, and the mean (SD) total cumulative morphine dose throughout all reference hospitalizations was 3.3 (1.8) mg/kg

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Hankins, 2005 <sup>101</sup>	R, Obs	ACS was defined by the appearance of a new infiltrate with consolidation on a chest radiograph, along with respiratory symptoms, fever, or both	Chest radiograph	Chronic transfusion therapy (CTX)	27	100	HU therapy was instituted gradually over a period of 4 mo, during which time transfusions were discontinued after gradual reduction of packed erythrocytes by 5 mL/kg/mo. In parallel with the progressive reduction of the volume transfused, HU doses were escalated each 8 weeks, from 20 mg/kg/d to 30 mg/kg/d. Packed red blood cells (PRBCs) or erythrocytapheresis was performed approximately every 4 weeks with the goal of maintaining a re-transfusion sickle cell hemoglobin (HbS) concentration <50%. All patients received PRBC units cross-matched for C, E, and Kell antigens	Acute	No	NA	NA	NA	Before the initiation of CTX, patients experienced an incidence of 1.3 episodes of ACS per patient-yr. The incidence of ACS episodes decreased to 0.1/patient-yr during CTX ( $p < .0001$ ). The median severity score for the 8 patients who experienced episodes of ACS during CTX was 0.8 (range: 0–5) before the initiation of CTX and 0.5 (range: 0–3) during CTX ( $p = .84$ ). The median hospital stay for ACS before the initiation of CTX was 5 d (range: 3–15 d). 8 of the 27 patients experienced ACS episodes during CTX. The median hospital stay during CTX was 3 d (range: 2–7 d) and was not significantly different ( $p = .38$ )

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Isakoff, 2008 <sup>108</sup>	R, Obs	A new infiltrate on x ray together with 1 or more associated findings, including tachypnea, fever $\geq 38.5$ , chest pain, cough, or wheezing. In addition, the episode was considered to be severe if the patient also developed hypoxemia with a room air oxygen saturation by pulse oximetry of at least 5% below baseline and hemoglobin decrease of $>1$ g/dL from baseline	All patients with SCD with the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for pneumonia 486.0 and ACS 517.3. We included the ICD-9 code for pneumonia in our initial screen in an effort to avoid missing patients with severe ACS as the ACS ICD-9 code was not regularly used in our institution before 2003	Usual care + corticosteroids	31	100	Dexamethasone 0.3 mg/kg/dose IV every 12 h for a total of 4 doses. Simple and exchange transfusion. For simple transfusions, 10–15 mL/kg of PRBCs were administered to reach goal hemoglobin of 10.0 g/dL. For exchange transfusions, 10–15 mL/kg of whole blood was removed, followed by the delivery of 15–25 mL/kg of PRBCs to reach a hemoglobin of 10.0 g/dL and an HbS of 30%	Length of hospital stay (median: 4.9 d)	No	NA	NA	NA	48 of the episodes were treated with simple transfusions and 5 episodes were treated with an exchange transfusion. The patients who were treated by exchange transfusion were noted by the attending to have more rapidly progressive disease; however, because of the retrospective nature of this review, the exact criteria used to determine severity could not be determined in most cases. 1 patient developed bleeding from a previously diagnosed gastric ulcer and no patients developed a severe life-threatening complication, including no episodes of hemorrhagic stroke. The average hospital duration overall was 4.9 d and 4.2 d for patients diagnosed with ACS in the first 24 h
Kalff, 2010 <sup>109</sup>	R, Obs	ACS not defined. The indications for enrolment were recurrent painful crises, ACS, silent cortical ischemia, pulmonary hypertension, multiorgan crises and pregnancy.	NR	Erythrocytapheresis, HU	13	100	HU used on 2 patients. Dose NR Automated red cell exchange (RCE), at an initial frequency of 4 weeks, and subsequently at 4–6 weeks	65–119 mo	No	NA	NA	NA	No patient experienced stroke, multi-organ crises or developed new and/or progression of end-organ dysfunction. Regular erythrocytapheresis reduced HbS levels to the target of $<30\%$ immediately postexchange. Alloimmunization rates were comparable to the literature and erythrocytapheresis was effective in preventing progressive iron overload

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King, 1996 <sup>110</sup>	R, Obs	Presence of fever, pulmonary pathology, and abnormal chest radiograph	Mean hemoglobin (standard error (SE)) was 8.4 g/dL (0.5) in the simple transfusion group and 7.3 g/dL (0.4) in the exchange transfusion group. Respiratory distress score for the simple transfusion group was 1.5 (0.22) and for the exchange transfusion group was 1.9 (0.11). The mean pediatric risk of mortality (PRISM) score was 3.3 (0.5) in the simple transfusion group and 5.4 (1.2) in the exchange transfusion group. 30% of patients in the simple transfusion group and 77% of patients in the simple transfusion group had pleural effusions	Simple transfusion	10 episodes (Patient N unclear)	100	Simple transfusion	NR	Exchange transfusion	9 episodes (Patient N unclear)	100	Exchange transfusion	Length of hospital stay was similar in both groups (11.9 d in simple transfusion vs. 11.8 in the exchange transfusion). 2/10 (20%) patients needed mechanical ventilation in the simple transfusion group vs. 5/9 in the exchange transfusion group ( $p=.11$ ). ICU stay was significantly longer in the exchange transfusion group compared to the simple transfusion group (5.6 d vs. 2.6 d for simple transfusion patients, $p=.03$ )
Kumar, 2010 <sup>112</sup>	R, Obs	ACS is defined as the presence of acute pulmonary findings in an individual with SCD	A diagnosis of ACS required a new pulmonary infiltrate in a patient who had at least 2 of the following symptoms: fever, wheezing, tachypnea, chest pain, or cough	Prednisone	53	100	15/53 patients received a blood transfusion while in the hospital	NR	Patients admitted for ACS who did not receive prednisone	25	100	Usual care	Group 1: Duration of hospitalization: 3.8 d, 8 (15.1%) patients were readmitted within 2 weeks. Group 2: Duration of hospitalization: 3.1 d, 2 (8.3%) patients were readmitted within 2 weeks

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Sobota, 2009 <sup>138</sup>	R, Obs	They defined ACS as an ICD-9 discharge diagnosis of sickle cell crisis (282.62, 282.64, 282.42, or 282.69) plus either ACS (517.3) or pneumonia (486, 481, 483.0, 480.8, or 482.8)	NR	Corticosteroids	874 (admissions)	100	Corticosteroids	NR	No steroids	4,373 (admissions)	100	No corticosteroid treatment while hospitalized for ACS	Group 1: The length of stay (LOS) in hospital was 8.0 d. (In the adjusted model, corticosteroids were associated with a 25% increase in LOS (95% confidence interval (CI): 14–38%). There were 38 readmissions within 72 h (4.4%). After adjusting for propensity score, the odds ratio for readmission with corticosteroids was 2.3 (95% CI: 1.6–3.4). Group 2: The LOS in hospital was 5.2 d. There were 83 (1.9%) readmissions in the noncorticosteroid group
Sprinkle, 1986 <sup>139</sup>	R, Obs	Symptoms and clinical signs of ACS associated with radiographic evidence of pulmonary infiltration, pleural effusion, or pulmonary edema	Clinical presentation, chest x ray	Antibiotics, transfusion	57 (100 cases)	100	Antibiotics were mostly beta lactam agents. PBRCs—50 transfusions during 26 admissions. 16 of 26 patients had experienced a decline in hemoglobin (mean 1.6 g/dL below admission value) before transfusion. Partial exchange transfusions—2 patients, with no great benefit	Median hospital stay for those diagnosed with ACS at admission: 5 d. Median hospital stay for those diagnosed after admission: 7 d. (Patients treated with narcotics had longer hospital stays: 7 d vs. 4 d)	No	NA	NA	NA	There were 2 deaths and 1 major neurological complication

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Strouse, 2008 <sup>226</sup>	R, Obs	A new pulmonary infiltrate (on the final radiology report) and 2 or more of the following: chest, upper abdominal, or rib pain; dyspnea; fever; tachypnea; grunting; nasal flaring; or retractions	Clinical evaluation + labs and images	39 episodes were treated with corticosteroids and 51 with transfusions	65 patients (129 episodes)	100 (only ACS cases were included)	Treated with corticosteroids (dexamethasone in 33 (0.3 mg/kg every 12 h in 30, with 25 receiving exactly 4 doses), prednisone in 5 (1 mg/kg/d in 2 and 2 mg/kg/d in 3 for 1–6 d), and prednisolone 2 mg/kg/d for 3 d in 1). 51 were treated with transfusions (13 with exchange mostly (62%) for severe ACS)	Not clearly reported	No	NA	NA	NA	Patients were readmitted within 14 d after 23 episodes (18%). Readmission was strongly associated with report of an inhaler or nebulizer at home (odds ratio (OR) 6.0, $p < .05$ ), diastolic blood pressure (DBP) at 48 h (OR 1.8 per 10 mm increase, $p < .01$ ), corticosteroids (OR 20, $p < .005$ ), or transfusion (OR 0.03, $p < .05$ ). Treatment with corticosteroids alone ( $p < .05$ ) and older age ( $p < .001$ ) were associated with longer hospitalization
Taylor, 2004 <sup>146</sup>	R, Obs	Lower respiratory tract symptoms and new pulmonary infiltrates on chest x ray	Clinical + chest x ray	NR	45 (63 presentations)	100	NR	During hospitalization	No	NA	NA	NA	The average LOS was 10 d (range: 3–35 d) with 60% of patients staying >8 d. Male patients on average were hospitalized longer than their female counterparts (mean male LOS: 11.4 d, and female LOS: 9.7 d). 5 patients died giving an in-hospital mortality rate of 7.9%
Turner, 2009 <sup>148</sup>	R, Obs	NR	To be included, patients had to have been consulted on by a hematologist experienced in sickle cell disorders who agreed with the diagnosis of ACS and was involved in the therapeutic decision	Exchange transfusion. The mean number of units transfused for the exchange transfusion group was 10.3±3	20	100	All patients in each cohort received antibiotics. HU use was 40% in the exchange transfusion group and 45% in the simple transfusion group, transfusion was the treatment	Postprocedure LOS: exchange transfusion 5.6±4.1 d vs. simple transfusion 5.9±4.3 d. Total LOS: exchange transfusion 8.4±4.1 d vs. simple transfusion 8.0±4.1 d	Simple transfusion	20	100	Simple transfusion, mean number of units transfused for simple transfusion group was 2.4±1.2	Among the 11 exchange transfusion-only cohort, the mean preexchange transfusion level was 7.8±1.5g/dL. After the procedure, the exchange transfusion group had higher peak Hb levels than did the simple transfusion group (10.4±1.4 g/dL vs. 9.3±1.0 g/dL, $p \leq 0.01$ ) as well as a higher discharge Hb level (9.6 ±1.5 g/dL vs. 8.7±1.2 g/dL, $p = .03$ )

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Van Agtmael, 1994 <sup>149</sup>	R, Obs	ACS refers to sudden episodes of respiratory distress in patients with SCD	Only patients with at least 2 of 3 characteristics (chest pain, temperature >38°C, and clinical tachypnea, crepitations, rhonchi, or decreased breath sounds) or radiologic evidence of pulmonary infiltrates) were diagnosed as having ACS (prevalence—42% of the SCD population)	Rehydration, meperidine, oxygen, IV heparin, and transfusion	53	100	<p>Rehydration—mean, 3.8 L/24 h; analgesia—42% patients required meperidine; supplemental oxygen was given in 87% of the episodes (mean, 5 L/min); IV heparin was given to 78% of patients (mean dose, 23 000 U/24 h; range, 10,000–45,000 U/24 h) for a mean period of 15 d (range: 3–45 d).</p> <p>Blood transfusions were given to 66% of patients because of increased hemolysis with decreasing hemoglobin levels and/or progressive hypoxemia. More patients with homozygous sickle cell disease (HbSS) received transfusions (60% vs. 29%; <math>p=.01</math>), but there was no difference in the mean number of packed cell units (4.8 U in transfused patients with HbSS vs. 3.5 U in transfused patients with sickle hemoglobin C disease (HbSC); <math>p=.5</math>)</p>	Mean hospital stay was 20.1±9.3 d	No	NA	NA	NA	The mean hospital stay did not differ between patients with HbSS and HbSC (23.3 vs. 17.7; $p=.18$ ). 5 cases were fatal, for a 6% case-fatality rate. All of the deaths were in female patients with HbSS, who died at a mean age of 32±12.3 yr after an average hospital stay of 27.6±40.3 d. These patients had more previous SCD-related admissions (19.6 vs. 8.4; $p=.06$ ) and more previous ACS episodes (3.4 vs. 0.8; $p=.02$ ) than the surviving patients with HbSS. Postmortem examination was performed in 3 patients; all had interstitial pneumonia. Differences in case-fatality rates between patients with HbSS and HbSC (8.7% vs. 0%; $p=.13$ ) and between male and female patients (0% vs. 9.4%; $p=.09$ ) did not reach statistical significance

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Velasquez, 2009 <sup>150</sup>	R, Obs	Presence of respiratory symptoms (cough, increased work of breathing, hypoxia) and radiographic pulmonary infiltrate, with or without pain and/or fever in a patient with SCD	Chest x rays, the clinical respiratory score (CRS) was used to assess respiratory distress	RCE transfusion	44	100	All exchange transfusions were performed with a COBE® Spectra 1 machine, (Lakewood, CO). Sufficient PRBC units (mean hematocrit 57%) were prescribed to achieve a predicted post-RCE patient HbS of <25%	The RCE was performed on median d 2 of admission	No	NA	NA	NA	The median length of hospital stay from the time of diagnosis of ACS to discharge was 7 d (interquartile range (IQR) 5–9 d) for all patients. All required oxygen and duration of oxygen need was a median of 4 d (IQR 3–6 d). Fever was present for a median of 1 d (IQR 0–3 d). In 4 of the 53 episodes (7.5%), the patients were placed on Bilevel Positive Airway Pressure (BiPAP) for management of respiratory distress, with 2 progressing to invasive mechanical ventilation. In total, the patients in 11 of the episodes (21%) required mechanical ventilation, which was started after a median of 1 d. The median duration of mechanical ventilation after RCE was 3 d. No patients died
Wales, 2001 <sup>151</sup>	R, Obs	ACS was defined as the development of a new pulmonary infiltrate in conjunction with a temperature >38.5°C, tachypnea, or cough	Chest radiograph	Patients received either a cholecystectomy or splenectomy, and the 2 groups were divided between patients who developed postoperative ACS vs. patients who had no postoperative ACS	Postoperative ACS (n=7);	25	All 7 children with ACS were treated with continuation of 1.5 maintenance IV hydration, supplemental oxygen, IV morphine, and chest physiotherapy. IV cefuroxime and erythromycin was given to all patients and these then received endotracheal intubation	NR	Patients who had no postoperative ACS	28	0	Hospital observation postinitial treatment of cholecystectomy or splenectomy	There was no mortality. Postoperative stay was prolonged in patients who had ACS (9 vs. 3 d; <i>p</i> <.05)

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Koren, 1990 <sup>225</sup>	Case control	The term ACS describes a patient with sickle cell anemia (SCA) who presents with the following signs and symptoms: acute chest pain, fever, leukocytosis, and unilateral or bilateral infiltrations on chest x ray	Clinically, chest x ray	Hypotonic fluids, analgesia and ampicillin	9 (52 episodes)	41 (9/22)	All the patients were treated with hypotonic fluids (0.18% NaCl-5% glucose) 5–7.5 ml/kg/h9 and analgesia on request and antibiotic cover with Ampicillin.	Acute, during hospitalization	Yes, children with acute pulmonary infections	21	Unclear	Similar to SCD group	There was constant and significant fall in hemoglobin levels from 8.8±1 g/dL to 6.8±1.5 g/dL. Unilateral or bilateral pulmonary basal infiltrations were found in 50 episodes. Pleural effusion was noticed in 60 episodes and it was bilateral in 3. No significant bacteriological findings were present. ACS was significantly more frequent among homozygous SCA patients than in patients with sickle hemoglobin beta-thalassemia (HbSβ-thal) (41 episodes/100 yr/patients vs. 3 episodes/100 yr/ patients). Recurrence was also frequent in the 1st group; 6.8 episodes/patient vs. 0.2 episodes/patient

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Al-Dabbous, 2002 <sup>164</sup>	P, Obs	ACS is defined as an acute episode associated with clinical and/or radiological evidence of new pulmonary abnormalities in patients with SCD, and often accompanied by fever, bone pain, chest pain, cough, dyspnea, hypoxia, leukocytosis, and decline in hemoglobin below the usual steady-state level	Clinical exam/investigations	Hydration, antibiotics (erythromycin, ampicillin, cephalosporin), transfusion, mechanical ventilation	132	100	Simple blood transfusion (114 patients) and exchange transfusion (3 patients); frequency not specified	Mean duration of hospitalization: 6.7 d	No	NA	NA	NA	132 patients with episodes of ACS (154 admissions which accounted for 7.7% of SCD admissions) were studied. Fever, cough, and chest pain were the most common symptoms. Raised temperature, tachypnea, and tachycardia were the most common findings. ACS was associated with painful crisis (46.8%) and infections (13%). It was mild in 31.2%, moderate in 57.1% and severe in 11.7% of admissions. Radiological studies revealed unilateral infiltrate in 69.5%, bilateral infiltrate in 20.8% and pleural effusion in 3.3%. There was a significant drop in hemoglobin and platelets, and a rise in white blood cell (WBC) count. Significant hypoxia was found in 10.4%, and bacteremia was found in 7.1%. Cephalosporin was required for 37%, simple blood transfusion for 74%, exchange transfusion for 2%, and mechanical ventilation for 0.7% of admissions. None of the patients died. Mean duration of hospitalization was 6.7 d

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Emre, 1995 <sup>179</sup>	P, Obs	ACS was defined as a combination of fever, clinical signs and symptoms of lung disease, and an abnormal chest radiograph (new infiltrate or effusion)	Patients were assigned a clinical severity score on the basis of criteria that were used previously (score 0=no respiratory distress; 1=tachypnea (age adjusted); 2=tachypnea and retractions); in all cases, scores were assigned after examination of the patient by the same author	Blood transfusion was given if the responsible physician perceived that a patient's respiratory distress was significant or if a substantial fall in hemoglobin concentration occurred. Patients also received administration of IVF at a rate of 1.5 times the calculated standard maintenance requirements, supplemental oxygen, and antibiotics (generally ceftriaxone and erythromycin)	Transfusions were given during 27 of 40 episodes (67.5%)	100	20 children received a simple packed cell transfusion, 4 received a partial packed cell exchange transfusion, and 3 were given a simple transfusion followed by whole blood exchange transfusion because of worsening clinical symptoms	NR	No	NA	NA	NA	Although most children had clinical severity scores of 1 or 2, the group that received transfusions had significantly higher scores ( $p=.01$ ; Table II). Children who received a transfusion had significantly lower PaO <sub>2</sub> , lower PaO <sub>2</sub> /PAO <sub>2</sub> , and higher P(Aa)O <sub>2</sub> values than children who did not, all suggestive of more severe lung disease. Mean hemoglobin concentrations were similar in both groups. Posttransfusion arterial blood gas (ABG) results were available from 24 of the 27 children given transfusions. There were highly significant changes in all indexes of oxygenation after transfusion. 6 children who did not receive transfusions had ABG sample collection repeated 24 h after the diagnosis of ACS. No significant changes were detected in any of the measurements of oxygenation. The duration of fever ( $3.1\pm 2.3$ vs. $4.8\pm 3.9$ d), tachypnea ( $2.6\pm 2.2$ vs. $2.9\pm 2.9$ d), retractions ( $1.3\pm 1.6$ vs. $0.4\pm 0.9$ d), and hospital stay ( $7.4\pm 3.2$ vs. $6.9\pm 3.4$ d) were similar in the transfusion group and the nontransfusion group

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Liem, 2004 <sup>190</sup>	P, Obs	ACS was defined by the presence of fever, chest pain, or any respiratory complaint	Chest x ray, electrophoresis	During the study period, exchange transfusions were done manually in the ICU. A double-volume exchange transfusion required 140 mL/kg in donor PRBCs and fresh frozen plasma (FFP) reconstituted to achieve a hematocrit of 60%. 1 patient required 2 d of assisted mechanical ventilation, and another required 2 d of positive pressure mask ventilation. Patients required an average of 3.4 d of supplemental oxygen	8	100	Exchange transfusions, double-volume exchange transfusion of 140 mL/kg in donor PRBCs and fresh frozen plasma (FFP)	Patients were hospitalized for a mean of 6.1 d (range: 3–9) with 1.8 d in the ICU	No	NA	NA	NA	Exchange transfusion achieved the target goal of reducing percent HbS to <20% in all patients, for a mean reduction of 55.6%. Exchange transfusion also significantly lowered WBC count, absolute neutrophil count (ANC), platelet count, and plasma levels of sVCAM-1. A greater decrease in % HbS correlated significantly with fewer days of both hospitalization ( $p<.02$ ) and oxygen requirement ( $p<.05$ ). The % HbS remained <30% in all patients by 24 h after exchange transfusion
Samal, 1997 <sup>205</sup>	P, Obs	Fever, clinical findings of pulmonary process, and x ray evidence of a new pulmonic infiltrate in a patient with SCD	Clinical, chest x ray	Fluids, analgesics and antibiotics	40	100	Fluids, analgesics and antibiotics whenever needed + PRBC transfusions (in 30 patients)	During hospitalization	No	NA	NA	NA	All patients were cured and discharged

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Strair, 1995 <sup>213</sup>	P, Obs	ACS was defined as symptoms and clinical signs of acute chest disease (chest pain, fever, and cough) associated with radiological evidence of pulmonary infiltration or plural effusion	Clinical presentation, chest x ray	Antibiotics, fluid therapy, oxygen, and transfusion if needed	50	100	Antibiotics: either cefuroxime or ceftriaxone with erythromycin. The patients were given oxygen if ABG showed a PO <sub>2</sub> <90 mmHg. Patients underwent PRBCs transfusion if their hemoglobin was <8 g/dL. Partial exchange transfusion was done on patients with extensive pulmonary involvement. 32 patients were anemic and required blood transfusion	NR	No	NA	NA	NA	All patients survived

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Vichinsky, 2000 <sup>219</sup>	P, Obs	The ACS was defined on the basis of the finding of a new pulmonary infiltrate involving at least 1 complete lung segment that was consistent with the presence of alveolar consolidation but excluding atelectasis. In addition, the patients had to have chest pain, a temperature of >38.5°C, tachypnea, wheezing, or cough	Clinical presentation, chest x ray	Matched transfusions, antibiotics, fluids, patient-controlled analgesia (PCA) and narcotics and non-steroidal agents, bronchodilators, and bronchoscopy	538 (671 episodes)	100	Pain-management protocol included guidelines for PCA and dosages of narcotics and nonsteroidal agents, with the goal being to prevent respiratory splinting and avoid hypoventilation and narcosis; cardiorespiratory monitoring was continuous. Bronchodilator therapy given to patients with evidence of reactive airway disease. Transfusion therapy given to patients for clinical distress, at physician's discretion. The mean number of transfusions per patient was 1.6, and the mean number of units per patient was 3.2. 68% of patients received simple transfusions, and 64% received phenotypically matched red cells. Oxygenation significantly improved with transfusion	The mean length of hospitalization was 10.5 d	No	NA	NA	NA	13% of patients required mechanical ventilation, and 3% died. Patients who were ≥20 yr of age had a more severe course than those who were younger. Neurologic events occurred in 11% of patients, among whom 46% had respiratory failure. Treatment with phenotypically matched transfusions improved oxygenation, with a 1% rate of alloimmunization. 20% of the patients who were treated with bronchodilators had clinical improvement. 81% of patients who required mechanical ventilation recovered. After adjustment for the remaining factors, an age of ≥20 yr, a history of VQEs, a platelet count of 0–199,000/mm <sup>3</sup> at diagnosis, pain in the arms and legs at presentation, extensive radiographic abnormalities, evidence of effusion on radiographic analysis, fever, treatment by transfusion, and respiratory failure were independently associated with prolonged hospitalization. Eighteen patients died, and the most common causes of death were pulmonary emboli and infectious bronchopneumonia. Infection was a contributing factor in 56% of the deaths
Al-Ansari, 2007 <sup>238</sup>	Case report/case series	Severe hypoxemia with respiratory distress	Clinical presentation, ABG, chest x ray	Noninvasive positive pressure ventilation, oxygen, IVF, macrolide, betalactam, exchange transfusion	4	100	Noninvasive positive pressure ventilation, oxygen, IVF, macrolide, betalactam, exchange transfusion	Mean of 40 h	No	NA	NA	NA	All patients discharged after 4 d in a good condition

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Al-Hawsawi, 2004 <sup>241</sup>	Case report/case series	A new pulmonary infiltrate and some combination of fever, chest pain, and signs of tachypnea	Clinical presentation, lab data, x ray	Antibiotics and transfusion	12	10%	Despite low incidence of bacteremia in patients, all received empirical IV antibiotics (ceftriaxone + erythromycin); vancomycin was added for those with severe ACS and prolonged fever. 8 patients (67%) received simple blood transfusion	NR	No	NA	NA	NA	The majority of patients received simple blood transfusion and all showed dramatic clinical improvement. Recurrence occurred in 2 (17%) and there was no mortality
Ataga, 2000 <sup>254</sup>	Case report/case series	NR	Clinical exam/investigations	Analgesics, hydration, and oxygen	3	100	Case 1: supplemental O2 and analgesics Case 2: antibiotics, analgesics, and O2 via a nasal cannula, and a total of 6 units of phenotypically compatible packed RBCs Case 3:transfusion support with platelets, fresh frozen plasma, and packed RBC	Case 1: 7 d Case 2: about 13 d Case 3: 32 d	No	NA	NA	NA	All patients recovered
Atz, 1997 <sup>255</sup>	Case report/case series	Presentation of fever, chest pain, and radiographic evidence of new pulmonary infiltrate, effusion, or edema in patients with SCD is a significant cause of morbidity and death	Clinical exam/investigations	Nitric oxide	2	100	Case 1: Inhaled nitric oxide (iNO) at 80 parts per million (ppm) for 15 min, then 5 ppm for 92 h. Case 2: iNO at 80 ppm for 15 min, reduced and discontinued after 47 h	Acutely	No	NA	NA	NA	Both cases were weaned off and extubated uneventfully. Case 1, 4 d later and case 2, 2 d later. No toxic side effects were incurred by either case
Baird, 1994 <sup>257</sup>	Case report/case series	NR	Clinical presentation, ABG, chest x ray	Combined pressure-control/high-frequency ventilation	1	100	NR	4 d	No	NA	NA	NA	Chest radiograph at 1 mo showed resolution of the majority of the infiltrates and the patient was asymptomatic

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Campbell, 2008 <sup>274</sup>	Case report/case series	The presence of a new pulmonary infiltrate (involving at least 1 complete lung segment) with 1 or more symptoms, such as fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia	Clinical presentation; fever, chest pain, leukocytosis, chest x ray	The patient was given supplemental oxygen via cold steam mask, started on azithromycin and ceftriaxone, transfused with 2 U of PRBCs, and prepared for exchange transfusion. The patient eventually required assisted ventilation due to decreasing PO <sub>2</sub> and tachypnea	1	100	NR The patient received a total of 3 U of PRBCs and 6 U of exchange transfusions	Hospital stay of <1 mo	No	NA	NA	NA	Her hematocrit stabilized at 31.3% from a nadir of 19.2%. On postoperative d 1, the patient was successfully extubated. She was discharged home on postop d 6 with a plan to complete a 14-d course of antibiotics
Ciurea, 2006 <sup>282</sup>	Case report/case series	Admitted with chest, back, and extremity pain, typical of her usual pain episodes, mild shortness of breath but no fevers, chills, or symptoms of upper respiratory tract infection	Chest x ray	Blood transfusions, anticonvulsants, heparin, warfarin	1	100	Anticonvulsant medications and was started on unfractionated heparin, which was subsequently changed to warfarin. Simple transfusions followed by exchange transfusions were instituted. Hemoglobin fractionation prior to exchange transfusion revealed that HbS of 41% decreased to 16% after treatment	NR	No	NA	NA	NA	Magnetic resonance imaging (MRI) and magnetic resonance venogram (MRV) examinations at 3.0 Tesla performed 4 d after the beginning of anticoagulation with heparin showed resolution of thrombosis and increasing shift of T <sub>2</sub> (spin-spin relaxation time) hyperintensity from the cortex into the white matter. Followup MRI at 3 weeks showed complete resolution of the all gray- and white-matter signal abnormalities

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Elsayegh, 2007 <sup>307</sup>	Case report/case series	Fever, shortness of breath, cough, chest pain, and diffuse body aches	Chest x ray; hemoglobin was 8.2 g/dL at presentation	Antibiotics, RBC exchange transfusion	1	100	Supplemental oxygen, IVF, analgesics and broad-spectrum antibiotics were administered. Over the next 24 h, the patient developed worsening tachycardia, tachypnea, and hypoxemia, and a decrease in hemoglobin to 7.7 g/dL. Repeat chest x ray showed worsening lower lobes infiltrates. Fetal monitoring demonstrated transient bradycardia. A 7 U RBC exchange transfusion was performed. Hemoglobin rose to 10.5 g/dL.	7 d	No	NA	NA	NA	The patient was intubated and underwent an emergency cesarean delivery. The neonate weighed 2.3 kg. The neonate required 2 h of continuous positive airway pressure (CPAP) for respiratory distress. Following delivery, the patient remained intubated. Repeat chest x ray showed diffuse bilateral infiltrates

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Feldman, 2003 <sup>312</sup>	Case report/case series	Criteria for making the diagnosis of ACS are respiratory symptoms, chest pain, or fever and the presence of a new pulmonary infiltrate on chest x ray	Clinical presentation, chest x ray	Enoxaparin and warfarin	1	100	NR	NR	No	NA	NA	NA	The patient was subsequently discharged with an international normalized ratio (INR) of 2.54 after a 9-d hospital stay. 1 mo later, the patient returned to the hospital complaining of shortness of breath and chest pain. He was found to be hypotensive and hypoxemic. His ABG analysis performed in the emergency department (ED) showed an O2 saturation 90%, PO2 72 mmHg, carbon dioxide partial pressure (PCO2) 21 mmHg, acidity (pH) 7.37, bicarbonate (HCO3) 12. He was admitted to the medical ICU and treated with nebulizer treatments, supplemental oxygen, and IVF. His heart monitor began to show bradycardia and then asystole and a code blue was called. Resuscitative efforts were ultimately unsuccessful and the patient died. Autopsy findings included a dilated right cardiac atrium and ventricle. The lungs showed multiple, small pulmonary intravascular thrombi. The cause of death was identified as acute right heart failure resulting from severe secondary PHTN due to thromboemboli from SCD
Gentile, 1999 <sup>322</sup>	Case report/case series	Progressive hypoxia, diffuse radiographic infiltrates, dyspnea, cough, fever, and chest pain	NR	High-frequency oscillatory ventilation HFOV	3	100	NR	The mean time on HFOV was 134±24 h	No	NA	NA	NA	The mean number of hours until the patients were extubated after HFOV was 144±96. All 3 patients survived without chronic lung disease, all were discharged home without the need for supplemental oxygen or respiratory medications

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Gillett, 1987 <sup>325</sup>	Case report/case series	NR	ABG, pulmonary angiogram, clinical presentation	Amikacin and cefuroxime, exchange transfusion, extracorporeal membrane oxygenation	1	100	NR	10 d	No	NA	NA	NA	The patient's pulmonary condition improved. Though her recovery was complicated by candidal septicemia, her chest radiograph showed gradual improvement and she was eventually discharged home. 6 mo later tests of pulmonary function and spirometric values were normal
Girad, 1979 <sup>327</sup>	Case report/case series	NA	Chest x ray, ABG	Furosemide	1	100	40 mg 6 hourly	3 d	No	NA	NA	NA	The patient improved, mechanical ventilation stopped after 3 d
Hamilton, 1978 <sup>335</sup>	Case report/case series	NR	Treadmill exercise test	Transfusion	1	100	PRBCs 150 mL/kg every 5–6 weeks	NR	No	NA	NA	NA	Normal age-related level of activity without angina

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Henderson, 2003 <sup>340</sup>	Case report/case series	The radiologic finding of a new pulmonary radiodensity on chest radiograph in association with chest pain, fever, tachypnea, wheezing, or cough	Chest x ray, clinical presentation	Supportive management during hospitalization, followed by transfusion therapy and/or HU. In patient 5, followup therapy was declined despite doctor recommendation	5	100	Multiple transfusions to decrease HbSS to <30%	4–60 mo	No	NA	NA	NA	All patients developed neurologic complications resulting from ACS episodes, including seizures (n=2), silent cerebral infarcts (n=3), cerebral hemorrhage (n=2), and reversible posterior leukoencephalopathy syndrome (n=3). Patients eventually required intubation, aggressive ventilatory support, and heavy sedation, and they experienced a prolonged hospitalization. All patients received multiple transfusions to decrease HbS to <30%. Prior to the ACS episode, none of the patients were diagnosed with hypertension or prior neurologic morbidity. 2 children had normal MRI studies within 1 yr of their severe ACS episode. 1 of 2 children also had a normal transcranial Doppler (TCD) velocity measurement within 1 yr of the episode. All 3 patients diagnosed with reversible posterior leukoencephalopathy syndrome (RPLS) exhibited characteristic MRI changes, positive fluid balance, and hypertension immediately prior to focal neurologic findings and clinical features associated with RPLS

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Honore, 1993 <sup>346</sup>	Case report/case series	NR	Clinical presentation, chest x ray, leukocytosis	Blood transfusion, antibiotics, IV saline and dextrose and analgesia	1	100	Antibiotics— piperacillin 4 g 6 hourly IV, gentamicin 80 mg 8 hourly I.V. and erythromycin 500 mg 6 hourly by mouth. IV saline and dextrose (3L/24 h), oxygen (40%), and analgesia (pethidine intramuscular (IM) 100 mg 2–4 hourly as required). Patient received 2 partial exchange transfusions at another hospital 3 d prior to admission	<1 mo	No	NA	NA	NA	By 2nd d of admission, there was a dramatic improvement in the patient's condition. He was no longer breathless and the physical signs of consolidation were resolving. Blood gases on breathing air were PO <sub>2</sub> 13.3 kilopascals, PCO <sub>2</sub> 5.5 kPa, pH 7.40, HCO <sub>3</sub> 26 mmol/L, O <sub>2</sub> saturation 97%. A repeat chest x ray showed substantial resolution of the radiological abnormalities. The patient was discharged the following day
Islam, 2005 <sup>354</sup>	Case report/case series	NR	Clinical presentation	IV hydromorphone initially, at 4 mg every 2 h	1	100	2 sessions of exchange transfusion for ACS	NA	No	NA	NA	NA	On d 2 of admission, he was found to be febrile with a temp of 102°F. A repeat chest x ray was done, his oxygen saturation dropped to 86% so he was put on 100% oxygen via nonrebreather mask. His hydration was increased, and he was commenced on Rochebin and Zithromax and transferred to the ICU. After 2 sessions of exchange transfusion, he was moved out of ICU after 2 d
Khattab, 2001 <sup>365</sup>	Case report/case series	Patient presented with cough, fever, chest pain, and anemia. A chest x ray showed a slight opacity in the left lower lobe. A diagnosis of pneumonia with sickle cell crisis was made. Computerized axial tomography (CAT) of the chest showed extensive consolidation	Chest x ray, CAT scan of chest	Antituberculosis therapy was commenced with improvement in his respiratory symptoms. 4 d later: aphasia, headache, and neck stiffness developed.	1	100	2 exchange transfusions were undertaken to reduce pulmonary sickling	NR	No	NA	NA	NA	The patient was continued on antituberculosis therapy and his neurologic status and MRI gradually improved

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Kleinman, 1980 <sup>368</sup>	Case report/case series	NR	Bilateral pulmonary infiltrates (2 patients), bilateral segmental and subsegmental defects on perfusion lung scan (2 patients), and fever (1 patient), PO <sub>2</sub> of 37 and 68 on room air	Exchange transfusion	2	100	Antibiotics (1 patient) Exchange transfusion with saline washed PRBCs: 5 U in 1 patient and 18 U in another	NR	No	NA	NA	NA	Both patients had hemoglobin levels of 11–12 g/dL following exchange transfusion and recovered
Kleinman, 1981 <sup>370</sup>	Case report/case series	NR	Clinical presentation, ABG, ventilation perfusion lung scan	Exchange RBC pheresis	1	100	1.5 volume exchange RBC pheresis	3 weeks	No	NA	NA	NA	The patient dramatically improved the following day postpheresis. Ventilation/perfusion scan on 7th postpheresis day showed complete resolution

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Kreindler, 2000 <sup>376</sup>	Case report/case series	The appearance of a new pulmonary infiltrate on the chest x ray. Although a new pulmonary infiltrate is necessary and sufficient, patients will usually have some combination of fever, chest pain, and signs and symptoms of pulmonary disease	Clinical presentation, chest x ray	IVF, antibiotics, oxygen	1	100	Ceftriaxone, cefotaxime, hydromorphone	NR	No	NA	NA	NA	The patient received IVF, hydromorphone and ceftriaxone, and was discharged home in stable condition with followup in the hematology clinic that afternoon. At approximately 2 pm that afternoon, he was seen in the hematology clinic. His pain was subjectively worse at that time and was unresponsive to appropriate doses of IV hydromorphone. His O <sub>2</sub> saturation was 92% on room air and rose to 100% on oxygen via nasal cannula. He was admitted to the hospital ward from the hematology clinic. On admission, his vital signs were T97.5F, heart rate 120, relative risk (RR) 20–24, BP 136/80, and O <sub>2</sub> saturation 100% on 1 L O <sub>2</sub> . Physical examination was significant for decreased air entry at both bases. IVF were started at maintenance, and his usual medications were continued. Cefotaxime was started, and he was placed PCA with hydromorphone. He continued on this treatment regimen for approximately 24 hr. In the later afternoon he began to complain of chest pain and shortness of breath
Lakki-reddy, 2002 <sup>381</sup>	Case report/case series	NR	ABG, autopsy	IVF, blood transfusion, oxygen, antibiotics	1	100	NR	NR	No	NA	NA	NA	Death

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Lanzkron, 2002 <sup>384</sup>	Case report/case series	Clinical findings of chest infiltrates, fever and hypoxemia	Computed tomography (CT) scan of chest, chest x ray, ultrasound (US)	PolyHeme was infused at a rate of 125 mL/h; each unit contained 50 g of hemoglobin in 500 mL. The goal was to maintain a total hemoglobin concentration of >5.0 g/dL	1	100	Management consisted of supplemental erythropoietin therapy (40,000 U subcutaneous 1 time), iron (325 mg ferrous sulfate 3 times/d), folate, oxygen, antibiotics, IVF, and pain medicine	16 d	No	NA	NA	NA	The patient improved and was discharged home on hospital d 20; a complete blood count (CBC) test performed 8 d after discharge revealed a hemoglobin of 7.4 g/dL
Laurie, 2010 <sup>386</sup>	Case report/case series	Chest VOC in a patient with SCD	Chest x ray (progressive interstitial infiltrate), the findings of a consumptive coagulopathy with hemolysis on blood testing	Transfusions + furosemide + glyceryl trinitrate + lung-protective ventilation + iNO (for worsening condition)	1	100	iNO was initiated at 10 ppm. Exchange transfusion, 3 U initially + 5 more later for lack of improvement. Patient did not require more exchange transfusion; however, he did receive multiple transfusion and blood products for ongoing coagulopathy	5 weeks of hospitalization	No	NA	NA	NA	After transfusion HbS dropped from 75.4% to 8.6%, and remained <8% until discharge. Patient made full recovery from ACS
Lombardo, 2003 <sup>397</sup>	Case report/case series	ACS describes a syndrome characterized by the presence of a new pulmonary infiltrate on a chest x-ray, fever, and respiratory symptoms and is the leading cause of death and hospitalization in SCD	Clinical exam/investigations	Red cell-exchange	21	29	Each patient received 4–200 mL/U with a 80% hematocrit	Unclear	No	NA	NA	NA	The patients who underwent erythroexchange showed a dramatic clinical and radiographic improvement with stabilized HbS levels between 20% and 30%. During followup (14–32 mo), none of the 6 patients developed viral complications related to transfusion therapy, alloimmunization, or recurrence of ACS

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Lowenthal, 1996 <sup>400</sup>	Case report/case series	Pleuritic chest pain, fever, rales on lung auscultation, and pulmonary infiltrates on chest x ray	Parvovirus B19 infection was established by polymerase chain reaction for parvovirus B19 deoxyribonucleic acid (DNA), and the presence of parvovirus B19 specific immunoglobulin M (IgM) antibodies ACS: Pt 1: CBC, CXR, ABG, clinical presentation Pt 2: CXR, clinical presentation Pt 3: CXR, ABG, clinical presentation	Gammaglobulin for parvo infection and supportive care for SCD (transfusion, oxygen, fluid support)	3	100	Patient 1 was treated with intravenous gammaglobulin 35 g/d for 10 days Patient 2 was treated postoperatively with 40 g of intravenous gammaglobulin daily for 5 days, along with mechanical ventilation, and transfusion to maintain a hematocrit of 25% Patient 3 was transferred to the medical intensive care unit and 100% oxygen was administered with a nonrebreather mask. Euvolemic red cell exchange was performed for suspected acute chest syndrome. One dose of intravenous gammaglobulin was also administered	Patient 1: 26d Patient 2: 19 d Patient 3 : 10 d	No	NA	NA	NA	Patient 1: Within 3 days of initiation of therapy, the platelet and WBC counts had returned to normal, and he was discharged home on the 26th hospital day. Patient 2's postoperative course was characterized by progressive respiratory failure with the development of bilateral patchy alveolar-interstitial pulmonary infiltrates. A hemoglobin electrophoresis post-splenectomy showed a transfused hemoglobin A level of 74%, therefore, exchange transfusion was not performed. The patient developed acute renal failure requiring hemodialysis, progressive pulmonary deterioration requiring 100% oxygen and maximal ventilatory support, and pressor-refractory hypotension, and died on the 19th hospital day. Patient 3 recovered well and was discharged on the 10th hospital day with a reticulocyte count of 6.9% and a hematocrit of 24%.

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Mak, 2003 <sup>403</sup>	Case report/case series	ACS consists of a combination of signs and symptoms including dyspnea, chest pain, fever, cough, multifocal pulmonary infiltrates on the chest radiograph, and a raised WBC count	ABG, CXR, clinical presentation	Subcutaneous opiate infusion using a syringe pump, intravenous fluids, oxygen, and fluid support	1	100	Exchange transfusion	NR	No	NA	NA	NA	Despite an exchange transfusion, he continued to deteriorate and was eventually intubated and ventilated. On intensive care his fraction of inspired oxygen ( $FiO_2$ ) was reduced from the initial 50% to 28% within 24 h. Sputum samples obtained by tracheobronchial suction showed no significant bacterial growth, but his C reactive protein (CRP) had risen to 150 mg/L so the antibiotic spectrum was broadened. After 3 d of mechanical ventilation, his chest radiograph showed significant clearing of the lower zones, he was extubated without incident, and discharged from the hospital after a further few days. Subsequent atypical respiratory serological examination did not show any rise in titers
Manna, 2003 <sup>406</sup>	Case report/case series	Plastic bronchitis, a condition associated with widespread mucous plugging of the tracheobronchial tree ACS: CXR, ABG, clinical presentation	Flexible bronchoscopy	Intratracheal rhDNase + adequate oxygenation and ventilation	1	100	2.5 mg in 20 mL of 0.9% saline once intratracheal	NA	No	NA	NA	NA	Conventional ventilation was successfully reinstated 12 h after rhDNase therapy

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Medoff, 2005 <sup>409</sup>	Case report/case series	The presence of a new pulmonary infiltrate on chest radiographs, with chest pain, fever, cough, dyspnea, or an elevated WBC count in a patient with SCA	Clinical presentation, chest x ray	Ceftriaxone, azithromycin, vancomycin, nitric oxide, mechanical ventilation, and transfusion	1	100	8 h after admission, an automated exchange transfusion of 5 U of PRBCs was performed. 20 h after her admission to this hospital, 2 U of 5% albumin were administered	NA	No	NA	NA	NA	Over the next 12 h, the patient's respiratory status continued to deteriorate. 20 h after her admission to this hospital, 2 U of 5% albumin were administered. 90 min later, cannulation for extra-corporeal membrane oxygenation was initiated at the bedside. During the procedure, the patient's BP dropped, transiently responded to the administration of norepinephrine and vasopressin, and then became unresponsive to maximal treatment with norepinephrine, vasopressin, phenylephrine, dopamine, epinephrine, and atropine. Cardiopulmonary resuscitation was unsuccessful, and the patient was pronounced dead 23 h after her admission
Modrykamien, 2007 <sup>416</sup>	Case report/case series	Clinical presentation, CT scan	CT	Analgesics and IV hydration, cefepime and vancomycin	1	100	Exchange transfusion with 8 U of packed RBCs	NR	No	NA	NA	NA	Two days after exchange transfusion, the clinical condition improved dramatically and the patient was transferred to the medical floor with stable vital signs receiving 2 L of oxygen via nasal cannula. CBC count at this time was as follows: WBC count, 19,900/_L; hematocrit, 31.2%; hemoglobin, 10.8 g/dL; platelet count, 168,000/_L; and reticulocyte count, 4.09%. The patient was discharged home asymptomatic

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Murtuza, 2009 <sup>425</sup>	Case report/case series	The differential diagnosis of ACS includes acute asthma, pulmonary thromboembolism, pneumonia, atelectasis and acute respiratory distress syndrome	Clinically, chest x ray	ACS treatment: iNO, oral sildenafil, and tracheostomy	1	100	Perioperative: Good hydration, oxygenation and analgesia, and a preoperative exchange transfusion that reduced her HbS fraction from 43.3 to 20.9%. Postoperative: She made a good initial recovery with aggressive management: oxygen therapy; strict pain control, maintenance of low HbS fraction; incentive spirometry postextubation; broad-spectrum IV antibiotics and bronchodilators. She deteriorated on the day of discharge; postoperative d 6, patient had acute chest wall and abdominal pain, pyrexia, tachypnea, and ensuing type II respiratory failure. A diagnosis of ACS was made and initial postoperative respiratory measures reinstated; the patient was also commenced on iNO and then oral sildenafil. She required a tracheostomy for respiratory weaning	NR	No	NA	NA	NA	She improved gradually over the next 14 d and was discharged after rehabilitation

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Noto, 1999 <sup>430</sup>	Case report/case series	The ACS is characterized by fever, chest pain, and infiltrates on a chest x-ray film	Clinically, chest imaging	Antibiotics, hydration, exchange transfusion, and surgery	1	100	Antibiotics, hydration and exchange transfusion 3 U exchange transfusion	13 d	No	NA	NA	NA	With these results, major pulmonary embolism and hypercoagulability were excluded, and anti-coagulant therapy was discontinued on the 10th d after transfer. The patient then received 3 U exchange transfusion to prevent a perioperative vaso-occlusive episode (VOE) and underwent subsequent surgery for the retinal detachment without complications
Oppert, 2004 <sup>435</sup>	Case report/case series	NR	Chest x ray	Orotracheal intubation was performed and low tidal volume, pressure-controlled mechanical ventilation was initiated. Hemoglobin went from 10.0 g/dL on d 1 to 9.8 g/dL on d 3. Because oxygenation remained impaired during conventional therapy, iNO was administered in a dose of 10 ppm. Continuous inhalation induced a substantial and sustained improvement in PaO <sub>2</sub> and a reduction in mean pulmonary artery pressure	1	100	Continuous IV norepinephrine was administered; transfusion of 2 U of PRBCs	14 d until the patient was discharged home	No	NA	NA	NA	Concomitantly, the patient's condition stabilized and it was possible to reduce the FiO <sub>2</sub> . Nitric oxide was discontinued 96 h after intubation. The initially impaired liver function normalized, a rise in serum creatinine proving transient. The patient was successfully weaned from mechanical ventilation and vasoactive medication 5 d after admission to the ICU and was subsequently transferred to a normal ward. 14 d after admission to hospital, the patient was discharged home. When last seen, he was well without pulmonary symptoms. Liver and renal functions were normal

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Padman, 2004 <sup>438</sup>	Case report/case series	Defined as a new pulmonary infiltrate with a combination of fever, chest pain, and signs and symptoms of pulmonary disease such as tachypnea, cough, and dyspnea	Clinical exam and investigations on admission	BiPAP	9	100	NA	3.1 d	No	NA	NA	NA	The patients' clinical values before and after BiPAP: oxygen support (L), 4.1±3.2 and 1.4±1.7; oxygen saturation (%), 96.3±2.8 and 97.9±1.6 ( $p<.05$ ); respiratory rate (per min), 28.5±8.6 and 25.1±6.6 ( $p<.05$ ); heart rate (per min), 109±18 and 92±13 ( $p<.001$ ). Patients' average highest intermittent positive airway pressure 12 cm H <sub>2</sub> O and average highest expiratory positive airway pressure was 6 cm of H <sub>2</sub> O
Pelidis, 1997 <sup>441</sup>	Case report/case series	Defined as a complication of sickle cell disease characterized by fever, chest pain and a new infiltrate on chest roentgenogram	ABG, chest x ray	Extracorporeal membrane oxygenation (ECMO), venovenous extracorporeal membrane oxygenation Antibiotics include ceftriaxone, gentamycin and erythromycin	1	100	Partial exchange transfusion	11 d	No	NA	NA	NA	The patient was successfully treated despite complications. A 5-yr followup showed normal pulmonary function test.

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Qureshi, 2006 <sup>446</sup>	Case report/case series	Chest pains and fever in patient with SCD	Clinical presentation	Diamorphine infusions, diclofenac, augmentin, transfusion	1	100	Automated RCE transfusion	Acutely	No	NA	NA	NA	On the 4th d, patient was pyrexial and, after new urine and blood cultures were obtained, was started on augmentin. In the evening, he complained of worsening abdominal distension and discomfort. Abdominal x ray findings were consistent with partial large bowel obstruction with a competent ileocecal valve. After he received exchange transfusion, his abdomen became tender and more distended. An enhanced CT scan the next morning revealed a large volume of free intraperitoneal air with no evident site of perforation and free fluid in the pelvis. A diagnosis of perforated bowel was made. He underwent a laparotomy and was found to have perforations of both cecum and transverse colon, with fecal peritonitis. He underwent extended right hemicolectomy with end-ileostomy. During a 3-week hospitalization for supportive care, physiotherapy, and rehabilitation, he was started on a regular chronic RCE transfusion program to eliminate the possibility of another catastrophic crisis. One yr later he developed insulin-dependent diabetes mellitus. His ileostomy was eventually reversed.

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Robertson, 1997 <sup>456</sup>	Case report/case series	ACS is characterized by fever, pulmonary infiltrates, pleuritic chest pain, and abnormal pulmonary auscultation	On admission, patient was restless and febrile, and a chest radiography revealed a right middle lobe pulmonary infiltrate	Transfusion and antibiotics	1	100	The patient initially received 125 mL of PRBCs without improvement. A femoral Quinton catheter was inserted, and the child was exchanged with 4 U of frozen deglycerolized phenotypically matched RBCs using a COBE® Spectra and heparin as the anticoagulant	NR	No	NA	NA	NA	A postexchange sample showed hemoglobin A (HbA)=70.4%, HbS 18%. Following exchange transfusion, the child was continued on antibiotics. He improved rapidly and was discharged home after 3 d
Rouxel, 2008 <sup>461</sup>	Case report/case series	NR	US coupled to TCD velocimetry	Analgesia	1	100	NR	NR	No	NA	NA	NA	NR
Saleem, 2007 <sup>466</sup>	Case report/case series	NR	Chest x ray, clinical presentation	O <sub>2</sub> , transfusions, antibiotics	1	100	Broad-spectrum antibiotics	2 weeks	No	NA	NA	NA	On the 5th hospital d, his restrained right wrist and hand were swollen and cool, thought due to peripheral IV line infiltration. The hand was elevated, ice packs were applied around the clock, and prophylactic, low-molecular-weight heparin was administered. The arm remained nonviable and was amputated below the elbow soon after hospital transfer. Pathologic examination showed occlusion of major vessels by sickled RBCs. After a 2-week hospital course, the ACS substantially improved, and the patient was discharged

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Shelat, 2010 <sup>482</sup>	Case report/case series	NR	Clinical presentation, chest imaging	Exchange transfusion	1	100	Antibiotics were administered but what was not specified. Erythrocytapheresis was first performed, which reduced the HbS level to 4.8%. Daily plasmapheresis treatments were performed with FFP as the replacement fluid (hospital d 1–12)	12 d	No	NA	NA	NA	After the platelet count exceeded 150,000/mL for 5 d (d 12), plasmapheresis was discontinued. The platelet count continued to steadily rise until discharge (d 17). The hemoglobin levels were relatively stable during treatment, though this may have reflected RBC priming of certain plasmapheresis procedures (d 2, 8, and 11)
Staser, 2006 <sup>499</sup>	Case report/case series	NR	Chest radiograph, CT scan and clinical presentation	Thoracentesis was performed	1	100	Supplemental oxygen, antibiotics, and analgesics for the chest pain and anticoagulants	24 d	No	NA	NA	NA	He was started on anticoagulants and discharged home 24 d later with a refractory right pleural effusion (no other results given)
Suara, 2001 <sup>504</sup>	Case report/case series	NR	Chest radiograph, abdominal US	IV antibiotics	1	100	IV vancomycin and ceftriaxone was instituted. The antibiotic treatment was changed to IV penicillin G. On d 3 in the hospital, she had minimal drainage from her right ear, culture of which grew group A $\beta$ -hemolytic <i>Streptococcus</i> . On d 6, she had thoracoscopic decortication of her right pleura owing to persistent fluid loculation. She also received exchange transfusion with HbA PRBCs and oxygen therapy	12 d	No	NA	NA	NA	She responded to treatment and was discharged home after 12 d in the hospital

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Sullivan, 2008 <sup>544</sup>	Case report/case series	The syndrome is defined by the presence of new pulmonary infiltrates, chest pain, dyspnea, cough, and hypoxemia	CXR, CBC, WBC, clinical presentation	Nitric oxide	1	100	Nitric oxide was bled into the inspiratory limb of the Puritan-Bennett 7200 ventilator and titrated to an inhaled concentration of 20 ppm Double-volume exchange transfusion was performed	<1 mo (hospital stay)	No	NA	NA	NA	Soon after the initiation of nitric oxide therapy, pulmonary vascular resistance (PVR) decreased and oxygenation improved markedly. P(A-a)O <sub>2</sub> gradient decreased from 231 to 174 mmHg and subsequently to 122 mmHg after 15 h of nitric oxide therapy. Shunt fraction decreased from 44% to 19%, cardiac output improved and oliguria resolved. Within 72 h marked clinical and radiological improvement were noted and patient was weaned from nitric oxide therapy. The ventilator was returned to the synchronous intermittent mandatory ventilation mode. By the 4th d after cessation of nitric oxide therapy, the patient had been weaned from the ventilatory support and extubated. The patient defervesced and made a complete recovery. He was discharged to his home on the 17th hospital d
Trant, 1996 <sup>511</sup>	Case report/case series	Fever, respiratory distress, new left-lower lobe infiltrate, complete opacification of the left lung and an opacity in the right basilar region	Chest radiograph, chest x ray, CT	Venoarterial extracorporeal membrane oxygenation (ECMO)	1	100	Initial management included IV hydration, IV antibiotics with cefuroxime, erythromycin, sulfisoxazole, and oxygen. 2 volume exchange transfusion, changing the HbS fraction to 20%	27 d	No	NA	NA	NA	He was discharged on hospital d 27 with a normal chest radiograph with normal neurologic function and no apparent complications secondary to ECMO

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients with complication	% of patients with complication	Medication details/transfusion details	Duration of treatment*	Secondary/control arm	N of patients with complication	% of patients with complication	Control treatment	Reported results
Wratney, 2004 <sup>532</sup>	Case report/case series	ACS occurs in patients with SCD and is classically characterized by fever, pleuritic chest pain, tachypnea, cough, hypoxemia, marked leukocytosis, and diffuse infiltrates on chest radiograph	Clinical exam/investigations on admission	HFOV	6	100	HFOV and bronchoscopy	Variable in all cases, range 3–5 d	No	NA	NA	NA	<p>Case 1: After 96 h on HFOV, oxygenation index had fallen to 11 and patient converted to conventional mechanical ventilation (CMV) and recovered.</p> <p>Case 2: After 6 d of HFOV the ventilation mode was converted to CMV, patient recovered, and was discharged.</p> <p>Case 3: After 96 h on HFOV the ventilation mode was converted to CMV, and he was extubated 3 d later and recovered.</p> <p>Case 4: She was successfully converted back to CMV after 5 d of HFOV, extubated 2 d later, and was discharged.</p> <p>Case 5: Bronchoscopy was performed on 3 consecutive d while the patient was on HFOV, and large mucus plugs were removed. He was weaned to CMV, extubated, and discharged.</p> <p>Case 6: After 84 h of HFOV the ventilation mode was converted to CMV, extubated, and discharged</p>

**Table 5. Acute Central Nervous System Stroke Incidence and Outcomes**

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Adams, 1998 (Stroke Prevention Trial in Sickle Cell Anemia (STOP) <sup>1</sup> )	RCT	Prior stroke is defined as either focal neurological symptoms associated with clear, residual evidence of hemiparesis and supporting radiological evidence of stroke, or participation in a chronic transfusion program for stroke indication	Focal symptoms on presentation, magnetic resonance imaging (MRI)	Transfusion + standard care	63	1.6	Exchange or simple transfusions were allowed to decrease sickle cell hemoglobin (HbS) to <30% within a period of 21 d without exceeding a hemoglobin concentration of 12 g/dL and a hematocrit of 36%, measured before transfusion. Once HbS was <30%, children received transfusions every 3–4 weeks	Median: 22.2 mo	Yes	67	16.4	Standard care	There were 10 cerebral infarctions and 1 intracerebral hematoma in the standard-care group, as compared with 1 infarction in the transfusion group—a 92% difference in the risk of stroke ( $p<.001$ ). This result led to the early termination of the trial
Lezcano, 2006 (STOP) <sup>29</sup>	RCT	NR	NR	Transfusion	50	NR	Chronic transfusion therapy (CTX) to maintain HbS <30% of the total hemoglobin	13.3 (SD) 4.8 mo	Yes.	62	NR	Standard care (None or up to 4 U of transfusion per yr)	Baseline (plasma-free hemoglobin PFH) values did not differ between treatment groups. PFH significantly declined with repeated transfusions (from 78.7±8.2 mg/dL to 34.4±3.4 mg/dL ( $p<.001$ )). The decline was less in the other group (from 80.9±7.5 mg/dL to 62.8±5.0 ( $p=0.019$ )). Regular transfusion, which lowers stroke risk was associated with a significant reduction in PFH
Pegelow, 2001 (STOP) <sup>37</sup>	RCT	Silent cerebral infarcts: structural defects in the brain, that are asymptomatic	MRI, transcranial Doppler (TCD)	CTX	56	3.6	NR	36 mo	Yes.	71	33.8	Standard care (no long-term transfusion therapy)	Group 1: 1 patient developed a stroke, and 1 patient had a new silent infarct. Group 2: 11 patients developed new silent lesions and 13 others developed new strokes. Comparing 40 patients who had no MRI abnormality at baseline and were available for analysis with 29 who had MRI abnormalities at baseline, 4 out of 40 (10%) suffered further strokes compared with 9 out of 29 (31%), $p=.02$ , while 5 out of 40 (12.5%) and 6 out of 29 (20.7%) developed new silent infarcts

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Vichinsky, 2001 (STOP) <sup>48</sup>	RCT	NR	NR	Transfusion	63	NR	CTX to maintain HbS <30% of the total hemoglobin	21±5.7 mo	Yes	67	NR	Standard care	Low frequency of Kell (2%), E (20%), and C (25%) antigens. 61 patients received 1830 U. 97% of all units were white blood cells (WBCs) reduced. Only 29 U were inadvertently not matched for E, C, and Kell. 5 patients (8%) developed a clinically significant allo-antibody. 4 developed a single antibody to E or Kell. 3 patients (5%) developed a warm auto-antibody. There were 11 transfusion reactions and 8 transfusion-associated events. Transfusion reactions included 6 febrile reactions (0.33%/U), 3 allergic (0.16%/U), and 2 hemolytic (0.11%/U). Associated events included 4 episodes of hypertension (0.22%/U), 3 crises (0.16%/U), and 1 transient ischemic attack (TIA) (0.05%/U)
Adams, 2005 (STOP 2) <sup>2</sup>	RCT	NA	TCD screening examination	Transfusion	38	0	Chronic transfusions matched for C, D, E, and Kell antigens	4.5 mo	Observation	41	4.9	Standard care	The study was stopped after 79 children of a planned enrollment of 100 underwent randomization. Among the 41 children in the transfusion-halted group, high-risk TCD results developed in 14 and stroke in 2 others within a mean (±SD) of 4.5±2.6 mo (range, 2.1–10.1) of the last transfusion. Neither of these events of the composite end point occurred in the 38 children who continued to receive transfusions. The average of the last 2 TCD results before transfusion was started was the only predictor of the composite end point ( $p=.05$ )
Al Hawsawi, 1998 <sup>59</sup>	R, Obs	Neurological deficit lasting >24 h	CT scan, which was abnormal in 8 of 9 patients	Exchange transfusion for acute presentation and chronic simple transfusions for prevention	9	100	NR	NA	No	NA	NA	NA	Both exchange transfusion for acute presentation and chronic simple transfusions for prevention were effective; low steady-state hematocrit was the strongest predictor of stroke (high WBC count was not)
Brousse, 2009 <sup>76</sup>	R, Obs	NA	MRI, magnetic resonance angiography (MRA)	CTX (secondary prevention)	9	78	NR	59.6 mo	Primary prevention group	9	33	CTX	Group 1: MRI demonstrated progression of score in 7 patients. Overt stroke recurred in 1 patient. It was concluded that chronic transfusion therapy failed in preventing progression of cerebral vasculopathy in children with sickle cell disease (SCD). Group 2: MRI demonstrated progression of score in 3 patients

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Enninfu-Eghan, 2010 <sup>96</sup>	R, Obs	NA	TCD, CT, MRI	Transfusion therapy	475	67	TCD screening, simple and exchange transfusion	16 yr	Yes: Pre/post	530	6	Transfusion therapy	The incidence of overt stroke in the pre-TCD period was 0.67 per 100 patient-yr, compared with 0.06 per 100 patient-yr in the post-TCD period ( $p < .0001$ ). However, the rate of transfusion therapy for stroke prevention increased from 0.67 per 100 patient-yr to 1.12 per 100 patient-yr since instituting of the program ( $p = .008$ )
Hulbert, 2006 <sup>107</sup>	R, Obs	First and subsequent strokes were defined as acute neurologic symptoms and signs lasting >24 h or, for symptoms lasting <24 h, with an imaging study demonstrating acute ischemia	NR	Transfusion	23	26	Simple transfusion	NR	Yes	67	74	Exchange transfusions	Recurrent strokes occurred in 57% (8/14) of patients treated with simple transfusion, compared with 21% (8/38) of those treated with exchange transfusion. Simple transfusion was associated with a 5-fold greater incidence of recurrent stroke compared with exchange transfusion (relative risk (RR)=5.0; 95% confidence interval (CI)=1.3–18.6). Among patients without a medical antecedent event who presented within 24 h of symptom onset, those who received simple blood transfusion were 8 times more likely to experience subsequent stroke (RR=8.0; 95% confidence interval CI=1.7–38.8) compared with patients treated with exchange transfusion (8 of 11 patients vs. 7 of 28 patients)
Scothorn, 2002 <sup>135</sup>	R, Obs	NR	Confirmed neuroimaging study documenting a stroke and a clinical history revealing a focal neurologic deficit (infarctive or hemorrhagic)	Regularly scheduled blood transfusion	137	22	Regular blood transfusion therapy consisting of a minimum interval of 6 weeks	At least 5 yr	No	NA	NA	NA	22% (31 of 137) of the patients had at least 1 recurrent stroke while receiving long-term transfusion therapy. The absence of an antecedent or concurrent medical event associated with an initial stroke was found to be a major risk factor for subsequent stroke while receiving regular transfusions
Strouse, 2006 <sup>140</sup>	R, Obs	Hemorrhagic stroke	Neuroimaging, autopsy or cerebrospinal fluid analysis	Transfusions	7	100	Type not specified, frequency at least once every 4 weeks	Not specified	Ischemic stroke	25	Unclear	Transfusions	An increased risk of hemorrhagic stroke was associated with a history of hypertension (HTN) and recent (within 14 yr) transfusion, therapy with steroids, and possibly nonsteroidal anti-inflammatory drugs (NSAIDs). Of the 35 surviving patients, 7/9 (group 1) and 25/26 (group 2) began therapy with transfusions at least q 4 weeks. The rate of composite end point, including recurrent neurologic event (TIA, stroke) and death was higher for patients with ischemic (8.1 per 100 patient-yr; 95% CI: 4.8–13.1) because there were no neurologic events or deaths in the patients who survived a hemorrhagic stroke (group 1)

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Wilimas, 1980 <sup>155</sup>	R, Obs	NR	Arteriography, brain and CT scans, electroencephalography (EEG), neurological testing (e.g., Wechsler Scale, Wide Range Achievement Test, Peabody Picture Vocabulary Test)	Transfusion	12	58	Transfusions of washed or frozen packed red blood cells (PRBCs) were given every 3–4 weeks. Approximately 15 kg/mL of PRBCs were administered with each transfusion. 10/12 patients stopped transfusion after 1-2 yr on protocol	Approximately 1–2 yr	No	NA	NA	NA	Arteriography did not improve during transfusion therapy, while neuropsychological testing did improve. 7/10 patients in whom transfusion was stopped had 2nd strokes within 5 weeks to 11 mo after cessation of transfusions. These patients experienced a decline in neuropsychological testing. 3 patients have been off transfusion therapy for 11–15 mo with no evidence of change in neurological function
Winter, 1997 <sup>158</sup>	R, Obs	NR	MRI, MRA for 6 patients, cerebral arteriography for 5 patients	Chronic transfusion	24	100	8 patients who had cerebrovascular accidents (CVAs) received long-term erythrocyte transfusion, 16 patients with no stroke were observed	Average 37 mo	No	NA	NA	NA	It was concluded that neurological imaging may add little to supplemental clinical judgment regarding the possibility of stroke
Pegelow, 2002 <sup>202</sup>	P, Obs	Stroke was defined as an acute neurologic syndrome secondary to occlusion of an artery or hemorrhage resulting in ischemia and neurologic symptoms and signs that lasted >24 h; for this report transient ischemic attack was not considered to be stroke	(MRI)	Transfusion	21 (with stroke)	100	CTX, otherwise not specified	120 mo	No	NA	NA	NA	A baseline prevalence of 21.8%, marginally higher than previously reported due to improved imaging technologies. Although no overall sex difference in prevalence was observed, most lesions in girls occurred before age 6, whereas boys remained at risk until age 10. Silent infarcts were significantly smaller and less likely to be found in the frontal or parietal cortex than were infarcts associated with stroke. Children with silent infarct had an increased incidence of new stroke (1.03/100 patient-yr) and new or more extensive silent infarct (7.06/100 patient-yr) relative to stroke incidence among all children in the cohort (0.54/100 patient-yr). Both events were substantially less frequent than the risk of stroke recurrence among children not provided CTX. All but 2 of the patients who developed stroke were on CTX

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Sumoza, 2002 <sup>214</sup>	P, Obs	CVA was defined as an acute neurologic syndrome secondary to occlusion of an artery or hemorrhage resulting in ischemia and neurologic symptoms or signs, including: TIA (TIA= neurologic signs corresponding to vascular deficits that resolved within 24 h), infarctive stroke (neurologic deficit lasting >24 h), and hemorrhagic stroke. The stroke classification was based on available clinical and imaging studies	The CVA was documented by clinical neurologic evaluation and cranial CT scan in 4 of the patients and MRI scan in 1 case. The type of prior CVA developed in our patients was as follows: 4 episodes of ischemic stroke in patients 1, 2, 4, and 5; 2 episodes of TIA in patient 3; and a 2nd CVA of patient 1	Hydroxyurea (HU)	5	100	HU was given at a single dose of 40 mg/kg/d in the first 4 patients and at 30 mg/kg/d in the last 1 (patient 5)	Range: 42–112 mo	No	NA	NA	NA	During HU therapy, none of the patients had recurrent CVA. Patient 1 had a 2nd CVA (TIA) when she was lost to followup and had stopped HU for many months. CT scan or MRI during followup in 2 of the 5 patients (patients 1 and 2) did not show new lesions, and in patient 1 there was a reduction of the affected area. 2 patients had a previous CVA: Patient 1 (right facial paresia) and patient 3 (left hemiparesis); they did not have CT scan done during those episodes, and both had complete clinical resolution. During HU therapy, no pain crises occurred in these 5 patients. The hemoglobin F (HbF) increased significantly in all the patients compared with the baseline concentration and remained elevated 14.7% (median) during HU therapy. The median venous hemoglobin concentration also increased, on average, 15.2 g/L above the pretreatment values. HU was well tolerated at the dose given. In no case was there leukopenia or thrombocytopenia, and none of the patients required transient discontinuation of therapy. Changes in reticulocyte counts were inconsistent and not significant. None of the patients presented gastrointestinal (GI) or dermatologic changes related to HU while on therapy. No bacterial infections were observed
Ware, 1999 <sup>221</sup>	P, Obs	The pathological event is usually infarctive and results from stenosis or occlusion of the large vessels, especially the internal carotid and proximal cerebral arteries	MRI and clinical symptoms	HU (combined with an aggressive periodic phlebotomy regimen to reduce iron overload)	16	19	Oral HU therapy was started at a dose of 15 mg/kg/d. The dose of HU was escalated by 5 mg/kg/d every 8 weeks as tolerated, up to a maximum of 30 mg/kg/d. If a patient developed hematologic toxicity, therapy was held until blood counts normalized. Patients ceased transfusion therapy for current study	Mean: 22 mo	No	NA	NA	NA	The current average HU dose is 24.9±4.2 mg/kg/d, range 19.1–32.7 mg/kg/d. Hematologic toxicity has been mild, with only occasional episodes of transient, reversible myelosuppression. 3 patients had new neurological events consistent with recurrent stroke. No patient has experienced a hemorrhagic neurological event while on HU therapy. 14 of the children had laboratory evidence of iron overload and have received phlebotomy for a mean duration of 18±12 mo. In conclusion, preliminary data suggest some children with SCD and stroke may discontinue chronic transfusions and use HU therapy to prevent stroke recurrence. Phlebotomy was well-tolerated and significantly reduced iron overload

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Ware, 2004 <sup>220</sup>	P, Obs	NR	NR	HU	35	100	HU started at 15–20 mg/kg/d, single oral dose, then escalated by 5 mg/kg/d every 8 weeks as tolerated to the maximum tolerated dose, or 30–35 mg/kg/d	42±30	No	NA	NA	NA	HU led to mild neutropenia ( $3.9\pm 2.3\times 10^9/L$ ) with significant increases in hemoglobin concentration, mean corpuscular volume (MCV), and HbF. Stroke recurrence rate was 5.7 events per 100 patient-yr, but children receiving overlapping HU therapy ( $n=20$ ), as opposed to those who ceased transfusions abruptly, had only 3.6 events per 100 patient-yr. It was concluded that HU successfully prevented secondary stroke
Al-Fifi, 2008 <sup>236</sup>	Case report/case series	NR	Head CT	Surgical evacuation of the epidural hematoma	1	100	Exchange transfusion and supportive care, later evacuation of epidural haematoma with blood clots	NR	No	NA	NA	NA	The patient was discharged in a good condition
Annobil, 1990 <sup>252</sup>	Case report/case series	Not defined	Clinical exam/investigations	Hydration, analgesics, transfusion, physiotherapy	8	100	Hydration, analgesics, transfusion, physiotherapy	NA	No	NA	NA	NA	Case 1: She completely recovered on the 18 <sup>th</sup> d Case 2: left with right wrist drop Case 3: not fully regained her speech and left with hemiplegia 22 mo after the stroke Case 4: left with right hemiparesis 9 mo after the onset of the cerebrovascular accident Case 5: 15 mo later she still walks with a hemiplegic gait Case 6: left with hemiparesis 3 yr and 9 mo after the accident Case 7: completely resolution on computed tomography Case 8: left hemiparesis 8 weeks after the accident
Brandao, 2009 <sup>271</sup>	Case report/case series	Sudden-onset, severe headache	Head CT	Surgical treatment with occlusion of the aneurysm neck with a clip + partial exsanguine transfusion	2	NA	Open surgery.	NR	No	NA	NA	NA	Case 1: Recovery was good. Postoperative angiography confirmed the total exclusion of the aneurysm, and the CT showed there were no operative complications. Case 2: NR (patient had periodic followup evaluations)
Carey, 1990 <sup>275</sup>	Case report/case series	NR	CT brain, angiography	Diazepam	1	NA	Diazepam	NR	No	NA	NA	NA	The patient was discharged free of symptoms 12 d after admission. No specific treatment described

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Dahdaleh, 2009 <sup>290</sup>	Case report/case series	Right frontal, right parietal, and left parietal acute epidural hematomas with multiple bilateral subgaleal hematomas	CT scan	Bilateral craniotomies and epidural hematoma evacuation	1	NA	The patient was transfused with PRBCs, platelets, and fresh frozen plasma (FFP) to maintain a hemoglobin level of at least 8.0 g/dL and a platelet count of at least 100,000 platelets/mm <sup>3</sup>	NA	No	NA	NA	NA	After surgery, a repeat CT showed complete evacuation of the hematomas. The results of his neurological examinations improved, and he was extubated 2 d later. The results of his lab tests normalized. He continued to improve and had a normal neurological examination by the 7th d following surgery. The patient was discharged home, and during his followup clinic visit, he was asymptomatic with a normal neurological exam and CT scan
Ris, 1996 <sup>454</sup>	Case report/case series	NR	MRI	NR	1	100	NR	NR	No	NA	NA	NA	Conclusion: MRI and neuropsychic testing pre- and poststroke demonstrated some inconsistency suggesting the need for both to better evaluate the extent of anatomic and functional impairment
Dowling, 2010 <sup>301</sup>	Case report/case series	For this report, we defined acute spinal cord injury (SCI) as an area of restricted diffusion on diffusion-weighted MRI in the absence of focal neurologic findings lasting >24 h	MRI	NR	7	100	NR	NR	No	NA	NA	NA	Our observations suggest that SCI are detectable in the acute phase, present with subtle neurologic symptoms, result in permanent neurologic injury, and may be caused by acute anemic events. A better understanding of the etiologies of SCI in the population at highest risk, children with homozygous sickle cell disease (HbSS), may also provide insight into the problem of SCI in the general population. This might allow for the prevention or the amelioration of the neurocognitive sequelae of these not-so-silent strokes
Freischlag, 1991 <sup>319</sup>	Case report/case series	NR	Neurological exam, duplex imaging, arteriogram	Procardia and transfusion	1	100	Exchange transfusion for a total of 6 U of PRBCs	1 transfusion, procardia; duration NR	No	NA	NA	NA	The patient has remained asymptomatic at 40 mo
Greenbaum, 1988 <sup>333</sup>	Case report/case series	NR	Cerebral angiography, EEG	Transfusion	2	100	Long-term transfusion therapy to maintain HbS <30%	Long-term, years	No	NA	NA	NA	Following cessation of transfusion therapy patients developed a 2nd stroke (after 1 and 2 mo). Patients were diagnosed with von Willebrand's disease, and remain on CTX

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Gupta, 2008 <sup>334</sup>	Case report/case series	NR	Head CT, MRA	Preinfarct, she was started on dexamethasone and other supportive treatment. Postinfarct, she was ventilated, started on intravenous fluids (IVFs), 20% mannitol	1	100	Postinfarct: exchange transfusion to reduce her HbS below 30%; postdischarge: regular exchange transfusions on a monthly basis	NA	No	NA	NA	NA	Posthemorrhage, she was continued on dexamethasone and other supportive treatment, however she suddenly worsened further neurologically, became unconscious, opening eyes only to deep painful stimulus and developed dense right-sided hemiplegia. Pupils remained equal and reacting. She was noted to be not taking adequate feeds for almost 24 h prior to this deterioration. Repeat CT scan of the brain showed resolving hematoma and left middle cerebral artery (MCA) infarct. Ipsilateral lateral ventricle was compressed, but there was no midline shift. She was ventilated, started on IVFs, 20% mannitol and given exchange transfusion to reduce her HbS below 30%. There was good improvement in the next 24 h. She was weaned off the ventilator within 24 h and underwent 4 vessel angiography that showed narrowing and occlusion of distal internal cerebral artery (ICA) and hypertrophied lenticulostriate vessels bilaterally at the origin of carotid bulb, more on the right and poor visualization of the left MCA branches. Her vasculitic and prothrombotic screening was normal
Hammersley, 1983 <sup>336</sup>	Case report/case series	NR	EEG	Simple transfusion + exchange transfusion + IV Dilantin	1	100	IV Dilantin Simple transfusion 15 mL/kg PRBCs. Exchange transfusion 75 mL/kg whole blood	5 d	No	NA	NA	NA	Symptoms were completely resolved, vision back to normal

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Helton, 2002 <sup>339</sup>	Case report/case series	NR	MRI, neuro-exam	HU and valproic acid	1	100	Treatment was begun at a dose of 15 mg/kg by mouth daily, with dose escalation (by 5 mg/kg every 8 weeks to a maximum of 30 mg/kg/d). 8 mo later valproic acid (250 mg by mouth twice daily) was initiated to treat complex partial seizures	Approximately 60 mo	No	NA	NA	NA	The patient had a 2nd stroke 1 mo after beginning HU therapy. CT examination of her head revealed extension of the right frontoparietal infarct. She was treated for 1 mo in an outpatient rehabilitation facility. She was also hospitalized for a pain crisis 2 mo after beginning HU treatment and for an episode of ACS 3 mo after beginning therapy. The patient received a neurology consultation 8 mo after beginning HU therapy. She was noted to have mild left hemiparesis and right exophoria, left-sided hyperreflexia, and a mild delay in answering questions. EEG revealed a right frontocentral region spike wave abnormality, and valproic acid was initiated to treat complex partial seizures. Approximately 4 yr after beginning HU therapy, the patient was examined again with MRI and MRA. Moderate diffuse cerebral atrophy was present, with prominent sulci and further exvacuo dilatation of the ventricular system. However, the vasculopathy had continued to improve
Henry, 2004 <sup>341</sup>	Case report/case series	NR	Elevated opening pressure in lumbar puncture (LP)	Acetazolamide	3	100	8–20 mg/kg d	3–10 mo	No	NA	NA	NA	Case 1: At the time of the review she was still having some symptoms and elevated opening pressure after being treated for 10 mo. Case 1 and 2 completely recovered
Hitchcock, 1983 <sup>344</sup>	Case report/case series	NR	Computed axial tomography (CAT) scan	Blood transfusion, surgical management of the aneurysm	1	100	7 U of blood	NR	No	NA	NA	NA	Symptoms resolved
Kato, 2006 <sup>362</sup>	Case report/case series	NA	MRI	Patient 1 : transfusions and then hydroxyurea Patient 2 : chronic transfusion Patient 3 : hydroxyurea Patient 4 :NR Patient 5 :NR Patient 6 :NR	6	50	NR	NA	No	NA	NA	NA	The study describes 6 cases of patients with SCD central nervous system (CNS) occlusive disease who also have pulmonary hypertension (PHTN) and hypothesize that the etiology/pathophysiology of both complications are similar. In comparison with a cohort of 240 patients with SCD being screened for PHTN, these 6 with stroke have significantly more hemolytic anemia (lower hemoglobin, higher lactate dehydrogenase (LDH))

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Kotb, 2006 <sup>375</sup>	Case report/case series	NA	MRI, CT	Transfusion	36	100	NR	NA	No	NA	NA	NA	In patients with SCD presenting with CNS symptomatology, head imaging (CT/MRI) shows cortical infarction in 30.6% (frontoparietal temporal region was the most involved), small vessel disease in 38.9% (bilateral involvement, deep white mater more than basal ganglia, and the caudate nucleus was the most commonly involved site), cerebral atrophy in 52.8%, epidural hematoma associated with skull bone infarctions and scalp edema in 1 patient; widening of the diploic space of the skull noted in 10 patients; adenoid hypertrophy was very common 72%
Lee, 2002 <sup>389</sup>	Case report/case series	Unclear	Clinical exam/investigations	Case1: Vancomycin and acyclovir, red blood cell (RBC) transfusion, erythrocytapheresis. Case 2: Triple antibiotics, then doxycycline	2	100	Case1: Vancomycin and acyclovir, red blood cell (RBC) transfusion, erythrocytapheresis. Case 2: Triple antibiotics, then doxycycline	Variable	No	NA	NA	NA	Case 1: The patient's mental status improved gradually over the next several days even though he developed respiratory failure as a result of worsening pneumonia. The patient's neurologic examination on discharge was normal except for minimal dysarthria Case 2: Doxycycline was started on hospital d 5 instead of zithromax. Her mental status and neurologic deficit rapidly improved and recovered almost fully within 5 d. Repeat MRI 8 weeks later showed complete resolution of the lesions in the bilateral thalamus and brain stem
Liaquat, 2010 <sup>393</sup>	Case report/case series	NR	CT, MRI	Neurosurgery	6	100	Neurosurgery	Once	No	NA	NA	NA	1 patient received coiling and died. 3 patients had no new deficits on neurological followup. 2 patients had persistent weakness (aneurysm clipping recipients)
Love, 1985 <sup>399</sup>	Case report/case series	NR	Lumbar puncture, CT scan	Case 1: Steroid, oxygen, partial exchange transfusion, surgical repair of the aneurysm. Case 2: Aminocaproic acid, oxygen, partial exchange transfusion, surgical repair of the aneurysm	2	100	Case 1: Steroid, oxygen, partial exchange transfusion, surgical repair of the aneurysm. Case 2: Aminocaproic acid, oxygen, partial exchange transfusion, surgical repair of the aneurysm	Case 1: 5 weeks, Case 2: 11 d	No	NA	NA	NA	Satisfactory clipping of the aneurysm had been performed and the patient remained free of symptoms for 5 yr and 6 mo, respectively

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Montero-Huerta, 2006 <sup>419</sup>	Case report/case series	Right-sided CVA in the distribution of the right middle cerebral artery, and severe bilateral internal carotid artery stenosis	MRI and MRA	Inhaled nitric oxide (iNO) was administered by facemask at 80 ppm by volume	1	100	Inhaled nitric oxide (iNO) was administered by facemask at 80 ppm by volume	48 h	No	NA	NA	NA	Nitric oxide metabolite levels were dramatically low (14.8µM) before initiating iNO therapy (fig. 1). Nitric oxide levels increased (82 µM) after 3 h of nitric oxide breathing and were further increased (106 µM) at 22 h (fig. 1). The patient became neurologically responsive within 3 h of iNO therapy and before exchange transfusion. iNO was continued for 48 h, at which time the patient had a near complete neurologic recovery
Pashankar, 2008 <sup>201</sup>	Case report/case series	Patient had surgery for a frontal lobe hemorrhage; postoperatively he had a seizure on d 1. MRI/MRA showed postoperative changes and T2 prolongation within the white matter of parietal and occipital lobes bilaterally, which was consistent with reversible posterior leucoencephalopathy syndrome	CT scan, MRI/MRA	Nitroprusside infusion	1	100	Intravenous (IV) fosphenytoin He received monthly RBC transfusion for 6 mo	11 d	No	NA	NA	NA	Hypertension continued despite therapy with systolic blood pressure (SBP) range 132–169 mmHg and diastolic blood pressure (DBP) range 61–90 mmHg. On hospital d 3, the patient was extubated as he was alert, interactive, and breathing spontaneously. After extubation, neurological examination was normal. On hospital d 5, blood pressure (BP) improved (SBP range 118–140, DBP range 60–88 mmHg) and nitroprusside drip was discontinued. He was switched to oral antihypertensives, including enalapril and isradipine. The patient was discharged home on hospital d 11 when his BP was well-controlled on oral antihypertensive medications (SBP range 112–124 mmHg, DBP range 56–66 mmHg). 12 mo after discharge he is doing well, BP is normal (100/58 mmHg), and he no longer receives antihypertensive medications
Russell, 1976 <sup>463</sup>	Case report/case series	NR	Angiography	Blood transfusion	3	100	1 or 2 U of PRBCs/mo	1 yr	No	NA	NA	NA	Case 1: Minimal left hemiparesis. Case 2 and 3: Learning difficulties. Case 3: Moderate left hemiparesis. Case 5: Recent acute aphasia and minimal right hemiparesis
Schmugge, 2001 <sup>471</sup>	Case report/case series	NR	MRI, TCD, MRA, and angiography	He underwent extracranial-intracranial (EC-IC) bypass surgery on the left side and, 1 mo later, on the right side	1	100	HU treatment was increased to 30 mg/kg/d and acetylsalicylic acid was started (2 mg/kg by mouth every 2nd d) 16 h after the stroke, the patient received a half blood volume exchange transfusion, which reduced hemoglobin SD disease (HbSD) to 30%	NR	No	NA	NA	NA	18 mo after the last stroke, neither MRI nor MRA showed any new ischemic lesions, by 28 mo after the last stroke, all neuromotor abnormalities had disappeared, except for inconstant right Babinski sign, mild weakness in the right arm, and asymmetric tendon reflexes

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Sidani, 2008 <sup>487</sup>	Case report/case series	NR	Cerebral MRI	Automated RBC exchange and was started on unfractionated heparin for 24 h without any clinical improvement. At this point intradural sinus thrombolysis with recombinant tissue plasminogen activator was started. Followup venograms revealed significant, but not complete, opacification of the superior sagittal, right transverse, and sigmoid sinuses	1	100	After discharge, the patient was transfused for 3 mo and hemoglobin maintained between 10.3 and 12 g/dL. Transfusions were stopped after 3 mo and oral anticoagulants started	NA	No	NA	NA	NA	The patient tolerated the procedure well and had significant clinical improvement manifested by disappearance of the headache and improvement in the aphasia. He was discharged within few days on low-molecular-weight heparin. After discharge the patient was transfused for 3 mo and hemoglobin maintained between 10.3 and 12 g/dL. Followup magnetic resonance venography (MRV) done at 1 and 3 mo from discharge showed a patent superior sagittal sinus with further decrease of the filling defects within the right transverse and sigmoid sinuses. Transfusions were stopped after 3 mo and oral anticoagulants started. At this time his hemoglobin values were noted to increase up to 14.2 g/dL. He was not receiving erythropoietin or any other agent that would cause an increase in hemoglobin. The hemoglobin level prior to HU therapy was 10.5 g/dL. He underwent phlebotomy once and hemoglobin stabilized at around 12.5g/dL on HU. He has had constant neurologic improvement over the last year and has had no pain crises. Hemoglobin values ranged between 11.5 and 13 g/dL. He required phlebotomy one more time because of hemoglobin above 13.5 g/dL and subsequently hemoglobin values remained in 12–12.7 g/L range. Factor VIII activity measured during steady state was 132%. However, he developed right hip pain and has clear radiographic evidence of avascular necrosis (AVN) of the right femoral head
Van Hoff, 1985 <sup>514</sup>	Case report/case series	NR	Clinical presentation, spinal tap, CT scan + EEG, and angiography for case 1	Case1: Single-volume exchange transfusion that night, several blood transfusions, phenytoin sodium (10 mg/kg) for seizures. Case 2: Single-volume exchange transfusion, several blood transfusions	2	100	Case1: Single-volume exchange transfusion that night, several blood transfusions, phenytoin sodium (10 mg/kg) for seizures. Case 2: Single-volume exchange transfusion, several blood transfusions	Case 1: NR Case 2: 4 weeks.	No	NA	NA	NA	Case 1: The patient began a long-term transfusion program to maintain a hemoglobin level >10 g/dL and a fraction of HbS of <30%. After 16 mo she remains asymptomatic. Case 2: He received transfusions several times over the next 4 weeks to maintain a fraction of HbS of <30%. Transfusion therapy was discontinued after 4 weeks, and he has had no further neurologic symptoms during the 22 mo since that episode
Van Mierlo, 2003 <sup>515</sup>	Case report/case series	NR	CT, MRI, and MRV	Exchange transfusion, blood transfusion, warfarin, nadroparin calcium	1	100	Warfarin for 3 mo, doses NR	3 mo	No	NA	NA	NA	Full neurological recovery

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Wali, 2000 <sup>521</sup>	Case report/case series	Acute clinically evident neurological event	Clinical presentation, head CT	Midazolam, IVF, partial exchange transfusion	1	100	Midazolam infusion 2 mg/h Exchange transfusion 20 mL/kg of PRBCs	3 d	No	NA	NA	NA	The child dramatically improved after exchange transfusion, she regained complete consciousness with some paresis in the right side of her body
Wolf, 2008 <sup>530</sup>	Case report/case series	NR	Clinical presentation neurological exam, head CT, brain MRI	Emergency right frontal craniotomy with evacuation of a right frontal hematoma	1	100	She was given mannitol, dexamethasone, and FFP prior to transport to intensive care unit (ICU) and subsequent surgery. An exchange transfusion was performed on postoperative d 1	>1 mo (duration of hospital stay)	No	NA	NA	NA	Her immediate postoperative course was complicated by hypertension and bradycardia treated with multiple mannitol doses, and insertion of an intracranial monitoring device. Her clinical status stabilized during her 2nd week of hospitalization. Her intracranial pressure (ICP) spikes resolved, and the intraparenchymal device was removed on postoperative d 7. She was successfully extubated on postoperative d 9 at which time she was responding appropriately to questions and obeying commands. She was transferred to a rehabilitation facility on postoperative d 15. Prior to discharge from our institution, she had a repeat TCD, which again was normal. A hemoglobin electrophoresis prior to discharge was notable for HbS level of 20%. The goal was to maintain her hemoglobin above 10 g/dL and her HbS level below 30%. A cerebral angiogram was negative for the presence of any aneurysm or abnormality of cerebral vasculature such as moyamoya syndrome. Successive CT scans of the brain showed resolution of the hematoma along with the expected postoperative changes

**Table 6. Acute and Chronic Ocular Complications Incidence and Outcomes**

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Farber, 1991 <sup>18</sup>	RCT	Proliferative sickle cell retinopathy (PSR)	Not defined	Clinical exam/investigations	Argon laser scatter photocoagulation therapy	(99 eyes)	100	Argon laser scatter photocoagulation therapy	NR	Yes. Untreated control arm not receiving photo-coagulation	(75 eyes)	100	No photo-coagulation for neovascularization anytime during the study	Prolonged loss of visual acuity was statistically significantly reduced in the treated eyes. Only 3 (3%) of the treated eyes, compared with 9 (8.3%) of the control eyes, experienced a loss of visual acuity. Kaplan-Meier survival analysis showed a statistically significant difference between the treated and control eyes ( $p=.019$ ). The incidence of vitreous hemorrhage was also significantly reduced in the treated eyes after controlling for the previously defined risk factors of vitreous hemorrhage and extent of PSR at entry into the study. The incidence of any vitreous hemorrhage was also reduced, 11.1% in the treated eyes compared with 18.7% in the control eyes (Mantel log-rank test=.111). Even after controlling for vitreous hemorrhage and the amount of neovascularization at entry a significant difference between the treated and control groups was evident (chi-squared =4.5, $df=1$ , $p\leq.05$ ). There were no complications associated with argon laser scatter photocoagulation

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Fox, 1993 <sup>20</sup>	RCT	Sickle hemoglobin C disease (HbSC) PSR	NR	Fluorescein angiogram	Sectoral, scatter laser photocoagulation	(74 eyes)	100	Sectoral, scatter laser photocoagulation	3 yr	Yes: Control	(60 eyes)	100	No treatment	Complete infarction of all PSR in an eye occurred in 7 of 74 treated eyes and 2 of 60 control eyes. Treatment resulted in significantly greater regression (decrease in number or size of PSR lesions) in eyes of patients aged <25 yr at enrollment but not in eyes of patients ≥25 yr at enrollment. Infarction of individual PSR lesions was significantly more common in treated eyes. Treated PSR was significantly more likely to infarct if small (<15° circumferential involvement) and if flat rather than elevated. New PSR was significantly less likely to develop in treated eyes
Jacobson, 1991 <sup>26</sup>	RCT	Peripheral PSR	Not defined	Clinical exam/investigations	Argon laser feeder vessel photocoagulation	(25 eyes)	100	Argon laser feeder vessel photocoagulation	10 yr	Yes: Control group receiving no treatment	(20 eyes)	100	No feeder vessel photo-coagulation was done	There were 20 control untreated eyes and 25 argon laser-treated eyes. Prolonged loss of visual acuity was rare in both groups. Argon laser photocoagulation has had a sustained effect on reducing the incidence of vitreous hemorrhage and visual loss from vitreous hemorrhage. 9 (45%) of 20 control eyes had vitreous hemorrhage, and it was recurrent in 6 (66%) of these 9 eyes. A single episode was the only hemorrhagic event in the treated eyes. The laser-induced complications of choroidal neovascularization or retinal detachment were not associated with long-term visual sequelae. New sea fan evolution in 47% of study eyes suggests that these patients require long-term surveillance

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Williamson, 2009 <sup>156</sup>	R, Obs	Vitreoretinal complications	NR	Clinical presentation	Surgery (pars plana vitrectomy)	17	100	Pupils were dilated with topical phenylephrine 2.5% and cyclopentolate 1% preoperatively. During the 1 mo postoperatively, topical Maxitrol was prescribed four times a day (q.d.s.) and atropine 1% twice a day (b.i.d.)	Acutely	Yes: Observation	10	100	Observation	Group 1: 18 eyes of 17 patients received surgery, and 15 of 18 eyes (83%) had improved vision postoperatively. Group 2: Of the presentations and visual outcomes of 10 patients who were observed, 2 patients demonstrated spontaneous resolution of their retinal conditions
Kimmel, 1986 <sup>188</sup>	P, Obs	PSR	Not defined	Clinical exam/investigations	Peripheral circumferential retinal scatter photocoagulation (PCRP)	44 (70 eyes)	100	PCRP	Acutely	No	NA	NA	NA	With an average followup of 3.3 yr, 33% of preexisting sea fans regressed completely, 46% regressed partially, 19% remained stable, and 2% showed progression. De novo neovascularization developed after treatment in only 1 eye (1.4%). 95% of patients treated had a final visual acuity of 20/30 or better, and only 1 patient (2%) developed a nonresolving vitreous hemorrhage requiring vitrectomy surgery. These results confirm the authors' previous report and continue to compare favorably to the natural history of PSR in which de novo lesions developed in 58%, and 12% of eyes ended with a visual acuity of 20/200 or less

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Sayag, 2008 <sup>208</sup>	P, Obs	PSR: stage III	Peripheral retinal neovascularization. Stage III was defined by leakage, associated or not with fibrosis, of IV-administered fluorescein	Direct and indirect ophthalmoscopy	PCRP	38	100	PCRP	4 yr	Yes: I	35	100	No treatment	The evolution was not statistically significant between treated and untreated groups concerning flat sea fan <1 Macular Photocoagulation Study (MPS) disc area (grade A) or elevated sea fan with partial fibrosis (grade C). Progression and regression were compared between the 2 groups for grade B, resulting statistically significant ( $p<.05$ ). 9 complications (13%) were observed, which only occurred in untreated patients with elevated sea fan and hemorrhage (grade B) or complete fibrosed sea fan with well-defined vessels (grade E) ( $p<.05$ )
Al-Abdulla, 2001 <sup>235</sup>	Case report/case series	Extensive perimacular arteriolar occlusions and acute chest syndrome (ACS)	NR	Ophthalmoscopy, fluorescein angiography	Transfusion	1	NA	Transfused with 1 U of packed erythrocytes	NR	No	NA	NA	NA	The patient subsequently received an exchange erythrocyte transfusion and was discharged from the hospital following resolution of his chest syndrome. In followup over the next month, acuity in his right eye remained hand motions at 3 ft, though the milky white, thickened retinal lesion resolved

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Benner, 2000 <sup>265</sup>	Case report/case series	Glaucoma associated with sickle cell hyphema	NR	NR	Transcorneal oxygen therapy	3	100	Each patient was treated with transcorneal oxygen therapy using humidified oxygen delivered through a pair of modified swimmer's goggles at a flow rate that ranged from 1 to 3 L/min. 5 patients: 1 and 2 were treated for a period of 4 d, whereas patient 3 was treated for 10 d	4–10 d	No	NA	NA	NA	All 3 patients in this report had a significant reduction in their intraocular pressure within hours after starting the transcorneal oxygen therapy. The intraocular pressure of the 1st patient was increased to >34 mmHg for almost 48 h despite the use of maximal antiglaucoma therapy. His intraocular pressure dropped rapidly from 37 mmHg to 32 mmHg after only 3 h of oxygen therapy and dropped further to 19 mmHg after a total of 8 h of oxygen therapy. He received only intermittent oxygen therapy, alternating 2 h of oxygenation with 2 h of rest. The 2nd patient received continuous oxygen therapy and had a more rapid reduction in his intra-ocular pressure. His intraocular pressure dropped from 47 mmHg to 39 mmHg within 1 h of starting the oxygen therapy alone. Methazolamide 50 mg and a single drop of apraclonidine 1% were administered at the end of the 1st h, because it was deemed unethical to withhold antiglaucoma medication and rely solely on oxygen therapy. After 8 h of oxygen therapy, his intraocular pressure had decreased to 20 mmHg. The final patient was treated with oxygen therapy alone and had a dramatic reduction in his intraocular pressure from 43 mmHg to 26 mmHg over a 3-h period. Transcorneal oxygenation was able to substantially lower the intraocular pressure in all 3 patients within 3 to 8 h after it was started

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Blank, 1981 <sup>288</sup>	Case report/case series	Orbital infarction	NR	Computed tomography (CT) scan, bone scan	Case 1: Ampicillin. Case 2: Ampicillin and nafcillin. Case 3: Intravenous fluids (IVF), ampicillin, and oxacillin	3	100	Case 1: Ampicillin. Case 2: Ampicillin and nafcillin. Case 3: Intravenous fluids (IVF), ampicillin, and oxacillin	8 d, 8 d, 11 d for cases 1, 2, and 3 respectively	No	NA	NA	NA	Symptoms resolved, bone scans were normal
Clarke, 2001 <sup>283</sup>	Case report/case series	Simultaneous, bilateral, retinal infarction with branch retinal arteriolar occlusion	NR	Retinal examination, fluorescein angiography	Hypertransfusion protocol	1	100	Started on a hypertransfusion protocol to keep his sickle cell hemoglobin (HbS) concentration <30%	NR	No	NA	NA	NA	4 mo later, he showed mild temporal pallor of the optic nerves, worse in the right eye than the left, with best corrected visual acuity in each eye of 20/200
Curran, 1997 <sup>289</sup>	Case report/case series	Orbital compression syndrome (subperiosteal hematoma)	NR	CT scan, Technetium-99m bone scan	Surgical evacuation of bilateral hematoma, IVF, antibiotics, analgesics, packed red blood cells (PRBCs) transfusion	1	100	Surgical evacuation of bilateral hematoma, IVF, antibiotics, analgesics, packed red blood cells (PRBCs) transfusion	NR	No	NA	NA	NA	Recovery was complete 13 d after surgery, a mild recurrence happened 14 mo later resolved with conservative treatment
Dixit, 2004 <sup>298</sup>	Case report/case series	Orbital compression syndrome	NR	CT scan, magnetic resonance imaging (MRI)	The patient was managed conservatively with IVF and broad spectrum antibiotics. He was given steroids also under antibiotic cover	1	100	Blood transfusions were required twice to maintain hemoglobin above 10 g/dL and he was started on hydroxyurea (HU) therapy	4 weeks	No	NA	NA	NA	His renal parameters improved gradually after hydration. His blood counts also normalized by the end of the 1st week. He showed gradual improvement with reduction in swelling and restoration of ocular movements. He recovered fully by 4 weeks. He was discharged and is doing well after 12 mo of followup and maintained hemoglobin above 10 g/dL without blood transfusions
Durant, 1982 <sup>304</sup>	Case report/case series	Exudative retinal detachment	NR	Slit lamp examination	Argon laser photocoagulation	1	100	Argon laser photocoagulation	NR	No	NA	NA	NA	7 mo after treatment, vision in the treated eye was 20/20, retina completely reattached

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Freilich, 1972 <sup>316</sup>	Case report/case series	Retinal detachment	Retinal detachment involving all but a small area in the superior nasal quadrant and a temporal retinal detachment with retinal tears with days of vision loss	NR	Scleral buckling procedure in a hyperbaric chamber under 2 atm oxygen	2	100	Scleral buckling procedure in a hyperbaric chamber under 2 atm oxygen	NR	No	NA	NA	NA	Both patients were successfully treated without the development of anterior segment ischemia or other complications
Freilich, 1973 <sup>317</sup>	Case report/case series	Retinal detachment	NR	Ophthalmologic exam	Scleral buckling procedure in the hyperbaric oxygen chamber	3	100	Scleral buckling procedure in the hyperbaric oxygen chamber	NR	No	NA	NA	NA	Patients improved: Case 1: Preoperative visual acuity Hand motion, 1 ft, postoperative 20/300. Case 2: Preoperative hand motion, 2 ft, postoperative 20/30+2. Case 3: Preoperative 20/40, postoperative 20/25+
Freilich, 1975 <sup>318</sup>	Case report/case series	Retinopathy and retinal detachment	NR	Visual acuity ranged from hand motion at 6 inches to counting fingers, to 20/40 vision	Scleral buckling technique to repair retinal tears. The operation is performed in a hyperbaric oxygen chamber	8	100	Scleral buckling technique: none of the recti muscles are removed and the cold applications are placed in scleral dissection bed only in the areas of retinal tears	NA	No	NA	NA	NA	Visual acuity improved, ranging from 20/300 to 20/20. No patients developed anterior segment ischemia or other complications
Goldbaum, 1976 <sup>328</sup>	Case report/case series	Proliferative sickle cell retinopathy (PSR)	Not defined	Clinical exam/investigations	Vitrectomy	5	100	Vitrectomy	NR	No	NA	NA	NA	Peripheral vitrectomy is riskier than central vitrectomy alone. If visualization of the sea fans is sufficient, it is safer to close the sea fans prior to vitrectomy in order to obviate the need for peripheral vitrectomy; then only central vitrectomy is performed. When sea fans cannot be closed prior to vitrectomy, peripheral vitreous is removed to allow early photocoagulation of the sea fans before they bleed again

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Goldberg, 1978 <sup>329</sup>	Case report/case series	Increased (intraocular pressure) IOP + hyphema	NR	Slit lamp examination, IOP measurement	Oral glycerin and acetazolamide (Diamox) and with topical atropine, epinephrine, and corticosteroids	4	100	Oral glycerin and acetazolamide (Diamox) and with topical atropine, epinephrine, and corticosteroids	Case 1: 8 d; Case 2 24h; and cases 3 and 4: NR	No	NA	NA	NA	<p>Case 1: 10 mo after initial admission, the patient still had elevated IOP (between 24 and 30 mmHg), unremitting pain, and blindness.</p> <p>Case 2: Postoperatively, the patient's course was uncomplicated. There was speedy resolution of the residual hyphema, and the IOP remained approximately 12mm Hg or less without any medication except topical atropine.</p> <p>Case 3: Following paracentesis, there was no visible hyphema, and the IOP remained below 12 mmHg.</p> <p>Case 4: Postoperatively, no hyphema was visible, and the IOP was very low. A retinal detachment was successfully repaired by a combined vitrectomy scleral buckling technique</p>
Goodwin, 2008 <sup>330</sup>	Case report/case series	Bilateral central retinal artery occlusion associated with moyamoya syndrome	NR	Ophthalmologic examinations (fluorescein angiogram and fundus photographs), MRI, magnetic resonance angiography (MRA)	Blood transfusion at the time of presentation then every 4 weeks for 6 weeks	1	100	Blood transfusion at the time of presentation then every 4 weeks for 6 weeks	NR	No	NA	NA	NA	Visual acuity improved
Hasan, 2004 <sup>338</sup>	Case report/case series	Central retinal vein occlusion	NR	Ophthalmic evaluation	Anticoagulation therapy initially with full doses of enoxaparin long-term warfarin	1	100	Anticoagulation therapy with full doses of enoxaparin and subsequently placed on long-term warfarin	NR	No	NA	NA	NA	The visual acuity improved gradually over a period of 4 mo, and repeat retinal examinations during this period showed resolution of central vein thrombosis

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Leen, 2002 <sup>390</sup>	Case report/case series	Anterior segment ischemia after retinal reattachment surgery	NR	Fluorescein angiography, slit lamp examination	Oral prednisone, oral ranitidine, topical prednisolone, ciprofloxacin and atropine eye drop, 3 U of PRBCS	1	NA	60 mg oral prednisone for 2 d, oral ranitidine 150 mg b.i.d., topical prednisolone acetate 1% 1 drop hourly, ciprofloxacin and atropine eye drops, 3 U of PRBCS	7 d	No	NA	NA	NA	Corneal edema resolved completely, shallow anterior chamber, and hypotony persisted
Liem, 2008 <sup>395</sup>	Case report/case series	Sudden onset blindness due to retinal artery occlusion	NR	Ophthalmic assessment	Emergent exchange transfusion + monthly simple transfusion	3	100	Simple monthly transfusion	6 mo	No	NA	NA	NA	Case 1: His vision remains reduced to finger counting on the right and light perception on the left. Case 2: Her vision was 20/20 in the left eye but remained at 20/200 on the right at last exam. Case 3: Her right visual acuity was 20/80 left was normal
Makhoul, 2010 <sup>404</sup>	Case report/case series	Macular infarction	NR	Funduscopy and angiogram	Erythrocyte transfusion, anterior chamber paracentesis	2	100	Erythrocyte transfusion	NR	No	NA	NA	NA	Erythrocyte transfusions-IOP rose again after a few days. Pressure later controlled with anterior chamber paracentesis
Merritt, 1982 <sup>411</sup>	Case report/case series	Bilateral macular infarction	NR	Funduscopy, fluorescein angiography, visual acuity	IVF 1.5 times maintenance, blood transfusion	1	100	2 U of PRBCs	5 d	No	NA	NA	NA	1 d after transfusion: visual acuity right eye, no light perception, left eye 20/15-1. 1 mo later, light perception was detected in the right eye, 6 mo later hand motion at 3 inches was detected in right eye, left eye is still 20/15-1
Morgan, 1987 <sup>421</sup>	Case report/case series	PSR	Not defined	Clinical exam/investigations	Surgery (vitrectomy)	4	100	NR	NR	No	NA	NA	NA	Severe complications including a high incidence of anterior segment necrosis have been reported in both vitrectomy and scleral buckling operations in the patients

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Mueller, 2009 <sup>423</sup>	Case report/case series	Unilateral exophthalmia due to orbital compression syndrome	NR	MRI	IVF, analgesics and intravenous (IV) antibiotics (Cefuroxime)	1	100	Cefuroxim and Clindamycin Single blood transfusion of PRBC	NR	No	NA	NA	NA	All the symptoms improved apart from the exophthalmia, The ophthalmological examination was normal apart from the exophthalmia and the visual acuity was still normal. The MRI scan of the orbita showed inflammatory signs of the eye muscles with oedematosus swelling and perineural edema. The optical nerve and the brain were normal. In summary it was assumed, that there were several vaso-occlusive events (VOEs) present at the same time
Periman, 1994 <sup>442</sup>	Case report/case series	Retrobulbar ischemic optic neuropathy	NR	Fundus photography	IVF, antibiotics, exchange transfusion, prednisone	1	100	Prednisone 100 mg daily for 4 d, then tapered down	NR	No	NA	NA	NA	Optic disk pallor and cupping continued to progress
Roy, 1987 <sup>462</sup>	Case report/case series	Retro equatorial red retinal lesions	NR	Slit lamp examination, fundus examination, fluorescein angiogram	Nifedipine	2	100	Nifedipine 10 mg every 8 h for 10 d	10 d	No	NA	NA	NA	Red retinal areas cleared completely, fluorescein angiogram showed reperfusion in case 1 and no change in case 2
Schubert, 2005 <sup>472</sup>	Case report/case series	Retinal schisis	A concave tractional retinal elevation, retinal nonperfusion, inner-layer breaks, absorption of laser by the outer layer, and a split pattern on optical coherence tomography	Clinical exam/investigations	Retinal repair, cataract extraction, and repeat capsulotomy	2	100	Retinal repair, cataract extraction, and repeat capsulotomy	NR	No	NA	NA	NA	Schisis was stable at the end of 4 yr after treatment, visual acuity was 20/80 in operated eye
Seiberth, 1999 <sup>473</sup>	Case report/case series	Proliferative sickle cell retinopathy	NR	Clinical exam/investigations	Transscleral diode laser photocoagulation	1	100	Transscleral diode laser photocoagulation	1 attempt, both eyes	No	NA	NA	NA	After coagulation, vascular proliferation receded completely. Vitreous bleeding was absorbed. There were no side effects during followup (22 mo)

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Sidman, 1990 <sup>488</sup>	Case report/case series	Orbital bone infarction	NR	Clinical presentation, CT scan	IVF, blood transfusion, oxygen, ceftriaxone, clindamycin, gentamicin, analgesics	1	100	3 U of PRBCs	10 d	No	NA	NA	NA	The patient recovered and was discharged on oral antibiotics after 10 d
Siegel, 1988 <sup>489</sup>	Case report/case series	Sickle cell retinopathy	NR	Biomicroscopy, indirect ophthalmoscope	Photocoagulation to cause regression of the neovascularization	1	100	Photocoagulation to cause regression of the neovascularization	NR	No	NA	NA	NA	Treatment was completed without complication
Sokol, 2008 <sup>494</sup>	Case report/case series	Orbital compression syndrome	NR	MRI	Methyl-prednisolone	3	100	Case 1: 1 g methylprednisolone daily Case 2: methylprednisolone 250 mg/d and intravehypotropic in primary gaze Case 3: IV Solu-Medrol was administered for 1 d followed by a tapering dose of oral prednisone starting at 30 mg daily	Case 1:NR Case 2: 3d Case 3: NR	No	NA	NA	NA	Symptoms resolved within 2, 3, and 11 d, respectively
Wolff, 1985 <sup>531</sup>	Case report/case series	Orbital infarction	NR	CT, Technetium-99m bone scan	Blood transfusion, moxalactam	1	100	2.5 g 6 hourly for 10 d	10 d	No	NA	NA	NA	The patient was discharged on d 15 without symptoms, remained asymptomatic for 6 mo
Zinn, 1981 <sup>540</sup>	Case report/case series	Retinal detachment with vitreous hemorrhage	NR	Slit lamp, funduscopy, indirect ophthalmoscopy	Scleral buckling surgery in a hyperbaric oxygen chamber	1	100	Scleral buckling surgery in a hyperbaric oxygen chamber	NR	No	NA	NA	NA	Retina reattached, vision improved from hand motion to 20/40

**Table 7. Acute and Chronic Renal Complications Incidence and Outcomes**

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	Reported results
Foucan, 1998 <sup>19</sup>	RCT	Microalbuminuria	Defined as urinary albumin excretion between 30 and 300 mg per 24 h on 3 separate occasions during the 6 mo period preceding the study	Microalbuminuria (MA) was measured by immunonephelometry	Captopril	12	100	Captopril for 6 mo, doses ranged between 6.25 mg/d to 25 mg/d	6 mo	Yes: Placebo (10 patients)	Captopril reduces albuminuria and slightly decreases blood pressure (BP) in patients with sickle cell anemia (SCA) at the end of 6 mo
Alvarez, 2006 <sup>70</sup>	R, Obs	Microalbuminuria	A screen for MA was positive when there was increased urinary albumin detected by spot urine sample, >2.9 mg/dL or adjusted for age, and the urine albumin/creatinine ratio was 30–300 mg/g creatinine	Urine analysis 24-h urine collections	Hydroxyurea (HU) Chronic blood transfusions	19	15.8	Hydroxyurea (HU) Chronic blood transfusions	NR	No	19 of 120 (15.8%) screened patients had MA detected by spot urine (mean albumin absolute value 6.95±.56 mg/dL) and abnormal albumin to creatinine ratios (79.8±0.62 mg/g creatinine). 24-h urine collections confirmed 57% of MA cases by spot urine. There was no difference in hyperfiltration between positive and negative patients. From the MA-positive patients, 15 had homozygous sickle cell disease (HbSS) (16.8% of HbSS group), and 4 had sickle hemoglobin C disease (HbSC) (18% of HbSC group). 19% of children 10 yr of age or older had MA, as compared to 8% of the younger children (p=0.018), demonstrating that increasing age is a risk factor for MA. There was a positive correlation between MA and acute chest syndrome (ACS). Young age at start of chronic transfusions was inversely related to MA and therefore reniprotective (p=0.03). We did not see a protective effect in the group of patients taking HU for a relatively short time, mean age at start of treatment 12±5 yr; however, the sample was small

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	Reported results
Couillard, 2007 <sup>84</sup>	R, Obs	Autoimmune and/or systemic disease and sickle cell disease (SCD)	SCD and systemic lupus erythematosus, autoimmune hepatitis; autoimmune hemolytic anemia; sarcoidosis; Crohn's disease, or polyarthritis	NR	Prednisone	16	100	Patients received prednisone in range of 0.5–1.3 mg/kg/d	≤6 mo	No	The steroid treatment was poorly tolerated. 15 severe complications were observed in 10/16 patients (62%). 8 patients had severe vaso-occlusive events (VOEs) within the 2 mo of starting steroid treatment, including a twofold increase in frequency of painful crises, a very severe pain episode, ACS, stroke, and renal infarction. Severe infections (3 patients) and avascular necrosis (AVN) (1 patient) of the femoral head also occurred. Occurrence of severe pain episodes led to withdrawal of steroid treatment (3 patients) or dose reduction (1 patient)
Little, 2006 <sup>116</sup>	R, Obs	Renal failure	NR	Clinical presentation	National Institutes of Health (NIH): Erythropoietin or darbepoietin with or without HU Published reports: erythropoietin median of >200 U/kg/dose	(NIH: 13. Published reports: 39)	(NIH: 100. Published reports: 100)	Erythropoietin or darbepoietin with or without HU Published reports: erythropoietin median of >200 U/kg/dose	NIH: median of 4 mo. Published reports: median 3 mo	No	Hematologic responses, suggest that Erythropoietin or darbepoietin therapy may allow more aggressive HU dosing in high-risk patients with SCD and in the setting of mild renal insufficiency, common to the aging SCD population. Furthermore Erythropoietin or darbepoietin appears to be safe with SCD, particularly when used in conjunction with HU
Ojo, 1999 <sup>122</sup>	R, Obs	SCD-end-stage renal disease (SCD-ESRD)	NR	NR	Renal transplant	82	100	Renal transplant	NA	No	Incidence of delayed graft function and predischage acute rejection was 24% and 26%, and similar to that observed in non-SCD ESRD. 3-yr cadaveric graft survival was 48%, which was less than that observed in non-SCD ESRD (60%, $p=.055$ ). There was a trend toward improved survival in the group compared to the dialysis-treated, wait-listed counterparts (relative risk (RR)=0.14, $p=.056$ ). It was concluded that short-term renal allograft results in recipients with end-stage sickle cell nephropathy was similar to that obtained in other causes of ESRD, but the long-term outcome was comparatively diminished
Warady, 1998 <sup>152</sup>	R, Obs	SCD-ESRD	NR	NR	Renal transplant	9 (10 transplants)	100	Renal transplant	NA	No	Patient survival was 89%. There had been 21 acute rejection episodes in 7 of 9 patients. 6 of the 21 rejections occurred within the first 100 d posttransplant. 9 (43%) of the rejections were completely reversed. It was concluded that renal transplantation is a viable option for adolescent patients with sickle cell nephropathy and ESRD

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	Reported results
McKie, 2007 <sup>194</sup>	P, Obs	MA and proteinuria (P)	NR	Urine sample testing	Treatment with HU	37	100	The dose of HU ranged from 15 to 30 mg/kg/d and was titrated to clinical improvement in symptoms	NA, "until improvement in clinical symptoms"	Yes: Comparison Patients with persistent MA/P and no other significant complications, and children who developed MA/P while on HU were referred for possible angiotensin converting enzyme inhibitor (ACEI) treatment (n=154)	The prevalence of MA/P at the last study visit was 19.4% (37 of 191 children). MA excretion normalized in 44% of patients treated with HU and 56% of patients treated with ACEI. Hyperkalemia developed in 4 ACEI patients resulting in discontinuation of treatment in 3 children. The preliminary data suggest that although both HU and ACEI therapy may be beneficial for MA/P, hyperkalemia may limit the utility of ACEI
Alebiosu, 2002 <sup>239</sup>	Case report/case series	Renal papillary necrosis	NR	Intravenous (IV) urography	Furosemide, Na bicarbonate, hematinics	1	100	Furosemide, Na bicarbonate, hematinics	4 weeks	No	Symptoms resolved
Al-Mueilo, 2005 <sup>246</sup>	Case report/case series	End-stage sickle cell nephropathy	NR	Proteinuria, hypertension, microscopic hematuria, and ineffective erythropoiesis with worsening anemia. Abdominal ultrasound (US)	Renal replacement therapy (maintenance hemodialysis and renal transplant)	2	100	NR	41 mo (in patient 1) and NA in patient 2 (surgery)	No	41 mo after initiation of maintenance hemodialysis in patient 1, the patient died suddenly at home. The patient's family reported his having increasing back pain for 1 d before the final event. Patient 2 had renal transplant. He is reported to enjoy excellent graft function 6.5 yr posttransplantation with blood urea nitrogen (BUN) of 8.57 mmol/L and serum creatinine (Cr) of 115 µmol/L
Davenport, 2008 <sup>293</sup>	Case report/case series	Nonoliguric acute renal failure	NR	Magnetic resonance imaging (MRI), urine dipstick, urine microscopy	Hemodialysis therapy	1	100	Hemodialysis therapy	10 d	No	Renal function recovered, and he was discharged from hospital, with a serum urea of 16 mmol/L and Cr of 313 mmol/L
Kelly, 1986 <sup>364</sup>	Case report/case series	Acute renal failure	NR	BUN/Cr, electrolytes, renal US	Case 1: Blood transfusion, hemodialysis, intravenous fluids (IVF), IV calcium, glucose and insulin, bicarbonate. Case 2: IVF and antibiotics	2	100	6 packed red blood cells (PRBCs) for patient 1	NR	No	Condition completely resolved, BUN/Cr back to normal

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	Reported results
Miner, 1987 <sup>414</sup>	Case report/case series	Nephropathy in a transplanted kidney	Upon admission, the patient was complaining of pain in his back, legs, and knees, and his hemoglobin was 6.8 g/dL. A renal scan demonstrated a wedge-shaped, photon-deficient area in the cortex of the superior pole consistent with an infarct and blunted upper pole calyces were noted and were consistent with papillary necrosis	Renal scan, kidney biopsy	Meperidine, IVF, nasal oxygen and blood transfusions	1	NA	Meperidine, IVF, nasal oxygen and blood transfusions	NR	No	In the 1.5-yr interval since the hospitalization, there have been no acute rejection episodes, but the frequency of his sickle cell crises has intensified and his renal function has further deteriorated
Montgomery, 1994 <sup>420</sup>	Case report/case series	Sickle cell nephropathy	Sickle cell nephropathy denotes a spectrum of functional and structural abnormalities. Functional: hematuria, proteinuria, hyposthenuria, hyperuricemia, nephrotic syndrome, and chronic renal failure. Structural perturbations include medullary and renal cortical infarcts, papillary necrosis mesangial expansion, and basement membrane duplication	Clinical exam/investigations	Renal transplantation	5	100	Renal transplantation	Graft survival time variable. 10 mo–13 yr	No	Patient and graft survival at 1 yr were 100%
Nasr, 2006 <sup>427</sup>	Case report/case series	Nephrotic syndrome and renal failure	NR	Renal function test, kidney biopsy, MRI	Exchange transfusion, IV methylprednisolone then oral prednisolone, and captopril	1	100	Oral prednisone 60 mg daily	NR	No	The patient remains fully nephrotic despite treatment with steroids and captopril

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Medication/transfusion details	Duration of treatment	Secondary/control arm	Reported results
Steinberg, 1991 <sup>500</sup>	Case report/case series	Anemia of renal failure	Patients with SCD, renal failure before dialysis and severe anemia	Patients had hemoglobin of 4.4 and 5.3 g/dL; Cr levels of 309.4 and 123.9 μmol/L	Recombinant human erythropoietin	2	100	100 U of erythropoietin/kg body weight 3x/week. Patients also received 300 mg oral ferrous sulfate, 3x/d. The dose was escalated until target packed cell volume of 0.20 reached	8 mo	No	Both patients had an increased in their packed-cell volume of about 45%. The Cr-labeled red cell mass also increased 45%, plasma volume fell 6%, and blood volume was unchanged. No effect on the level of fetal hemoglobin (HbF) was seen
Taksande, 2009 <sup>507</sup>	Case report/case series	Renal abscess	Fever, lumbar pain, abdominal pain, and occasional flank mass are presenting features.	Laboratory, physical examination, radiograph, ultrasonography and CT	IV ceftriaxone and amikacin were started	1	100	Packed blood transfusions were administered to the	7 d	No	A 5-yr-old boy presented with a 10-d history of fever, cough, and pain in the abdomen. On physical examination, he had fever with temperature of 39.5°C, severe pallor, pulse rate of 98/min, respiratory rate of 32/min and BP of 90/60 mmHg. There were no signs of dehydration. On abdominal examination, he had no hepatosplenomegaly. Crepitations were heard in both lung fields on respiratory examination, while other systemic examination was essentially normal. Initial lab investigations demonstrated a hemoglobin of 6 g/dL; white blood cell (WBC) count of 56,200/mm <sup>3</sup> (65% neutrophils, 32% lymphocyte), platelet count of 350,000/mm <sup>3</sup> , and an erythrocyte sedimentation rate of 92 mm/h. Renal function tests and urinalysis were normal. Despite 7 d of antibiotic therapy, fever persisted although the chest signs had resolved. Repeat WBC count was 32,000/mm <sup>3</sup> . Blood and urine cultures yielded no growth. Widal test was negative, and the Mantoux test was nonreactive. The possibility of an occult abscess was considered. A US of the abdomen revealed an enlarged left kidney with evidence of a hypoechoic collection measuring 4.6×3.2×2.9 cm in the midpole

**Table 8. Acute Pain Incidence and Outcomes**

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/medication	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Adams-Graves, 1997 <sup>3</sup>	RCT	Acute pain crisis of SCD	Acute pain, requiring hospitalization, with onset between 4–18 h prior to hospitalization	Clinical presentation	Poloxamer 188 (a nonionic block co-polymer surfactant)	28	100	Intravenous (IV) infusion, 60-min loading dose of 300 mg/kg followed by a 47-h maintenance infusion of 30 mg/kg/h	Acutely	Yes: Placebo	22	100	Placebo	Compared with placebo and depending on the subgroup, RheothRx-treated patients showed a 16–45% decrease in duration of painful episodes, a 1–2-d reduction in hospital stay, a 3-fold to 5-fold reduction in analgesic requirements, and a 1-point reduction (using a 5-point scale) in average pain intensity scores at 72 h. RheothRx was well tolerated; no clinically significant differences were observed between treatments with respect to adverse experiences or other safety measures. In addition, there were no differences between treatment groups in the incidence of recurrent painful episodes
Al-Jam'a, 1999 <sup>4</sup>	RCT	Sickle cell painful crises	NA	Clinical presentation,	Isoxsuprine	22	100	Isoxsuprine 5–10 mg every 4 h (a tocolytic agent that improves erythrocyte deformability)	NA	Yes: Meperidine	21	100	Meperidine 50–100 mg intramuscularly	No differences between the two groups in terms of duration of crisis, hospital stay, and side effects. However, pain scores at 30 and 60 min were better with meperidine
Bartolucci, 2009 <sup>7</sup>	RCT	Pain from vaso-occlusive crises (VOC) event	Severe VOC was defined as pain or tenderness, affecting at least 1 part of the body, including limbs, ribs, sternum, head (skull), spine, and/or pelvis that required opioids and was not attributable to other causes	Clinical presentation, visual analogue scale (VAS)	Ketoprofen	33	100	In conjunction with IV morphine, patients received a continuous intravenous (CIV) infusion of ketoprofen (300 mg/d for 2 d) with a programmable syringe pump, then 100 mg of oral ketoprofen (100 mg q 8 h)	5 d	Yes: Placebo	33	100	Placebo plus standard adjunctive treatment. (IV morphine in conjunction with IV and oral placebo)	7 VOC were excluded from each group because of treatment failure. No significant differences between groups were found for duration of hospitalization, morphine consumption, pain relief, and treatment failure

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/medication	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Benjamin, 1986 <sup>10</sup>	RCT	Acute VOC	The sudden onset of pain involving 1 or more sites (extremities, back, abdomen, chest) typical of the patient's usual crisis for which there was no other explanation	Clinical presentation	Cetiedil at 3 different doses (0.2 mg/kg, 0.3mg/kg, and 0.4mg/kg)	47	100	IV cetiedil at 0.2, 0.3, and 0.4 mg/kg q 8 h	4 d	Yes: Placebo	16	100	IV saline	The paired t within-group analyses of change from baseline documented significant improvement from baseline on all 4 d for both the middle dose (0.3 mg/kg) and high dose (0.4 mg/kg) of cetiedil ( $p$ .02), while improvement from baseline in the low dose (0.2 mg/kg) and placebo groups was significant only on d 4. When treatment groups were compared to placebo (utilizing the baseline score as a covariate), only the high dose of active drug, cetiedil 0.4 mg/kg, significantly superior ( $p < .05$ ) on all 4 treatment d. These results for the 0.4 mg/kg dose compared with placebo were corroborated by analysis of the slopes calculated by using either the summary statistics for each patient ( $p < .05$ ) or the raw data for each patient at each time point ( $p < .001$ ). For within-group analysis of average pain, only the placebo group was not significantly improved on d 1: all treatments showed significant improvement on each day thereafter ( $p < .02$ ). Comparisons of active drug to placebo (using baseline score as a covariate) indicated improvement in average pain intensity of statistical significance for the 0.3 mg/kg dose group on d 1 and 2 ( $p = .02$ ). Cetiedil was not significantly superior to placebo at any doses upon analysis of the slopes of summary statistics for each patient. Analysis of the slopes calculated by multiple linear regression analysis of raw data for each patient at each time point indicated improvement in pain intensity by the 0.4 mg/kg dose when compared with placebo ( $p < 0.01$ ). Cetiedil dosages of 0.3 mg/kg and 0.4 mg/kg were significantly superior to placebo ( $p < 0.05$ ). There was no significant correlation between the degree of shortening of crisis after administration of study medication and the length of time in crisis within the 4- to 24-h period prior to treatment

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Cabannes, 1983 <sup>12</sup>	RCT	VOC	Sudden onset of pain involving 1 or more sites	Past history of SCD and by electro-phoretic examination of hemoglobin	Cetiedil	15	100	(0.37 mg/kg) was administered by IV infusion every 6 h	4 d	Yes: Placebo	15	100	Placebo was administered by IV infusion every 6 h for 4 d	There was definite reduction in pain rating from a mean of 2.3 to <1.0; this persisted for 24 h after the last cetiedil injection. 2/3 of the patients treated with cetiedil showed termination of crisis within 24 h, and 1/3 showed termination of crisis within 72 h. On the other hand, none in the placebo group showed termination of crisis within 24 h, and more than half were symptomatic after 72 h
Charache, 1995 <sup>13</sup>	RCT	Recurrence of pain crises	A painful crisis was defined as a visit to a medical facility that lasted >4 h for acute sickling-related pain	Clinically	Hydroxyurea (HU)	152	100	Initial dose of 15 mg/kg/d, which was increased by 5 mg/kg/d q 12 weeks, unless marrow depression was present. If marrow depression occurred, treatment was stopped until blood counts recovered; it was then resumed at a dose that was 2.5 mg/kg lower than the dose associated with marrow depression, starting a new 12-week cycle	Mean: 21 mo	Yes: Placebo	147	100	The dose of placebo was adjusted by the data coordinating center in a similar manner in order to maintain blinding	Patients assigned to HU treatment had lower annual rates of crises than the 147 patients given placebo (median, 2.5 vs. 4.5 crises/yr, $p<.001$ ). The median times to the 1st crisis (3.0 vs. 1.5 mo, $p=.01$ ) and the 2nd crisis (8.8 vs. 4.6 mo, $p<.001$ ) were longer with HU treatment. Fewer patients assigned to HU had chest syndrome (25 vs. 51, $p<.001$ ), and fewer underwent transfusions (48 vs. 73, $p=.001$ ). At the end of the study, the doses of HU ranged from 0 to 35 mg/kg of body weight per d. Treatment with HU did not cause any important adverse effects. HU therapy can ameliorate the clinical course of SCA in some adults with 3 or more painful crises per yr. Maximal tolerated doses of HU may not be necessary to achieve a therapeutic effect. The beneficial effects of HU do not become manifest for several months, and its use must be carefully monitored. The long-term safety of HU in patients with SCA is uncertain
Co, 1979 <sup>14</sup>	RCT	Painful crisis of SCA	2 areas of pain in each of 2 extremities with a similar degree of pain	NR	Acupuncture	5	100	Needling on acupuncture point	NR	Needling on Sham sites (placebo of acupuncture treatment)	5	100	Sham treated points were 5 cm from standard acupuncture points but otherwise were treated identically to the acupuncture points	There were 16 painful episodes in the 10 patients. The results showed that pain relief was obtained in 15 of the 16 painful episodes regardless of whether an acupuncture point or sham site was treated, and that needling at acupuncture points for pain relief is not significantly superior to treatment at sham sites

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Cooperative Urea Trials Group, 1974 <sup>15</sup>	RCT	Acute sickle cell pain crisis	The sudden onset of pain in the extremities, back, abdomen, or chest and considered by the patient to be typical, and for which the patient was able to establish accurately the time of onset of the pain	Clinical presentation	Urea treatment	16 (23 crises)	100	Urea was given as a 15% solution in 10% invert sugar at an initial dose of 0.68 g/kg/h, or approximately 4.5 mL/kg/h to rapidly produce the desired blood urea nitrogen (BUN) level of 150–160 mg/dL. The patients were given maintenance doses to keep the BUN at that level	Acute	Yes: Invert sugar (control)	21 (27 crises)	100	No urea treatment, invert sugar IV drip at a similar rate to the treatment group	Of 23 crises treated with urea infusion, 10 (43%) were halted successfully within the 24-h observation period. Of 27 treated with 10% invert sugar alone, 10 (37%) were 24-h successes. This difference was not statistically significant. It is concluded that rapid infusion of large amounts of urea is not beneficial for treatment of painful crisis
de Abood, 1997 <sup>16</sup>	RCT	Acute pain crises	NR	Clinically	Depo-Provera (DMPA)	13	100	150 mg intramuscularly (IM), monthly for the first 3 mo, thereafter 150 mg IM at a 3-mo interval	1 yr	Oral contraceptive medications, and surgical sterilization	30 (14 and 16 in groups 2 and 3 respectively)	100	Group 2: A combined oral dose of 0.15 mg levonorgestrel + 0.003 ethinyl estradiol (microgynon) daily for 12 mo. Group 3: Surgical sterilization	No changes were observed in any of the groups in the hematological parameters. At the end of the study, 70% of the patients receiving DMPA were pain-free, and only 16% of those still reporting painful crises rated them as intense. Patients receiving microgynon also had an amelioration of the painful crises, although at a lower rate; after 12 mo, 45.5% still experienced some crises. Although less marked than in the other groups, 50.5% of the control patients also reported an improvement of their painful crisis, which may be a result of closer medical care

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Eke, 2000 <sup>17</sup>	RCT	Severe osteoarticular pain	Osteoarticular pain attacks requiring hospitalization for pain relief	Clinical	Piroxicam	29	100	Once daily piroxicam 1 mg/kg/d	3 d	Aspirin	29	100	Soluble aspirin, 100 mg/kg/d given in 6 divided doses for 3 d	The mean pain score over the 3 d followup period was 1.93 (standard error (SE) 0.37) in Group A and 7.73 (SE 0.64) in Group B, with a difference between means of 5.8 (95% confidence interval (CI), 2 3.90 to 2 6.37). Using the nonparametric Mann Whitney U-test for pain scores over the followup period, intergroup differences showed $Z=-5.13$ , $p<.05$ ; for mobility scores, $Z=4.95$ , $p<.05$ . Insomnia, agitation, or fever was present in all 58 patients on d 1 but by d 4 had disappeared in 28 of the 29 patients in Group A and in 22 of 29 patients in Group B (chi square=31.76, $p<.001$ ). 19 patients (65.5%) in Group A and 5 patients (3.4%) in Group B had immediate sedation and disappearance of symptoms within 24 h of treatment. 8 patients in Group A and 21 in Group B had symptoms disappear within 24–48 h. For 3 children in Group B, but none in Group A, improvement was not seen until 72 after start of treatment. Piroxicam was well tolerated by mouth and no adverse effects were noted during the study. Nausea and vomiting were noted in 9 patients (31%) in Group B. Liver function tests showed no significant differences within or between the 2 groups before and after treatment
Gonzalez, 1988 <sup>21</sup>	RCT	Pain consistent with sickle cell crisis	Acute pain in patients with SCD, otherwise not attributable to any medical cause	Clinical presentation	Butorphanol	6	100	2 mg IM butorphanol, repeated within 30–60 min if needed until initial pain relief was achieved. This dose was repeated every 2–4 h to maintain a pain relief of 50 mm or less until the patient was discharged	Acute, during hospitalization	Morphine	6	100	6 mg IM morphine given as described above for group 1	11 patients (out of 18) were randomized more than once, resulting in a total of 45 randomizations. The 2 therapies did not differ significantly ( $p>.40$ ) with respect to pain or relief of pain scores, level of alertness, or vital signs. The discharge rate was 69.6% and 68.2% with morphine and butorphanol respectively ( $p=.92$ ). The incidence of adverse effects was 13% and 23% with morphine and butorphanol, respectively ( $p=.46$ ). It was concluded that the 2 medications are equally effective in treatment of sickle cell crisis pain

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Gonzalez, 1991 <sup>22</sup>	RCT	Sickle cell crisis pain	NR	Clinical exam/investigations	Analgesic, morphine sulphate administered by intermittent needle therapy IV (INT-IV) injections	Phase 1:10, Phase 2:12	100	Phase 1: INT-IV group=4 mg IV every 30–60 min as necessary for linear analog scale for pain >50 mm. Phase 2: 8 mg IV every 30–60 min as necessary for linear analog pain scale >50 mm	Until pain is controlled or 8-h emergency room (ER) treatment period elapses	Patient-controlled analgesia (PCA)	Phase 1:10, Phase 2:13	100	Phase 1: 2 mg bolus then 1.0 mg with a 6 min lockout. Phase 2: 5 mg bolus then 2.7 mg with a 10 min lockout	During phase 1, 10 patients (28.3±7.3 yr) received INT-IV and 10 patients (33.9±12.5 yr) received PCA. Treatment groups did not differ significantly regarding duration of pain, amount of morphine administered, linear analog scale for pain intensity, verbal pain scale, level of alertness, or vital signs except for a significantly lower final respiratory rate with INT-IV. In phase 2, 12 patients (28.4±5.6 yr) received INT-IV and 13 patients (26.8±8.1 yr) received PCA. The PCA groups had a significantly shorter elapsed time between onset of pain and treatment (7.3±6.5 h) when compared with the INT-IV group (18±16.9 h). Treatment groups did not differ significantly with respect to total amount of morphine administered, linear analog scale for pain intensity, verbal pain scale, vital signs, or level of alertness. The PCA group had a significant reduction in length of stay in the emergency department (ED) during phase 2 when compared with phase 1. The ED discharge rate and the incidence of side effects did not differ significantly between groups
Griffin, 1994 <sup>23</sup>	RCT	NR	Acute pain that remained despite management at home and in the ER with fluids and analgesics in patients <21 yr age with SCD	Clinical exam/investigations	Methyl-prednisolone (MP)	26 episodes	100	15 mg/kg body weight to max of 1,000 mg IV over 30 min, on admission and 24 h later	24 h	Placebo	30 episodes	100	IV saline placebo	In 56 episodes, age adjusted duration of inpatient analgesic therapy was significantly longer in patients getting placebo than for those getting MP (mean, 71.3 vs. 41.3 h; <i>p</i> =.030. 7 episodes complicated by development of acute chest syndrome (ACS) (3 in MP group and 4 in placebo group). Excluding those 7, the age-adjusted difference between the 2 groups remained significant (mean, 31.0 vs. 62.5 h; <i>p</i> =.010); removing atypical cases, 38 left. for these 38, age-adjusted duration of inpatient analgesia remained significantly different (mean, 53.6 h in placebo vs. 35.8 h in the MP group; <i>p</i> =.012)

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Grisham, 1996 <sup>24</sup>	RCT	Vaso-occlusive crisis (VOC) pain	NR	Pain assessment included a VAS, a categorical scale, and a facial affective scale	Ketorolac tromethamine (KT)	10	100	KT-1.0 mg/kg. Patients received the 1st dose as parenteral and then generally via infusion	150 min	Meperidine	10	100	Patients received the 1st dose as parenteral and then generally via infusion	KT provided significantly ( $p<.01$ ) more pain relief than meperidine, with both drugs producing the greater decrease in pain within 30 min (from mean VAS of 73–39 in KT group and 54 in meperidine group). Further, significantly more patients were pain-free and discharged home after KT (4 patients, 40%) than after meperidine (2 patients, 20%). After meperidine, patients were more sedated ( $p<.01$ ) and experience more minor complications ( $p<.01$ ) than after KT
Hardwick, 1999 <sup>25</sup>	RCT	VOC	NR	Clinical, visual analog scale(VAS)	Ketorolac + morphine	22	100	IV ketorolac 0.6 mg/kg and 0.1 mg/kg IV morphine sulfate simultaneously with the study medication. (Additional doses of morphine sulfate were administered every 2 h based upon pain intensity as rated on the VAS)	6 h	Yes: IV saline placebo + morphine	19	100	Equivalent volume of IV saline, placebo and 0.1 mg/kg IV morphine sulfate simultaneously with the study medication. (Additional doses of morphine sulfate were administered same as above)	The patients in the ketorolac group received an average of $0.28\pm 0.08$ mg/kg of morphine sulfate, while those in the placebo group received an average of $0.32\pm 0.08$ mg/kg ( $p=.118$ ). While both groups experienced a decrease in pain as measured by the VAS, the reduction in pain severity was not significantly different between the 2 groups at any point during the study period. 9 of the 22 patients (41%) in the ketorolac group were admitted to the hospital for continuation of therapy, while 10 of the 19 visits (53%) by patients who received placebo resulted in hospital admission ( $p=.662$ ). Likewise, rates of return to the ED for discharged patients were similar for patients who had received ketorolac (3/13, 23%) and for those in the placebo group (0/9, 0% $p=.358$ ). Patients in each group tolerated the study procedure well. There were no significant differences in vital signs between the patient groups. 1 patient experienced local histamine response to morphine and was removed from the study. No other adverse effects were noted

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Jacobson, 1997 <sup>27</sup>	RCT	NR	An episode of pain was defined as the occurrence of pain in the extremities, back, abdomen, or chest that could not be explained except by SCD	Clinical, VAS	IV morphine	26	100	Mean daily dose of IV morphine was 0.81 mg/kg	<1 week	Oral morphine	24	100	Mean daily dose of oral morphine was 2.99 mg/kg (standard deviation (SD) 0.75)	There were no significant differences between the 2 treatments in CHEOPS (Children's Hospital of Eastern Ontario Pain Scale), Oucher, faces, and clinical pain scales. The correlations between Oucher, CHEOPS, faces, and clinical pain scales were moderately to highly significant (range $r=0.5865-0.8980$ ; $p=.0001$ for all)
Opio, 1972 <sup>35</sup>	RCT	Bone pain crisis	NR	Patients had been in crisis an average of 59 h before starting treatment and an average of 3 sites were involved in each patient. PC was assessed as intense in 12 and moderate in 8	Urea	12 pain episodes	100	IV urea (16% urea in 10% invert sugar). The solution was administered over a 3-h period at 0.68g/kg/h	3 h	Yes: Control	11 pain episodes	100	Infusion of 10% invert sugar	Good pain relief was defined as pain that steadily regressed, with little or no pain at 3 h. 3/12 patients (25%) in the urea group and 1/11 patients (9%) in the control group had good pain relief. All patients who did not respond to urea or the control solution continued to have pain that required analgesics. Complications: 4 patients had a headache during infusion and 3 patients vomited while on urea infusion. Pain at the infusion site occurred in 3 patients

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Orringer, 2001 <sup>36</sup>	RCT	Acute VOC	NR	Clinical presentation	Purified poloxamer 188	126	100	A loading dose of 100 mg/kg for 1 h followed by a maintenance dose of 30 mg/kg/h for 47 h	Acutely	Yes: Control	123	100	Placebo Saline solution delivered at a volume and duration identical to that of the active drug	Mean (SD) duration of the painful episodes was 141 (42) h in the placebo group compared with 133 (41) h in those treated with purified poloxamer 188, a 9-h reduction ( $p=.04$ ). Subset analyses indicated an even more pronounced purified poloxamer 188 effect in children aged 15 yr or younger (21 h; $p=.01$ ) and in patients who were receiving HU (16 h; $p=.02$ ). Finally, the proportion of patients achieving crisis resolution was increased by purified poloxamer 188 (65/126 (52%) vs. 45/123 (37%); $p=.02$ ). There were no differences between the 2 treatment groups in the overall incidence of adverse events. There was 1 death due to pulmonary fat embolism in a patient in the PP188 group; the patient had not received study drug infusion for 3 d prior to death. The underlying cause of death was judged by the investigator to be SCD and not study drug treatment. Renal function was not influenced by PP188 treatment. However, the group randomized to PP188 did exhibit a modest but statistically significant increase in levels of alanine aminotransferase and direct bilirubin, each of which returned to its respective baseline level by the 35-d followup visit
Perlin, 1993 <sup>38</sup>	RCT	VOC pain	NR	McGill-Melzack pain scale, 100 mm VAS, verbal categorical descriptor	IV meperidine and hydroxyzine	10	100	Meperidine via IV infusion at the rate of 25–30 mg/h and 2x 2.5–5.0 mg IV bolus doses per h together with hydroxyzine 50 mg every 6 h	3 d	IM meperidine and hydroxyzine	10	100	Meperidine 75–100 mg and hydroxyzine 50–75 mg, both IM every 3–4 h. Patients were treated for 3 d	There was no significant difference in the amount meperidine used by the 2 groups (1420±493 in the control vs. 1871±681 in the IV group). The control group used significantly more hydroxyzine (mean 335 mg/d compared to 200 mg/d). There was a wide range of variation in pain scores in each group. There was no significant difference between the control group and the IV group with either method of pain assessment. No significant adverse events were noted in either group

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Perlin, 1994 <sup>39</sup>	RCT	Acute VOC pain	NR	Clinical presentation	Ketorolac	9	100	IV infusion, with a loading dose of 30 mg and thereafter received an infusion of 120 mg at 5 mg/h, for a total dose of 150 mg ketorolac on the 1st d. For the remainder of the study the patients received 120 mg/d	Up to 5 d	Yes: Control	9	100	Placebo: IV infusion of normal saline at the same rate as the ketorolac in the therapy group	Over the 5 d the KT patients required 33% less meperidine than did the placebo treated patients (PL), $p=.04$ , and had significantly better pain relief as assessed by categorical scale, VAS, and pain relief scale. By the end of 5 d infusions had been discontinued in 6 KT and 1 PL. The time to discontinuation of the infusion was significantly shorter in KT, ( $p=.009$ ). The median duration of hospital stay from the start of treatment was 3.3 d for KT and 7.2 d for PL, $p=.027$ . Adverse events were mainly related to the digestive system
Qari, 2007 <sup>40</sup>	RCT	Painful vaso-occlusive crisis of SCA	NR	Clinical presentation	low-molecular-weight heparin (LMWH) tinzaparin	127	100	175 IU/kg subcutaneously once daily of tinzaparin	7 d	Yes: Control	126	100	Placebo + supportive care	Statistically significant reduction in number of days with the severest pain score, overall duration of painful crisis and duration of hospitalization ( $p<.05$ for each comparison of tinzaparin vs. placebo)
Sangare, 1993 <sup>41</sup>	RCT	Acute painful articular attacks of SCD	NR	Clinical presentation and biologic findings	Piroxicam	56	100	IM piroxicam 40 mg for the first 2 d and 20 mg on the 3rd d	3 d	Yes: Control	44	100	2 g daily of IM lysine acetylsalicylate for 3 d	Piroxicam showed a statistically superior efficacy and more rapid onset of action than lysine acetylsalicylate. Both treatment regimens were equally well-tolerated
Schnog, 2001 <sup>42</sup>	RCT	Acute VOC events and bleeding complications	Episodes of acute pain in extremities and/or abdomen not otherwise explained and leading to hospital or ER visit, ACS (a new pulmonary infiltrate on chest x ray, or a perfusion defect shown on a lung radioisotope scan), acute cerebrovascular disease, or major bleed	Clinical exam/ investigations	Acenocoumarol	(11 in each phase.) Total=22	17 (in acenocoumarol group)	6 tabs on d 0 and 3 tabs on d 1 and 2, followed by 1st international normalized ratio (INR) determination (target range INR 1.6–2.0)	14 weeks	Yes: Control	(11 in each phase) Total=22	17 (in placebo group)	Placebo controlled with switch over after 14 weeks' treatment with a 5-week wash-out period in between	Acenocoumarol treatment did not result in a significant reduction of vaso-occlusive events (VOEs) (3 painful crises during acenocoumarol, 5 during placebo). There was a marked reduction of the hypercoagulable state (depicted by a decrease in plasma levels of prothrombin F1.2 fragments ( $p=.002$ ), thrombin-antithrombin complexes ( $p=.003$ ), and D-dimer fragments ( $p=.001$ )) without the occurrence of major bleeding

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Teuscher, 1989 <sup>45</sup>	RCT	Acute VOC	The sudden onset of pain involving 1 or more sites (extremities, back, abdomen, chest) typical of patient's usual crisis for which there was no other explanation	Clinical presentation	Pentoxifylline	18	100	20 mg/kg/d IV pentoxifylline in 0.9% NaCl (sodium chloride) (max daily dose 1,600 mg)	Acute	Control	18	100	0.9% saline in matching vials	There was no difference in analgesic drug administration between the 2 groups. No antimicrobial therapy had to be instituted. The mean intravenous fluid (IVF) volumes given were not different. Mean duration of acute VOC was significantly shortened by 25 h on average (95% CI: 2.00–47.5) in the pentoxifylline treated group as was the mean duration of inpatient therapy. Evaluation over the time of the drug's efficacy shows that active therapy improved mobility and decreased pain scores significantly ( $p < .05$ ) by 48 h in comparison to baseline. 4 patients developed additional pain sites under therapy (1 active, 3 placebo, $p < .05$ ). The proportion of patients cured within the 1st 48 h was significantly higher in the actively treated group (active: 10/18, placebo: 2/18, $p = .002$ )
Uzun, 2010 <sup>46</sup>	RCT	VOC	NR	Clinical presentation	Meperidine	34	100	The initial dose was 1 mg/kg, IV slow infusion in 20 min. Additional analgesic medication was prescribed if VAS score was 5 or higher after 2 h of narcotic administration	Acutely	Yes: Control	34	100	Tramadol: The initial dose was 1.5 mg/kg, IV slow infusion in 20 min	Administration of both opioids had resulted in a decrease in pain intensity in both groups as measured by a 1-to-10 VAS; meperidine was more effective compared to tramadol. The difference in VAS scores was significant at 15 min and afterward between the 2 groups ( $p < .05$ ). However, meperidine caused more sedation within the same period. Efficacy in pain relief was more rapid and better in the meperidine group, although the degree of relief was significantly improved compared to baseline levels in both groups ( $p < .05$ ). Notably, despite a significant decrease in pain intensity compared to baseline levels in the tramadol arm, additional analgesic requirement was significantly higher ( $p < .05$ ). At the end of the study, 26 (38%) of the 68 patients were hospitalized. Among these, 11 and 15 were in the meperidine and tramadol arms, respectively

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van Beers, 2007 <sup>47</sup>	RCT	Acute VOC	The occurrence of pain in the extremities, back, abdomen, chest, or head that led to a clinic visit, and could not be explained except by SCD	Clinical presentation	IV morphine using a PCA pump	12	100	A single bolus injection of 5 mg morphine followed by patient-controlled bolus of 0.01 mg/kg. Maximal 1 bolus every 5 min could be administered (a lockout of 5 min). If this dosage did not result in adequate pain relief, the bolus dose was increased to 0.02 mg/kg with a lockout of again 5 min	The median duration of admission in the PCA group was 6.0 (4.3–9.3) d and in the CIV group 9.0 (6.0–12.0) d (p=.15)	Yes: Control Dose-adjusted continuous infusion of morphine (CIV group)	13	100	A single bolus injection of 5 mg followed by CIV of 0.03 mg/kg/h. After pain assessment by the attending nurse, the morphine dose was increased when needed with cumulative steps of 1 mg/h until adequate pain relief was obtained or side effects became intolerable. The continuous morphine dosage was decreased in steps of 1 mg/h if pain scores were 5 or lower or at the patient's request	Mean morphine dosage (mg/h) during treatment in the CIV group was 2.4 (1.4–4.2) mg/h and in the PCA group 0.5 (0.3–0.6) mg/h (p<.001). (B): In the CIV group, the least verbal response pain score was 4.2 (3.1–5.1) the mean score 4.9 (3.9–5.8), and the worst score 5.8 (4.5–6.2). These scores did not differ significantly from the least, median, and worst scores in the PCA group, 4.2 (3.4–5.8), 5.3 (4.5–6.9), and 6.3 (5.5–7.8), respectively (p=.14, p=.09, and p=.39)
Wade, 1996 <sup>49</sup>	RCT	Pain crisis	NA	Clinical presentation	Fluosol	7 (cross-over)	100	Fluosol, 20 mL/kg, given IV over 4–10 h	Acute	Yes: Crossover	7	100	Standard care	At 48 h, pain intensity and narcotic use were not measurably different between Fluosol-treated crises and those treated with standard supportive care. Acute toxicity, in the form of hypertension and vomiting, prompted the withdrawal of 1 patient, and 2 others experienced hematuria and worsening of back pain, respectively, following Fluosol administration

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Wang, 1988 <sup>50</sup>	RCT	NA	Severity rating for pain in baseline form comments section	Clinical exam/investigations	Transcutaneous electric nerve stimulation (TENS)	22 (60 trials)	100	TENS	4 h	Yes	22	100	Placebo controlled The TENS electrodes were set but the reading was set to 0, and no stimulation was therefore given	Pain ratings and analgesic requirements at 1 and 4 h from onset of study were similar in the TENS and placebo groups. Overall, 37% improved their pain rating by 1 h and 49% by 4 h. The 2 groups were similar in analgesic usage. A significant difference in the patients' assessments of the overall value of TENS and placebo treatment was found in 17 of 23 trials with TENS (74%) patients felt treatment was helpful, in 5 neither helpful nor harmful and in 1 trial it was thought to be harmful. Of 28 placebo trials, 11(39%) were felt to be helpful, 15(54%) were neither helpful nor harmful and 2 were judged harmful
Weiner, 2003 <sup>51</sup>	RCT	Acute VOC	Acute debilitating episodic pain, contributing to infection, ACS, splenic sequestration, stroke, acute and chronic multisystem organ damage, and shortened life expectancy	Clinical presentation	Inhaled nitric oxide (iNO)	10	100	iNO (80 ppm with 21% final concentration of inhaled oxygen)	Acute	Yes	10	100	Placebo (21% inspired oxygen)	Preinhalation VAS pain scores were similar in the iNO and placebo groups ( $p=.80$ ). The decrease in VAS pain scores at 4 h was 2.0 cm in the iNO group and 1.2 cm in the placebo group ( $p=.37$ ). Repeated-measures analysis of variance for hourly pain scores showed a 1-cm/h greater reduction in the iNO group than the placebo group ( $p=.02$ ). Morphine use over 6 h was significantly less in the iNO group (mean cumulative use, 0.29 vs. 0.44 mg/kg; $p=.03$ ) but was not different over 4 h (0.26 vs. 0.32 mg/kg; $p=.21$ ) or 24 h (0.63 vs. 0.91 mg/kg; $p=.15$ ). Duration of hospitalization was 78 and 100 h in the iNO and placebo groups, respectively ( $p=.19$ ). No iNO toxicity was observed

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Wright, 1992 <sup>53</sup>	RCT	VOC pain	VOC pain is characterized by deep, gnawing pain the extremities and torso	Patients rated pain on categorical and 100-mm VAS at baseline and every 30 min for the 4-h period	Ketorolac + meperidine and promethazine	12	100	Ketorolac 60 mg IM. Meperidine 50 mg IV and promethazine 12.5 mg IV were administered simultaneously. Patients were then given meperidine IV every 30 min as needed	4 h	Yes: Control	12	100	Saline placebo IM. Meperidine 50 mg IV and promethazine 12.5 mg IV were administered simultaneously. Patients were then given Meperidine IV every 30 min as needed	The patients in the ketorolac group received an average of 231±92 mg meperidine during the 4 h study period, while those in the placebo group received an average of 250±85 mg ( $p=.61$ ). The amount of pain measured on the VAS gradually decreased in the patients in each group over the 4 h. The total relief of pain score was similar between the ketorolac (44±34) and placebo (37±31) groups ( $p=.49$ ). There were no noted side effects or adverse reactions in either group. 11 of the 12 (92%) patients in the ketorolac group stated that they would want the drug at a future ED visit; 7 of 12 patients (58%) in the placebo group felt that they would want the drug again ( $p=.08$ ). 4/12 patients in the ketorolac group were admitted to the hospital for continuation of therapy for pain control; 3/12 patients in the placebo group required admission
Zipursky, 1992 <sup>54</sup>	RCT	VOC pain	VOC pain is characterized by severe pain and/or tissue injury	Clinical, severity of pain	Oxygen	15	100	50% oxygen delivered through a Venturi mask	NR	Yes	10	100	Air delivered through a Venturi mask	There was no significant difference between the air and oxygen groups in any of the 4 indices of disease severity. Hospitalization (days): Air=5.4 (2.6), O2=6.7 (3.6); Opioid Therapy (days): Air=3.9 (2.3), O2=4.7 (1.9); Severe Pain (days): Air=0.94 (1.08), O2=0.95 (1.19); Mean hourly dose of morphine (ug/k/h): Air=40 (15), O2=48 (29). In 4 subjects, O2 therapy produced a profound and sustained reduction of reversible sickle cell (RSC) numbers, reaching 0 in all cases. This did not affect the course of crisis. 15 of 27 patients had evidence of desaturation during crisis. Hemoglobin levels fell in the oxygen group, but not in the air group. This difference significance was borderline when analyzed by 2-factor analysis of variance (ANOVA) ( $p<.06$ ). Reticulocytes fell significantly ( $p<.03$ ) in both, but there was no significant difference between groups

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Robieux, 1992 <sup>55</sup>	RCT within 1 arm of the observational prospective	Acute VOC	NR	Clinical presentation	Phase A: routine intermittent opioid	32	100	Phase A: routine intermittent opioid Phase B: CIV infusion of morphine	Acute	Phase B: CIV infusion of morphine	34	100	CIV of morphine; a loading dose of 0.15 mg/kg of morphine sulfate was followed CIV of morphine at an initial rate of 40 µg/kg/h	Duration of hospital stay and of opioid therapy was not different between groups A and B. The mean dose of opioids was similar as well. The number of hours for which children experienced moderate or severe pain was reduced by more than half in phase B compared to group A. Progression of crisis with appearance of new pain sites was observed in 9 patients (28%) of group A and 12 (35%) of group B. In group B, 22 patients were randomized to receive 50% O2 mask or room air. The duration of pain was similar in the 2 groups. Progression of the crisis with appearance of new pain sites was observed in 5 of 14 patients (35.7%) receiving O2 and 4/11 patients (36.3%) on air
Brookoff, 1992 <sup>75</sup>	R, Obs	Sickle cell crisis pain	NR	Patients with the diagnosis of hemoglobin S disease (HbS) with crisis (ICDM-9 282.62)	1985–1988–Meperidine; 1989–1990–Morphine	99	100	IM morphine infusions and oral controlled-release morphine: patients were immediately given an IV injection of 5 mg of morphine sulfate usually with 50 mg of diphenhydramine. A CIV morphine infusion was also started	NR	Yes: Comparison	196	100	IM meperidine in doses ranging from 75 to 125 mg every 3 h	With the institution of the new regimen, the use of the ED and inpatient services by patients with SCD decreased, but the total number of patients treated remained stable. In the 1st full 6 mo of the protocol, the number of admissions for sickle cell pain decreased by 44%, total inpatient days by 57%, length of hospital stay by 23%, and the number of ED by 67% after initiation of the morphine protocol. The mean duration of stay per admission declined by 2 d. Hospital use remained at these lower levels 1 yr later. Similar declines were seen for a subset of 15 patients who had a history of frequent admissions for sickle cell pain and who had used this hospital exclusively and accounted for more than half of the admissions for SCD. There was no evidence that any of the patients were addicted. No deaths occurred that were related to the use of opioid drugs

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Cole, 1986 <sup>83</sup>	R, Obs	VOC pain requiring hospitalization	Severe pain; patient is crying, grimacing, is extremely uncomfortable and has pain on movement of involved extremities, and the pain persists despite IVF and morphine/meperidine, or patient present	Clinically	Morphine or meperidine	98 episodes (38 patients)	100	76/98 of patients were treated with a CIV narcotic infusion. At the time of arrival, patient received a bolus IV injection of 0.15 mg/kg of morphine sulfate or 1.0 mg/kg of meperidine hydrochloride. This was followed by a morphine sulfate infusion at a dose rate of 0.07–0.10 mg/kg/h or a meperidine hydrochloride infusion at a dose rate of 0.5–0.7 mg/kg/h. 22 patients who were believed to have less severe pain did not receive a CIV narcotic infusion, but rather as needed	Acute, during hospitalization	No	NA	NA	NA	The mean time from beginning of infusion to patient comfort was 3.3 h. Infusion rates were increased an average of 1.7 times per infusion. In 31 cases, the CIV infusion was supplemented by additional bolus injections of narcotic analgesic. On 7 occasions (9%) re-initiation of the CIV infusion was necessary. Those patients who had received both only bolus and CIV infusions uniformly expressed a preference for the CIV infusion regimen. Side effects of narcotic therapy were frequent, but were not usually serious (nausea, lethargy, abdominal distention being the most common). The frequency and severity of side effects were generally related to the amount of narcotic received. Certain side effects (e.g., lethargy and abdominal distention) were more frequent with morphine than with meperidine infusions. Chest syndrome developed in 18 patients while receiving IV narcotic therapy

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Frei-Jones, 2008 <sup>98</sup>	R, Obs	VOC pain	NR	Pain is assessed by nurses using the 0–5 Wong-Baker FACES scale or, rarely, a verbal “how much from 0 to 10” scale	IV morphine and oral analgesics as needed	105	100	After physician assessment, IV morphine at 0.1 mg/kg (maximum dose, 8 mg) was administered with IVFs and additional oral analgesics at the discretion of the ED physician. After the initial IV morphine dose, pain is reassessed every 15–30 min using the FACES scale, with appropriate intervention until the patient’s reported pain is ≤3 on a scale of 5	NR	No	NA	NA	NA	VOE was diagnosed 279 times in 105 patients; 45 of the patients had 1 ED visit, 25 had 2 ED visits, and 16 had >5 ED visits. The overall admission rate was 178/279 (64%), 166 on the 1st ED visit and 12 on a return visit within 72 h. Use of home opioids, duration of VOE, and hemoglobin concentration were not associated with disposition. The average number of IV morphine doses administered regardless of disposition was 2.5. Average time between 1st and 2nd doses of morphine was 52 min (range, 15–120 min). Pain relief after 1 dose, using a FACES scale of 1–5, differed significantly between the admitted patients and the discharged patients (1.1 vs. 2.5; $p<.0001$ ). The patients who were admitted received 1.5 more doses of morphine than those who were discharged (admitted mean, 3; range, 1–7; SD, 1.1 vs. discharged mean, 1.5; range, 1–4, SD, 0.7; $p<.0001$ ). After 1 dose of IV morphine, a reduction in pain score of ≤1 increased the likelihood of being admitted (relative risk (RR)=1.99; 95% CI=1.6–2.5), whereas a reduction in pain score of at least 2 resulted in a decreased likelihood of being admitted (sensitivity, 73%; specificity, 73%; c-statistic, 0.78). For the 11 visits in which the patient was discharged prematurely, an average of 1.8 doses (range, 1–4) of morphine was dispensed. After receiving 2 doses of IV morphine, 33/79 (42%) patients were successfully discharged without premature return to the ED

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Holbrook, 1990 <sup>106</sup>	R, Obs	Pain	Pain not associated with bone infection or other major condition associated with SCD	NR	PCA: Meperidine or morphine	10	100	Patients were treated using with a loading dose of either meperidine 0.5 mg/kg or morphine 0.05 mg/kg. The continuous infusion dose and the PCA dose were altered based on patient response. Once pain relief was achieved, the continuous infusion rate was gradually lowered	Acute	Yes: Comparison Conventional analgesia treatment	10	100	Patients were generally treated with IV meperidine 0.5–1.0 mg/kg on a fixed schedule and more frequently if needed	The patients treated on the PCA protocol averaged 90±41 standard error of the mean (SEM) h of hospitalization compared with 80±27 SEM h for the children treated with more conventional bolus narcotic on a fixed schedule. While the time from the start of pain management until a major dosage reduction of narcotic was roughly equal in each group (43±27 SEM h in group 1, 37±21 SEM h in group 2), the time until relief of pain was almost significantly shorter in the PCA-treated group: 5 of the 10 children in group 1 experienced relief within 6 h, only 1 of 10 in the conventional group did ( $p=.052$ ). The average narcotic dose (meperidine equivalent in mg/kg) was greater in the PCA group
Kalff, 2010 <sup>109</sup>	R, Obs	Recurrent pain crises, ACS, silent cortical ischemia, pulmonary hypertension, multiorgan crises and pregnancy	Pain crisis not defined	NR	Erythrocytapheresis, HU	13	100	HU used on 4 patients. Dose NR, plus automated red cell exchange (RCE), at an initial frequency of 4 weeks, and subsequently at 4–6 weeks	Range: 65–112	No	NA	NA	NA	Eight patients did not have any acute events following commencement of erythrocytapheresis. A total of 16 acute events occurred in five patients in 846 months of cumulative patient followup.
Lawrence, 1980 <sup>113</sup>	R, Obs	Pain	Recurrent attacks of pain in any region of the body	Patients assessed their own relief of pain. When they were not able to do so, the physician responsible for the patient did so	IV distilled water± oxygen, hydration and narcotics	12 (37 crises)	100	Sterile water was given as a rapid IV push. Patients received hydration for >30 min with 1/4N or 1/2N saline and narcotic analgesics	NR	No	NA	NA	NA	37 incidences of painful crisis were treated with IV distilled water Relief of symptoms was obtained if no prior attempts with other forms of therapy had been initiated. The earlier that treatment was begun after onset of the pain symptoms, the more likely was the patient to positively respond regardless of prior treatment
Raphael, 2008 <sup>128</sup>	R, Obs	Vaso-occlusive pain crises	NR	Clinical presentation	IV hydration and analgesics, supported by home treatment over night with oral analgesic for the day hospital group	70	100	IV hydration and analgesics, supported by home treatment over night with oral analgesic for the day hospital group	NR	No	NA	NA	NA	Day hospital care resulted in a 39% reduction of the average length of stay compared to inpatient admissions

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Sartori, 1990 <sup>134</sup>	R, Obs	Pain	NR	On 19 occasions, the site of pain was in the limbs. On 11 occasions, site was in the back or abdomen. On 15 occasions, there were multiple sites	Papaveretum	24 (45 crises)	100	The infusion was made up of papaveretum 1 mg/kg in 60 mL of dextrose saline solution and delivered via a syringe. A 3 mL bolus (50 µg/kg) was given initially and the rate set at 3 mL/h for the 1st hr. The infusion rate was adjusted by nursing staff to keep the child pain-free or comfortable	Range: 1–9 d of infusion	No	NA	NA	NA	During most painful episodes ( <i>n</i> =30) infusions were given for 1–3 d, but a few ( <i>n</i> =6) required CIV analgesia for 5–9 d. The total dose administered ranged from 0.3 to 21 mg/kg (median 2–4 mg/kg). Variation in dose was wide, with more than half of the infusions peaking at a daily dose in excess of the standard recommended dose (0.9 mg/kg daily, derived from 150 µg/kg every 4–6 h). Older children were more likely to receive higher doses (per kg) and infusions of longer duration (significant for both max hourly rate and daily dose). Children with sickle hemoglobin beta-zero thalassemia (HbS <sup>0</sup> -thal) required higher doses than children with homozygous sickle cell disease (HbSS) or sickle hemoglobin C disease (HbSC), but this is based on small numbers. No respiratory toxicity was observed. Most of the patients were tachypneic on admission, with a subsequent fall in respiratory rate. Neurological toxicity was seen on one occasion
Shapiro, 1993 <sup>137</sup>	R, Obs	VOC pain	NR	Patients who require parenteral opioid therapy for sickle cell pain are eligible to start on PCA	PCA with 1 of the following analgesics: morphine, nalbuphine, or hydromorphone	46 (92 times)	100	The average dose and hourly basal infusion rate were 0.04 mg/kg. The lockout interval was usually 7 min. Average total hourly max dose allowed—0.24 mg/kg. Average max dose used—0.09 mg/kg. Patients received 37% of the allowed dose on the day of maximum use	NR	No	NA	NA	NA	The number of times patients triggered the device per h varied widely (range: 0.3–20.5). The average injections per h ranged from 0.2 to 4.1. For 70% of the uses, oral opioids around the clock were substituted for the basal infusion once the pain began to improve. Patients spontaneously stopped using the PCA dose an average of 1.5 d later. Of the 46 patients, 33 patients expressed an opinion regarding PCA. 14 (30%) had significant problems with PCA: 11 disliked PCA and 2 families disapproved of the technique. 1 patient had respiratory compromise, and 1 patient tampered with the machine. 22 patients liked PCA. Satisfaction with PCA was significantly associated with the ratio of attempts and injections: patients with a higher ratio were more likely to dislike PCA

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Trentadue, 1998 <sup>147</sup>	R, Obs	Vaso-occlusive pain crisis	NR	Clinical presentation	HPCA/LBI (high-dose PCA/low basal infusion)	30	100	Morphine, a high PCA (at least 0.25 mg/kg/dose) with a low basal infusion at nighttime (0.01–0.03 mg/kg/h) and a 1-h maximum starting at approximately 0.1–0.15 mg/kg/h	Acutely, during hospitalization	Yes. Comparison LPCA/HBI (low-dose PCA/high basal infusion)	30	100	Morphine, a low PCA (0.01 to .02 mg/kg/dose) with a high basal infusion (0.05–0.2 mg/kg/h) and 1 h maximum starting at approximately 0.05–0.2 mg/kg/h	Children in Group 1 (HPCA/LBI) used significantly less morphine during their hospitalization, were hospitalized fewer days, and reported lower pain scores on d 2. There were considerable cost savings due to decreased length of stay, less morphine consumed overall, and fewer days required for rental of the PCA pump
Woods, 1990 <sup>159</sup>	R, Obs	Painful episodes in children with SCD	Uncomplicated acute painful episodes	Clinical presentation	Meperidine	17	100	Mean dose of meperidine 9.24 mg/kg/hospitalization period	Mean hospitalization period was 3.56 d	Yes: Nalbuphine	14	100	Mean dose of Nalbuphine 2.57 mg/kg/hospitalization period	There were 12 patients in the meperidine-treated group, accounting for 25 painful episodes. There were 9 patients in the nalbuphine-treated group, accounting for 20 painful episodes. 5 patients were in both the meperidine- and the nalbuphine-treated group. Clinically acceptable pain relief was achieved in 20 episodes in nalbuphine-treated group, and 23 episodes in meperidine-treated group
Yaster, 1994 <sup>161</sup>	R, Obs	Severe Vaso-Occlusive Sickle Cell Crisis	Painful VOCs, unresponsive to high-dose systemic opioids, nonsteroidal anti-inflammatory drugs, and adjunctive measures	NR	Local anesthetic	9	100	Placement of an epidural catheter for the administration of a continuous infusion of local anesthetic, alone, or in combination with fentanyl	Catheters remained in place for 4 ± 1 d	No	NA	NA	NA	Pain scores decreased from 9 ± 1 to 1 ± 1 in 8 of 9 patients ( $p < .003$ ) within 15 min of the insertion of the epidural catheter. 5 patients developed tachyphylaxis to lidocaine (pain scores _5) within 24–72 h after administration and required either the addition of fentanyl to the epidural solution and/or the substitution of bupivacaine for lidocaine. Changing the epidural solution provided complete pain relief (pain score _3)

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Zemsky, 2008 <sup>162</sup>	R, Obs	VOC pain	NR	Clinical	Opiates and IV or oral non-steroidal anti-inflammatory drugs (NSAIDs)	59	100	All patients received opiates (57.5% used a PCA pump) and 127 (94.8%) received either IV or oral NSAIDs	Acute, during hospitalization	No	NA	NA	NA	Frequent vs. infrequent hospitalizations: The frequent group (25 patients with 77 hospitalizations (3 in the previous 12 mo)) was not significantly different from the infrequent group (34 patients with 57 hospitalizations (<3 in the previous 12 mo)) in regards to gender (12 (48%) vs. 18 (52.9%) males ( $p=.80$ )), or age ( $11.5\pm6.0$ vs. $11.5\pm4.0$ yr ( $p=.99$ )). Although the frequent group demonstrated longer length of hospital stay ( $4.8\pm3.0$ vs. $4.2\pm2.2$ d ( $p=.161$ )), a greater percentage of patients with HbSS genotype (25 (100%) vs. 28 (82.4%) with HbSS ( $p=.086$ )), and higher pain score on admission ( $7.5\pm2.8$ vs. $6.7\pm3.2$ ( $p=.135$ )), none of these differences reached statistical significance. The frequent group used greater quantities of opiate per 24 h on hospital d 1–4; however, this difference reached statistical significance only on hospital d 1 and 3. Short vs. extended hospitalization
Al-Jama, 2002 <sup>60</sup>	P, Obs	Recurrent severe VOCs	Recurrent pain crises, occurring 4+ times/yr, and requiring hospitalization every time	Clinical presentation	HU	27	100	Starting dose of 500 mg/d for patients weighing >50 kg. Patients weighing less were started on 500 mg every other day. The dose was increased by 500 mg at monthly intervals until the maximum tolerated dose or a dose of 35 mg/kg/d were reached	12 mo	No	NA	NA	NA	There was a significant reduction in leukocyte, platelet counts and rise in total hemoglobin (from $9.7\pm1.2$ to $10.74\pm1.4$ $p<.05$ ) and hemoglobin F (HbF) (from $12.57\pm5.4$ to $25.8\pm7.3$ $p<.05$ ). HbF rose by 1.2–13 folds from baseline. 74% of patients had at least a twofold rise of maximum HbF. There was a significant reduction in hospital admissions and hospital stays. Admissions for VOC decreased from a median of 6/yr to a median of 0/yr

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Beiter, 2001 <sup>168</sup>	P, Obs	VOC pain	NR	Clinical presentation, VAS	IV KT	51 (70 episodes)	100	Infusion of 0.5–1.0 mg/kg (60 mg max)	Acutely	No	NA	NA	NA	Of the 70 episodes of VOC pain, 37 (53%) adequately resolved with IV KT and IVFs and required no IV opioids (group A). 31 episodes (47%) required the addition of an IV opioid (group B). Group B had a significantly greater proportion of episodes reporting 4 or more painful sites than group A, 43% (12/28 patients) vs. 9% (3/33 patients), respectively ( $p<.01$ ). Group B also had significantly higher mean initial VAS scores than group A as assessed by the patient (81 vs. 60), parent (71 vs. 54), nurse (78 vs. 51), and physician (69 vs. 53). $p<.01$ for all previous interactions. Of the patient assessments with an initial VAS score >70, 69% (18/26) required the addition of an opioid
Booz, 1999 <sup>171</sup>	P, Obs	Pain associated with VOC	NR	The diagnosis of osteoarticular infection rather than VOC was made when pus or extensive inflammatory cells were aspirated or a positive culture was obtained from the aspirate	Pain relief (not specified)	33	30	13 VOC patients were already on antibiotics on admission. Antibiotics were stopped after diagnosis	NR	No	NA	NA	NA	13 VOC patients were already on antibiotics on admission. Antibiotics were stopped after diagnosis. No difference in the speed of recovery was noticed whether they were on antibiotics or not but those who were aspirated needed analgesics less frequently

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Brousseau, 2004 <sup>172</sup>	P, Obs	Pain due to sickle cell crisis	Requiring admission to the hospital for sickle cell pain crisis	Continued severe pain after multiple doses of IV opioid	IV magnesium + usual care	12	100	Magnesium dose: 40 mg/kg (max.1.5g) of IV magnesium sulfate over 20 min in ED. Repeat same dose at 8-h intervals for 2 doses. Usual care: All admitted patients were maintained on PCA infusions of IV morphine, or hydromorphone if they were allergic to morphine	Duration of pain and hospital stay	No	NA	NA	NA	A difference was seen in length of stay (LOS) among the 3 admissions ( $p=.033$ ), with a shorter LOS for the magnesium admission compared with each of a patient's 2 previous admissions (median LOS, 3.0 d compared with 4.5 and 4.0 d for the previous 2 admissions). No child experienced any adverse effects. Secondary outcomes revealed a decrease in the average amount of morphine required (magnesium admission: 136 mg vs. 207 mg for previous admissions; $p=.002$ ). There was a nonsignificant increase in the mean magnesium level (from 2.0 mg/dL to 2.2 mg/dL; $p=.06$ (normal magnesium, 1.9–3.0 mg/dL)), a nonsignificant decrease in mean cellular adhesion (Lam, 348.9 vs. 311.9; $p=.237$ . Tsp, 108.4 vs. 93.5; $p=.291$ ), and no change in the mean corpuscular hemoglobin concentration (MCHC) (33.5 g/dL vs. 33.4 g/dL; $p=.78$ )
Christensen, 1996 <sup>174</sup>	P, Obs	Sickle cell pain crisis	Pain crisis requiring narcotic analgesics	Clinically	Trans-dermal fentanyl (TF) + PCA morphine	10	100	Patients had a TF system applied to the chest wall, back, or upper arm. Generally, initial TF system delivered 25 µg/h. If prior morphine use was >2.5 mg/h, the initial dose was 50 µg/h. The TF dose was increased in the 2nd and 3rd 24-h periods if inadequate analgesia were achieved during the previous 24-h period. The maximum TF dose was 75 µg/h. Patients were also placed on PCA morphine	2 d	No	NA	NA	NA	All patients were treated with morphine or meperidine prior to study TF initiation. The average TF dose was $0.77\pm0.37$ µg/kg on d 1 and $1.17\pm0.46$ µg/kg/h on d 2. While the median amount of morphine used decreased during the first 2 d of TF use compared pre-TF use; if fentanyl is converted to morphine equivalents, the total amount of narcotics used during the periods (1.98 and 3.33 mg/kg/d) was greater than that used prior to study entry. Sedation rates were significantly higher during TF use compared to morphine alone. There was no difference in any of the clinical monitoring parameters between d 1 and d 2. However, 7 of 10 patients reported subjective improvement in pain control over that achieved with PCA alone. No adverse events were noted

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de Montalembert, 1997 <sup>176</sup>	P, Obs	Prevention of VOC pain	NR	NR	HU	35	100	HU was given at an initial dose of 20 mg/kg/d in a single dose, on 4 consecutive d each week. In the absence of toxicity, this dose was increased by 5 mg/kg/d at 4-week intervals. The maximal dose was 40 mg/kg/d	The mean duration of treatment was 32 mo. Mean doses were 27.3±5.8 mg/kg/d at 3 mo of HU; 33.6±5.7 at 6 mo and 32.5±7.4 at 3 yr	No	NA	NA	NA	HU use in children with SCD showed a reduction in pain crisis and days of hospitalization and an increase in HbF levels. Short- and middle-term tolerance was good. The data support the efficacy of HU in reducing painful events in children with SCD
Jacob, 2003 <sup>185</sup>	P, Obs	Acute VOC pain managed in hospital	Severe painful episodes require hospitalization for pain management	Clinical	PCA	27	100	PCA, morphine. Opioids (100%–majority morphine). In addition to morphine, ketorolac and diphenhydramine were prescribed and administered in 77.5% and 52.5% of the cases, respectively	The mean LOS at hospital was 5.9±2.19 d	No	NA	NA	NA	Using PCA, children self-administered only 35% of the analgesic medications that were prescribed and reported little pain relief. No significant relationships were found between changes in pain relief scores and the amount of analgesics administered
Jayabose, 1996 <sup>186</sup>	P, Obs	VOC	VOC as any painful episode involving the extremities, abdomen, back, or chest, including ACS that resulted in hospitalization. ACS itself (considered as VOC of the lungs) was defined as an episode of respiratory distress associated with infiltrates in the lung and requiring hospitalization	NR	HU	14 (Group 1: 9 patients with SCA and frequent VOC,	100	HU therapy was started at 20 mg/kg/d, and increments of approximately 5 mg/kg were made at intervals of 4–8 weeks	Range: 15–59 mo	Yes. Comparison	Group 2: 5 patients with severe anemia)	100	HU therapy was started at 20 mg/kg/d, and increments of approximately 5 mg/kg were made at intervals of 4–8 weeks	The number of VOCs per patient-yr for all 14 patients decreased from 2.5 before HU therapy to 0.87 during HU therapy, a decrease of 65% (p<.00001). 2 of 5 patients in group 2 had an increase in hemoglobin of 27 g/L and 34 g/L over the baseline. The median rise in hemoglobin was 19 g/L (range, 7–37) for all 14 patients. The number of transfusions given per patient-yr decreased from 1.83 (101 transfusions for 55.2 yr) before HU therapy to 0.2 (7 for 35.2 yr) during therapy. It was concluded that HU decreases the severity of anemia in some patients, and it may decrease the frequency of VOC

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Khosla, 1984 <sup>187</sup>	P, Obs	VOC	NR	A scale of 0–3, with 0 being able to move and walk normally and 3 being total immobilization due to pain	Pentoxifylline	20	100	Dose was based on 20 mg/kg, divided into 8 hourly infusions for a maximum period of 5 d or patient was pain-free for 24 h	NR	No	NA	NA	NA	6 patients were pain-free within 24 h; 9 patients were pain-free within 48 h. The remaining 4 cases showed a measurable improvement in duration and intensity of pain. All patients were walking normally within 96 h. Adverse reactions were noted in 2 patients: bilateral periorbital edema in 1 and bilateral rhonchi in the other. Additional analgesics were used in 3 cases. There was a fall of 0.75 g/dL in mean Hg during infusion (to 7.33). There were no changes in liver enzymes
Koch, 2008 <sup>189</sup>	P, Obs	Sickle cell pain crisis	NR	Clinical	Morphine, diphenhydramine, hydroxyzine, ondansetron, promethazine, and naloxone	16	100	CIV infusion morphine was initiated at 0.05 mg/kg/h, and patients self-administered additional doses of 0.03 mg/kg morphine as needed every 20 min according to our institutional management protocol. Thereafter, morphine dosing was adjusted by the patient's care team as clinically needed. Ibuprofen was administered by mouth at 10 mg/kg every 4 h. Diphenhydramine and hydroxyzine were available as needed for itching. Ondansetron and promethazine were available as needed for nausea	<1 mo (duration of hospital stay)	No	NA	NA	NA	The mean time to initiation of the naloxone infusion after starting the CIV morphine infusion was 164 min (range 0–690, median 60). The naloxone infusion was begun >2 h after the continuous infusion morphine in 6 patients, because a parent was not immediately available earlier to provide informed consent. On d 1, 11 (69%) patients reported their pain and 7 (43%) reported their pruritus to be controlled the same as or better than a previous hospitalization. On d 2, 9 (75%) patients reported their pain and 6 (50%) reported their pruritus to be controlled the same as or better than a previous hospitalization. (Note: 2 patients had sufficient pain relief to transition to intermittent morphine administration by d 2.) Frequency of other adverse effects: nausea occurred in 10 of the 16 patients (63%) on d 1 and 7 of 14 (50%) patients still on CIV infusion morphine on d 2. Vomiting occurred in 7 of 16 patients (44%) on d 1 and 2 of 14 (14%) on d 2. There were no episodes of respiratory depression during the trial. Although the study was not powered to detect a difference between groups, the itching scores and diphenhydramine use were compared between the high- and low-dose naloxone groups. The high-dose group had a lower median "team VAS itch now" on d 1 (4.8 vs. 7.3, $p=0.08$ ) and used less diphenhydramine (median of 0 vs. 1 mg/kg, $p=.31$ on d 1, and 0.4 vs. 1.6 mg/kg, $P=0.04$ on d 2)

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McCurdy, 1971 <sup>193</sup>	P, Obs	Acute sickle cell pain crisis	Acute painful crises severe enough to require ER admission	Patient self-report	IV infusion of urea	14 (24 pain crises)	100	Patients received 40 g urea in 250 mL of 10% invert sugar solution via IV over 45–90 min. Additional 40 g infusions was given at about the same rate if there was no clinical response. Max dose over 24 h was generally 120 g (range: 40–320). Analgesics were generally withheld during treatment	NR	No	NA	NA	NA	Acute pain crises were treated 24 times in 14 patients. In 17 crises, the patient became essentially pain-free and was able to be discharged. For those 17 pain crises treated successfully, the duration of crisis had been <12 h. In 7 crises, urea therapy was not successful. Apart from 1 patient with 5 d duration of crisis, the duration of pain before therapy was the same in these patients as in those for whom therapy was successful. The plasma urea nitrogen concentration in those who responded was not different from that in patients who did not respond. Side effects included headache, puffiness of the eyelids, diuresis (1 patient passed >9,000 mL of urine during and shortly after the infusion of 160 g of urea)
McPherson, 1990 <sup>195</sup>	P, Obs	VOC pain	VOC pain was defined as otherwise unexplained pain and/or tenderness in 1 or more discrete sites for at least 24 h	2 methods were used to evaluate pain: the McGill-Melzack categorical pain scale and a 100-mm VAS	PCA: Meperidine	16	100	The protocol consisted of 3 d of therapy using a background of CIV infusion meperidine. The starting dose was 20 mg/h and was escalated to 30 mg/h. The average amount given was 25.8 mg/h. 1–2 boluses of 2.5–5.0 mg/dose were also allowed each hr. 8 patients were also given hydroxyzine 50 mg po q 6 h	3 d	No	NA	NA	NA	Mean pain intensity difference (PID) decreased an average of 28% over 3 d of therapy (baseline pain score of 71.60–54.98 on d 1 and 47.28 on d 3). Most patients said they had achieved some relief of pain on d 1 and 2, with a scatter of responses on d 3. The overall ratings of pain control at the end of the study were: 1 poor, 1 fair, 3 good, 6 very good, 4 excellent, and 1 no comment. No adverse events were noted in any patient. 3 patients discontinued treatment after 1 d due to inadequate pain relief. Most patients used approximately 20 boluses

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Melzer-Lange, 2004 <sup>196</sup>	P, Obs	VOC	NR	NR	ED-PCA	31 (crises)	100	PCA dose was based on either documented effective dose from previous hospitalization or the recommended morphine dose of 0.025–0.05 mg/kg for demand dose and 0.10–0.25 mg/kg for hourly max dose. PCA had a lockout interval of 10 min. Prior to PCA, patients received IVFs and bolus IV morphine therapy	NR	Inpatient (IP)-PCA IP-PCA narcotic infusion therapy was initiated following transfer to an inpatient bed	38 (crises)	100	PCA dose was based on either documented effective dose from previous hospitalization or the recommended morphine dose of 0.025–0.05 mg/kg for demand dose and 0.10–0.25 mg/kg for hourly max dose. PCA had a lockout interval of 10 min. Prior to PCA, patients received IVFs and bolus IV morphine therapy	The mean interval from the last narcotic bolus dose to PCA initiation was 35±7 min in the ED-PCA group as compared with 211±17 min in the IP-PCA group ( $p<.001$ ). The mean number of narcotic bolus doses and the mean length of hospital admission were not significantly different between the 2 groups (Table 1). No respiratory or cardiovascular complications were noted in either group. Preference was assessed in 25 patients who received both ED-PCA and IP-PCA. ED-PCA administration was preferred by 23 of 25 (92%) of the study subjects. 2 patients indicated that they had no preference
Poflee, 1991 <sup>203</sup>	P, Obs	Painful crises	By grades: not as severe crisis=0 to severe crisis=3	NR	Pentoxifylline	9	100	IV pentoxifylline in a dose of 20 mg/kg/d in 5% dextrose drip as CIV infusion for 48 h	NR	9 patients with sickle cell not receiving treatment	9	100	Observation	5 patients in the intervention group were pain-free within 48 h, while the other 4 in the intervention group and all 9 in control had no relief after 48 h
Rombos, 2002 <sup>204</sup>	P, Obs	Frequent painful crises	NR	Clinical exam/investigations	Venesection to remove blood and decrease iron overload	13	100	NR	11–96 mo with sessions ranging 16–152	No	NA	NA	NA	The parameters studied indicate that there is a significant reduction in crises requiring hospitalization ( $p=.00003$ ); in crises treated on an outpatient basis ( $p=.02$ ) and in crises treated at home ( $p=.01$ ). 1 common finding in 11 of 13 cases, following venesection, was the reduction of serum iron and ferritin levels; (exceptions are cases 10 and 12 who suffered from chronic hepatitis). No significant reduction in hemoglobin, mean corpuscular volume (MCV), and MCHC was observed in the cases, if considered as a group
Sangare, 1990 <sup>206</sup>	P, Obs	Painful articular attacks	Painful crises particular in articular localizations	Clinical exam, functional symptomatology	IM piroxicam	52	100	40 mg each d for 2 d and 20 mg on the 3 <sup>rd</sup> d	NR	No	NA	NA	NA	71% of patients showed excellent and very good results after 2 injections of piroxicam 20 mg. Toleration was excellent and no systemic or local side effects were reported

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Serjeant, 1994 <sup>211</sup>	P, Obs	Painful crisis	Episodic pain unaccounted for by other obvious pathology and of sufficient severity to require narcotic analgesia	Patient reports/ clinical exam	NR	118	100	NR	NR	No	NA	NA	NA	Painful crises developed most frequently between 3 p.m. and midnight, most commonly affected patients aged 15–29 yr, affected the sexes equally, and were not obviously influenced by menstrual cycle. Of the perceived precipitating factors, skin cooling occurred in 34%, emotional stress in 10%, physical exertion in 7%, and pregnancy in 5% of women of childbearing age. Cold as a precipitant was not less common in patients with more subcutaneous fat. Pain affected the lumbar spine in 49%, abdomen in 32%, femoral shaft in 30%, and knees in 21%. There was a highly significant excess of bilateral involvement in limb and rib pain. Recurrent painful crises occurred in 40 patients but showed no evidence of involving similar sites on successive occasions. Abdominal painful crises were associated with abdominal distention in 18 (31%) and with referred rib pain in a further 15 (26%) of crises. Fever was common even in apparently uncomplicated painful crises, suggesting that fever is characteristic of the painful crisis itself and not necessarily indicative of infection. Following investigation and treatment in a daycare center, >90% of patients returned home

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Sporrer, 1994 <sup>212</sup>	P, Obs	VOC pain	NR	Clinical presentation	Analgesics: morphine, ketorolac, ibuprofen, acetaminophen, and codeine	17	100	IV morphine sulfate 0.15 mg/kg q3 h and acetaminophen 10 mg/kg q 4 h. If 2 h pain score was >2, the dosing interval was changed to every 2 h. If pain scores persisted >2, ketorolac 30–60 mg IM loading dose, followed by 50% of the loading dose, given q 6 h, or ibuprofen 20 mg/kg q/4 h was added to the regimen. CIV infusion could be started if severe pain persisted for >24 h. Once pain was under control, patients were converted to oral medication (acetaminophen 300 g with codeine 30 mg)	5–12 d	No	NA	NA	NA	2 of the 17 children required CIV infusions of morphine for severe pain that persisted beyond 24 h. Children (3–12) reported significantly less severe pain than adolescents (13–18) (2.1 vs. 3.7 respectively, p<.01). The severity of pain reported was not related to the number of painful sites. However, the length of stay was significantly longer among patients with greater number of painful sites (p<.05). Patients who reported pain scores of >2 at 24 h had significantly longer periods of hospitalization

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Tefler, 2009 <sup>215</sup>	P, Obs	Acute pain	Pain that had not responded to home analgesia	Patient report	Intranasal diamorphine (IND)	22	100	Group 1: 0.1 mg/kg given as a single dose immediately on arrival, followed if required by IV morphine bolus (100 µg/kg) and infusion via PCA. Group 2: IND 0.1 mg/kg given simultaneously with oral morphine 0.4 mg/kg immediately on arrival, followed by further oral morphine 0.4 mg/kg after 1 h if required	Hourly	No	NA	NA	NA	There was a rapid improvement in pain score; the proportion of children in severe pain at t=0, 15, 30 and 120 min in phase 1 were 78%, 11%, 0% and 11%, respectively, while in phase 2 they were 77%, 30%, 15% and 0%, respectively. Pain severity scores appeared to improve more rapidly in phase 1 compared with phase 2, but numbers were too small to make a formal statistical comparison. There was a recurrence of severe pain in 1 child in phase 1, following cannulation difficulties prior to the administration of IV morphine. In phase 1, 6 patients were given additional morphine, 2 did not require any additional analgesia and were sent home from the ED, and 2 had oral morphine because of difficulty with cannulation. In phase 2, all children received oral morphine in addition to IND. There were no episodes of respiratory depression or sedation. 8 children in total reported minor side effects, consisting of nasal irritation, pruritus and nausea. In response to the question: "How well did the medication work for you?" the mean score was 8.2 out of 10, and to the question: "Was this type of medication acceptable to you?" the mean score was 8.5
Thomas, 1984 <sup>216</sup>	P, Obs	Sickle cell pain	NR	Clinical presentation	Biofeedback therapy	15	100	Biofeedback therapy (progressive relaxation, thermal biofeedback, cognitive strategies, and self-hypnosis)	6 mo	Control (same group)	15	100	Regular management (no biofeedback therapy)	Results show a 38.5% reduction in the number of ER visits, a 31% reduction in the number of hospitalizations, and a 50% reduction in the inpatient stay during the 6 mo since the beginning of therapy compared to 6 mo prior to therapy. Analgesic intake was reduced by 29% for those who were using it regularly
Udezue, 2007 <sup>218</sup>	P, Obs	Sickle cell pain	NR	Clinical presentation	Regular pain management	849	100	IV ketorolac, 30–60mg repeated if necessary 6 hourly; IV morphine 2–5 mg half hourly until pain is controlled or IV pethidine 50–100 mg, 4 hourly when necessary	Acutely	Yes, Comparison	305	100	On-demand pain medication administration	Acute pain crises were either terminated or controlled in >80% of patients within 72 h. Male patients fared worse. Regular IV narcotic analgesia was more effective than intermittent or "on-demand" dosing, with a higher discharge rate (83% vs. 71%, p<.05)

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Conti, 1996 <sup>223</sup>	R-P, Obs	Sickle cell crisis pain	NR	Clinical exam/investigations	Analgesic, morphine sulphate	9 (84 episodes)	100	Morphine sulfate elixir 60 mg with oral ibuprofen 800 mg followed by morphine 20 mg by mouth every 30 min	Not specified	No	NA	NA	NA	The oral morphine protocol (OMP) was attempted in 102 of 116 ED visits. In the 102 instances in which it was started, it was completed 84 times (82%). The number of ED visits decreased significantly following implementation of the OMP. The study patients averaged 16.7 ED visits (range 7–27) for the 12 mo preceding OMP compared with an average of 12.9 visits (range 6–19) for the post-OMP period (p<.01). The total number of hours spent in the ED decreased in all 9 patients after OMP. Admission rates also decreased significantly. 6 patients followed OMP without deviation at every ED visit. In this group there were 116 visits during the year before the protocol and 87 visits for the year after the protocol (p<.01). The admission rate for this subset of patients dropped from 6.9% to 3.4% after OMP (p<.01)
Aisiku, 2009 <sup>232</sup>	Case report/case series	Sickle cell pain	NR	Clinical presentation	Morphine, blood transfusion	1	100	Morphine 5 mg at presentation then 10 mg hourly for a total of 35 mg plus 1 U of packed red blood cells (PRBCs)	24 h	No	NA	NA	NA	Pain resolved
Al-Momen, 1997 <sup>245</sup>	Case report/case series	Acute bone pain	NR	Clinical presentation	Opioid derivatives, non-steroidal anti-inflammatory drugs, and clodronate	1	100	IVFs, (paracetamol 500 + codeine 30 mg) 2 tabs every 6 h, pethidine 100 mg IM every 6 h for 24 h. Then she received clodronate 900 mg in 500 cm <sup>3</sup> saline IV over 4 h	5 d	No	NA	NA	NA	No further pain. Patient discharged home pain-free

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Ballas, 2004 <sup>259</sup>	Case report/case series	Severe chest pain	Clinically	Clinical presentation	Nebulized morphine	2	100	The opioid used was morphine sulfate (MOSO4) solution, 20 mg in 3 or 5 mL of buffered physiologic saline solution (PSS). It was inhaled through the mouthpiece of an Acorn Porta-Neb jet nebulizer driven by air flowing at 8 L/min over 10–15 min	4 and 11 d	No	NA	NA	NA	Patient 1: MOSO4 (20 mg in 3.0 mL PSS), dispensed via a nebulizer over 10–15 min, resulted in 90% relief of chest wall pain and a decrease in the pain intensity score to 0/10 within a few minutes. The patient requested the nebulized morphine treatment daily for 4 d, after which the chest wall pain resolved. Patient 2: MOSO4 dispensed via a nebulizer over 10–15 min resulted in 50% pain relief and decreased the pain intensity score to 4.5/10 within 5 min. Subsequently, the patient requested the nebulized morphine treatment for the chest wall pain, 3–4 times/d for 11 d, after which the chest wall pain resolved
Boulmay, 2009 <sup>270</sup>	Case report/case series	Acute painful episodes complicated by cocaine abuse leading to multiorgan dysfunction	NR	Urine toxicology screen	Partial RCE transfusion	2	100	Partial RCE transfusion	NR	No	NA	NA	NA	1 patient resolved, 2 died
Chang, 2008 <sup>278</sup>	Case report/case series	Generalized bone pain and severe back and leg pains	Sequelae from both pathways (namely ACS, bone pain, and hemolysis)	Chest x ray, computed tomography (CT)	iNO	1	100	Albuterol breathing treatments, oral hydrocodone/ Tylenol for bone pain but without antibiotics	Acute	No	NA	NA	NA	Her methemoglobin levels were 0.7, 0.5, 0.9, and 1.2% on d 0 through 3 of iNO therapy, respectively, and her blood pressure (BP) did not decline. Patient's fever resolved 24 h after initiation of iNO therapy, her partial oxygen pressure (PO2) also improved markedly from 80 mmHg on the day of initiation of therapy to 155 mmHg upon completion of therapy. The patient also reported no pain upon completion of iNO therapy. Her hemoglobin and hematocrit remained stable then gradually increased to 5.5 g/dL and 16.8%, respectively, the day after cessation of iNO therapy. A chest x ray performed on the day of discharge indicated a marked improvement in pulmonary infiltrates and left lower atelectasis. She was discharged 3 d after stopping iNO therapy
Darbari, 2008 <sup>292</sup>	Case report/case series	Sickle cell pain	NR	Clinical presentation	PRBC transfusion 2 patients, exchange transfusion 2 patients	4	100	PRBC transfusion 2 patients, exchange transfusion 2 patients	NA	No	NA	NA	NA	Symptoms resolved

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Erhan, 2007 <sup>311</sup>	Case report/case series	Sickle cell pain	Patient had an upper respiratory tract infection in which VOC was predicated. On admission he had fever, severe abdominal and leg pain	NR	Paracetamol, ibuprofen and morphine	1	100	Paracetamol (40–60 mg/kg, 1/day) and ibuprofen (20 mg/kg /day) were administered to relieve pain. The pain did not subside so tramadol drops (1–2 mg/kg, 1/6 h, 1 orally) were added to the analgesia. Since he still complained of pain, tramadol infusion was started (0.25 mg/kg, 1/h) and rescue analgesic included morphine (0.1 mg/kg) 1 SC as necessary. He was transfused with PRBCs	3 d	No	NA	NA	NA	During the tramadol infusion no morphine was required; the intensity of pain gradually decreased and the child was able to move his legs. At the end of 3 d splenomegaly regressed, no fever and pain were observed and the infusion was stopped. No side effects attributed to nonopioids and tramadol were seen during his therapy
Gabrovsky, 2010 <sup>320</sup>	Case report/case series	Acute flank pain	NR	CT scans showed clots in the left renal pelvis and bladder	Oral Epsilon amino-caproic acid	1	100	The patient underwent an exchange transfusion with the goal of 30% fractional cells remaining and a hematocrit of 30%. The HbS fell from 45.4% to 9.7% and hemoglobin C (HbC) fell from 48% to 9.3%. 5 h after electrophoresis, the hemoglobin was only 8.4 g/dL, which subsequently fell to 7.1 g/dL about 15 h later. He was transfused with 2 U of PRBCs. The patient received PRBCs support on hospital d 4, 5, 10, and 11 to maintain the hemoglobin above 10 g/dL	23 d	No	NA	NA	NA	On hospital d 22, EACA (Epsilon Aminocaproic Acid) was again discontinued and gross hematuria recurred. EACA was therefore restarted 24 h later at an even lower dose of 5 mg/kg every 8 h. There was intermittent, mild flank pain. He continued at this dose for d 22–23 and the flank pain resolved. The urine remained clear and he was discharged to home on hospital d 23 on low-dose, oral EACA (5 mg/kg every 8 h), trimethoprim/sulfasoxazole prophylaxis for urinary tract infection, and citric acid. At discharge, the hemoglobin was 13.0 g/dL, hematocrit was 36.9%, platelet count was 110,000, BUN was 11 mg/dL, and creatinine was 1.0 mg/dL

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Gerber, 1993 <sup>324</sup>	Case report/case series	Sickle cell pain	Patient presented with severe back pain	NR	Meperidine, morphine	1	100	He was IV hydrated and received 160 mg of meperidine, followed by morphine, 20 mg subcutaneously for 11 h. An IV infusion of 0.5 mg morphine per hour was started, which gradually increased to 6 mg/h	4 d	No	NA	NA	NA	After the patient had received a total of 298 mg of morphine he had a cardiopulmonary arrest and died
Green, 1975 <sup>332</sup>	Case report/case series	Sickle cell pain	NR	Clinical presentation	Large-scale exchange transfusion	2	100	Case 1: 6 L of blood were removed and 9 U of whole acid-citratexdextrose-treated blood (group B Rh-positive) and 6 U of PRBCs (group O Rh-positive) were simultaneously transfused. Case 2: 15 U of whole acid-citratexdextrose-treated blood (within 7 d of donation) were used	NR	No	NA	NA	NA	Complete recovery for both

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Hillyer, 1991 <sup>343</sup>	Case report/case series	Painful sickle cell crisis	NR	Over 4 d, hematocrit decreased to 13% with reticulocytopenia suggestive of aplastic crisis	Blood transfusion, analgesics and IV hydration	NA	NA	4 U of incompatible PRBC	NA	No	NA	NA	NA	Pain crisis resolved, patient was discharged from hospital and then readmitted 8 d following transfusion for another painful crisis. A diagnosis of delayed hemolytic transfusion reaction was made. Over the next 2 d hematocrit decreased to 14%, MCV 66 fL, corrected reticulocyte count 2.2% and total bilirubin 23.6 mg/dL. The peripheral blood smear showed poikilocytosis, polychromatophilia, targets, spherocytes and basophilic stippling. 11–36 nucleated red blood cells (RBCs) per 100 leukocytes were observed during this period. The urine showed 4+ hemoglobin and no RBSs in sediment examination. 4 d later patient was discharged without having received any further transfusions. Laboratory values included hematocrit 20%, reticulocytes 15.3% (6.9% corrected), and 200 nucleated RBCs/100 white blood cells (WBCs). Spherocytes were absent on blood smear examination
Hsiao, 2005 <sup>349</sup>	Case report/case series	Sickle cell pain	NR	Chest radiograph, ECG, US, abdominal radiograph, clinical presentation	IV neostigmine	1	100	The patient was started on IVF, oxygen via nasal cannula, and PCA with IV hydromorphone. A bowel regimen consisting of senna and docusate sodium was initiated. He was transfused with 2 U of PRBCs. When this patient did not respond to 24 h of conservative therapy, he was given 2 mg of IV neostigmine while on a cardiac monitor	NR	No	NA	NA	NA	Within 10 min, he had prompt decompression of his bowels. His abdominal discomfort and distension immediately improved. Evidence of successful treatment was captured on a repeat abdominal radiograph. His pain and bowel regimens were adjusted, and he was discharged in excellent condition

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/medication	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Ives, 1987 <sup>355</sup>	Case report/case series	Pain crisis	NR	Clinical presentation	Meperidine hydro-chloride, haliperidol, morphine, methadone	1	100	Meperidine hydrochloride 100 mg 3 hourly, then hourly, the patient developed toxic psychosis as a side effect. So meperidine was discontinued and haliperidol 10 mg twice a day (b.i.d.) started, along with morphine infusion 500 mg in 1,000 mL 5% dextrose in water, at a rate of 50 mg/h to achieve analgesia; this was tapered down to 10 mg/h, which continued to 58 h. Then the patient was shifted to oral methadone 15 mg/h 6 hourly	6 d	No	NA	NA	NA	Good control over the pain was achieved
Keller, 1979 <sup>363</sup>	Case report/case series	Sickle cell pain	Acute hemolytic sickle cell crisis with fever and diffuse abdominal pain; she also had findings suggesting epicardial ischemia and necrosis of both femoral heads	ECG, x ray	The necrosis of the femoral heads was operatively treated by a bowel prosthesis of both femoral heads	1	100	3× 800 mg pentoxifylline daily	NR	No	NA	NA	NA	This medication did not prevent hemolysis, but the hemolysis was no longer associated with painful crisis. The patient no longer needed analgesic medication during the hemolytic phase. Her surgery produced good orthopedic results
Kleinman, 1981 <sup>370</sup>	Case report/case series	Prolonged VOC pain	Acute pain crisis lasting >8 d	Clinical presentation	Erythrocytapheresis	4	100	RCE transfusion	During hospitalization	No	NA	NA	NA	3 of 4 patients resolved their pain crises within 24–48 h following transfusion. 1 of those patients showed a prompt response during treatment for the initial presentation, but only a slow response following transfusion for a subsequent crisis. The 4th patient, with a documented history of bone infarcts, showed only a partial response to treatment, characterized by resolution of abdominal pain with no relief of persistent lower extremity bone pain

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Knight-Perry, 2009 <sup>371</sup>	Case report/case series	Methacholine challenge-induced acute pain episode	NA	Patient reported diffuse body pain	CIV morphine drip with transition to oral pain medication prior to discharge. Course of corticosteroids was continued and then tapered over 7 d	1	100	Morphine 5 mg/h	Hospital stay of 9 d	No	NA	NA	NA	At the outpatient followup 19 d after discharge, patient denied any pain or respiratory symptoms
Kruse 1983 <sup>377</sup>	Case report/case series	Abdominal pain, paralytic ileus, sore throat	NR	Clinical presentation, throat swab, abdominal x ray	Blood transfusion, IVF, antibiotics	1	100	900,000 U benzathine penicillin, 300,000 U procaine penicillin G + 4 U of PRBCs	NR	No	NA	NA	NA	Symptoms resolved
Labat, 2001 <sup>379</sup>	Case report/case series	Acute abdominal pain and priapism	Severe abdominal pain (8/10) on a VAS	VAS	To treat the priapism that developed 9 h into admission, a lumbar epidural catheter was placed. The patient received a 17-mL bolus of 0.25% bupivacaine with epinephrine	1	100	A CIV morphine infusion was started, along with hydration, propacetamol, nalbuphine and oxygen, partial exchange transfusion to reduce the concentration of HbS from 63 to 36%	48 h	No	NA	NA	NA	Priapism resolved within 15 min after the initial bolus and abdominal pain improved (VAS 3/10). The epidural catheter was removed 48 h later. The patient did not require supplemental analgesia and did not have further episodes of pain or priapism during the course of his hospital stay
Ludmerer KM, 1982 <sup>401</sup>	Case report/case series	Pain in both legs and the left maxilla, and an effusion in the left elbow	X ray showed mottled lucencies in the left humeral condyle with cortical destruction, and abnormalities in the distal right femur, the right midtibia and left elbow were found	X ray, bone scan, bone biopsy	Antibiotic therapy	1	100	Hypertransfusion resulted in a hematocrit value of 41%	1 mo	No	NA	NA	NA	Despite "appropriate therapy" the patient died

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/medication	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Moukarzel, 2000 <sup>422</sup>	Case report/case series	VOC and possible bacteremia	NR	Chest x ray, physical examination, lab tests, CT scan	2 weeks into her hospital course the patient began to develop increasing abdominal distention and her diarrhea increased to 12 bowel movements a day; she was placed on bowel rest and parenteral nutrition for the next 4 weeks	1	100	She was started on IV hydration, cefoxitin, vancomycin and analgesics. During her hospitalization, multiple transfusions of PRBCs were given to maintain her hemoglobin levels below 28%	7 weeks	No	NA	NA	NA	Hematochezia, abdominal distention, and tenderness subsided with improvement in her general condition. Feedings were gradually introduced. The patient was finally discharged after 7 weeks in the hospital, and she has remained asymptomatic with no gastrointestinal (GI) complaints for >1 yr
Navaid, 2010 <sup>428</sup>	Case report/case series	Recurrent acute sickle cell pain requiring	NA	Clinical presentation and physical exam	HU, transfusion, PCA Dilaudid	1	100	Dose was escalated up to a maximum dose of 2 g/d, plus monthly exchange transfusion	1 yr	No	NA	NA	NA	Hospitalizations and ER visit went down from 9 and 16 in the yr prior to transfusion regimen, to 3 (1 related to VOC) and no ER visits in the yr on the exchange transfusion treatment
O'Neil, 2001 <sup>434</sup>	Case report/case series	Case 1:SCD swollen spleen, Case 2: priapism	NA	Clinical presentation, physical exam, lab tests	IV pain control switched to po prior to discharge	2	50	Case 1: oxygen, two 20g IV lines and a fluid bolus of 40 cm <sup>3</sup> /kg, 0.9% saline. 5 cm <sup>3</sup> /kg of uncross-matched blood and later additional 5cc/kg of crossmatched blood. Case 2: oxygen, morphine 0.1mg/kg and 0.9% normal saline 20 cm <sup>3</sup> /kg, ceftriaxone 2g IV	Case 1: 2 days Case 2: 5 days	No	NA	NA	NA	Adequate pain control

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Pollack, 1991 <sup>443</sup>	Case report/case series	Sickle cell pain crisis	NR	Patient report/clinical exam	All cases received ketorolac. Case 1 also got promethazine. Cases 2, 3, and 4 got amitriptyline	4	100	Case 1: Ketorolac 60 mg, promethazine 25 mg, initially and then an additional 50 mg of meperidine and 50 mg promethazine, Case 2: 60 mg ketorolac and amitriptyline 50 mg Case 3: 60 mg ketorolac and amitriptyline 50 mg initially. Then 30 mg ketorolac and amitriptyline 25 mg repeated twice Case 4: 60 mg ketorolac and amitriptyline 50 mg	Variable, 6–12 h	No	NA	NA	NA	All 4 patients recovered and returned to the ED 2–6 weeks later for next pain
Rada, 1987 <sup>447</sup>	Case report/case series	Sickle cell crisis	Sickle cell crisis is the clinical term describing the onset of acute symptoms caused by in vivo sickling in patients with SCD	Clinical exam/investigations	Case 1: Hydration, meperidine, hydroxyzine, analgesics, folate Case 2 also received antibiotics and transfusion	2	100	PRBC in case 2 (2 U)	NR	No	NA	NA	NA	Case 1: Patient recovered after treatment and was scheduled for definitive outpatient care. Case 2: Recovered after treatment and was scheduled for definitive treatment, too
Schechter, 1988 <sup>470</sup>	Case report/case series	Sickle cell crisis in adolescents	NR	Clinical exam/investigations	Morphine, analgesic via PCA pump	3	100	A loading dose of 0.10 to 0.14 mg/kg of morphine followed by pulse doses of no >0.2 mg/kg over first 4 h divided into smaller doses and given at least 15 min apart. After first 4 h, pulse dose of 0.01–0.035 mg/kg also with a 15-min lockout	Until pain subsided enough to be controlled with oral analgesics	No	NA	NA	NA	All 3 patients preferred PCA to standard treatments and had no problems handling the PCA pump

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Sodipo, 1986 <sup>493</sup>	Case report/case series	Agonizing pain in legs and left shoulder and inability to walk	NR	Clinical presentation	Acupuncture	1	100	NR	16 d (started on a daily basis for the first 5 d, then every other day until d 16)	No	NA	NA	NA	Pain completely resolved, patient was able to walk without limping
Spinapolice, 1982 <sup>498</sup>	Case report/case series	Hemoglobin SD disease associated with cholecystitis and cholelithiasis in pregnancy	NR	Clinical exam/investigations	Antibiotics, folate, multivitamins	1	100	Not specified	NR	No	NA	NA	NA	Patient delivered viable fetus at 39 weeks and was discharged with antibiotics and methadone but never returned and was lost to followup
Stewart, 2009 <sup>503</sup>	Case report/case series	Sickle cell-induced ischemic colitis	Sickle cell-induced ischemic colitis is a rare yet potentially fatal complication of sickle cell anemia. Frequent pain crises with heavy analgesia may obscure and prolong this important diagnosis	Clinical presentation, physical exam, lab tests	PCA	1	100	Aggressive hydration, hydromorphone PCA, antibiotics	7 d	No	NA	NA	NA	The patient was given hydromorphone PCA, IVF hydration with normal saline, and lactulose for sickle cell crises with opiate-induced constipation. After 2 d of failed lactulose therapy, the patient was given an enema to induce a bowel movement, which only resulted in scant watery diarrhea. On hospital d 5, the patient spiked a fever of 39°C, and her WBC count increased to 19,000/mL. She was started on IV piperillin/ tazobactam and vancomycin, and a repeat chest x ray and abdominal CT were obtained. Colonoscopy showed a 10-cm segment of colon beginning at the splenic flexure with ulceration and a friable cobblestone appearance. Biopsy revealed fragments of ischemic bowel with inflammatory infiltrate and pseudomembrane formation. Intravascular spaces revealed marked sickling of erythrocytes leading to a diagnosis of sickle cell-induced ischemic colitis. The patient continued to be aggressively hydrated and was kept on IV vancomycin and piperillin/tazobactam. Her pain was significantly improved after exchange transfusion, and she began having normal bowel movements shortly thereafter. All studies for infectious organisms returned as negative. She had an uneventful recovery and was discharged home 7 d later

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Zempsky, 2010 <sup>538</sup>	Case report/case series	VOC pain	A primary diagnosis of sickle cell pain (SCA with VOC pain (282.62), or sickle cell thalassemia with crisis (282.42)	Patient reported pain score (0–10 numerical rating scale)	Ketamine	5	100	The starting dose of ketamine ranged from 0.06–0.1 mg/kg/h. Titration of the ketamine infusion was based on patients' pain score, adverse events, and attending preference. The ketamine infusion was increased no more frequently than every 4 h with a maximum increase of 0.05 mg/kg/h. The maximum ketamine infusion was limited to 0.2 mg/kg/h. 2 patients received a 0.1 mg/kg bolus of ketamine before infusion initiation	Duration of the CIV infusion ranged from 19 to 90 h	No	NA	NA	NA	4 patients received ketamine after several days of inadequate pain relief on IV opioids delivered via PCA. The patients were given ketamine as an adjuvant to their patient-controlled opiate regimen of either morphine or hydromorphone. 1 patient had dramatic reduction in her headache symptoms after the onset of the ketamine infusion. The other 3 did not have clear improvement in pain relief; however, patient 1 used considerably less opiate during the infusion of ketamine. 1 patient received low-dose ketamine infusion as the only analgesic for her VOE. Although this patient's pain score was low at the time of hospitalization, this was typical of her usual presentation. Her pain scores did decrease during the ketamine infusion. The infusion was discontinued when she reported adequate pain relief. Her hospitalization duration was at least 24 h shorter than her 4 previous hospitalizations all of which had occurred within the previous 12 mo. 3 patients had decrease in average heart rate and 1 patient's average heart rate increased while on ketamine. 3 patients had increases in BP during the infusion and in 1 this did reach the borderline hypertensive range. None of these patients had clinical symptoms associated with these vital sign changes. There were not clinically relevant changes in the average temperature, respiratory rate, oxygen saturation, or diastolic blood pressure (DBP) in any patient during the ketamine infusion. Adverse events: Two patients had adverse events. One of these patients complained of dysphoria after the initial bolus, and this dysphoria remained while she was on the CIV infusion. She asked that the ketamine be discontinued after 19 hr. The other patient developed unexpected nystagmus, hypertension, and unresponsiveness when a new infusion of ketamine was begun, 24 h after the initial infusion. He did not have these symptoms before the change in ketamine solution. Staff members felt this patient likely received an inadvertent bolus of ketamine during the transition to the new infusion

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Zolezzi, 2001 <sup>541</sup>	Case report/case series	VOC pain	NR	Clinical presentation	Acetaminophen, codeine phosphate, IV diazepam, and naloxone	1	100	The patient was started on IVF for hydration, and a dose of acetaminophen 250 mg orally for pain control was given. 1 h later, the patient was examined and found to have increased pain. As a result, IV codeine phosphate 30 mg (2 mg/kg) was given	LOS in hospital (<1 mo)	No	NA	NA	NA	10 min after its administration, the patient became tachycardic, with a heart rate of 195 beats/min, tachypneic with shallow breathing, and an RR of 60 breaths/min. His BP decreased to 106/43 mmHg. The patient then became apneic and had seizures that lasted for approximately 30 s. He was spastic and unconscious, with bilaterally dilated pupils (5 mm) that reacted sluggishly. The patient was immediately given 100% O <sub>2</sub> , and the lungs were ventilated manually. IV diazepam 10 mg (0.67 mg/kg) and naloxone 2 mg (0.134 mg/kg) were given. The seizures were controlled with these medications, but he remained unconscious, with a General Conscious Scale score of 6. CT showed no evidence of stroke or bleeding. A complete blood count (CBC) showed laboratory values within normal ranges, except for significant low values for hemoglobin (6 g/dL) and RBCs (2.99×10 <sup>6</sup> /mm <sup>3</sup> ). Arterial blood gases were within normal limits, except for a significantly elevated PO <sub>2</sub> (210 mmHg). Random glucose concentration was high (264 mg/dL). All values of urea and electrolytes were within normal ranges. The patient was transferred to the pediatric general intensive care unit for close observation. On arrival, he was comatose, breathing without assistance, and unresponsive to painful stimuli. Pupils were 3 mm and reactive bilaterally. 2 subsequent doses of naloxone had no effect. His neurologic status started to improve after 10 h, and he had full recovery after 24 hr. The patient was discharged after 48 h, having made a full recovery

**Table 9. Chronic Pain Incidence and Outcomes**

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/ medication	Duration of treatment	Secondary/ control arm	N of patients	% of patients	Control treatment	Reported results
Alvim, 2005 <sup>5</sup>	RCT	Recurrent vaso-occlusive crises (VOC) pain	Painful episodes in the limbs, vertebral spine, thorax, or abdomen, of variable intensity and duration, without other identified cause, with or without medical assistance, preferably recognized by patients and relatives as the characteristic pain caused by sickle cell disease (SCD)	Clinical presentation	Piracetam	73	100	Oral, 4.8 g/m <sup>2</sup> , 4 times/d	6 mo	Yes, Control	73	100	Placebo	57 (78.1%) of patients had pain scores up to 5; 12 (16.4%) had pain scores from 5 to 10; and 4 (5.5%) had pain scores >10. Differences in median pain scores between different genotypes were not statistically significant. Levels of pain did not differ significantly when groups were compared. In the 1st semester of the study, medians were 2.51 and 3.03 respectively, for placebo and piracetam ( $p=.46$ ), in the 2nd semester the scores were 1.4 and 1.43, respectively ( $p=.96$ ). Nor were the pain scores different when the piracetam period was compared with the placebo period in the same children. The difference was not significant when only homozygous sickle cell disease (HbSS) patients were analyzed either. The median pain scores for both semesters of the study, including all children whether they were receiving piracetam or placebo were 2.8 and 1.43 respectively ( $p=.02$ ). There were no significant difference between the piracetam and placebo in days of hospitalization or school attendance. It was concluded that although nearly all patients and relatives reported an improvement in clinical course during the trial, the drug was ineffective in the prevention of painful crises. The placebo effect was attributed to an unplanned and unsystematic "cognitive-behavioral" management of the children

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Myers, 1999 <sup>32</sup>	RCT	Chronic sickle cell pain	NR	Clinical presentation, visual analogue scale (VAS)	Massage therapy + progressive muscle relaxation (PMR)	6	100	Individual sessions of 30 min or progressive muscle relaxation instruction, ending with relaxing guided imagery. Patients underwent 6 sessions of PMR	6 session over range of 6–33 weeks	Yes only	10	100	30-min massages. Patients underwent 6 sessions of massage therapy (MT) over range of 6–33 weeks	Assessment of pain immediately before and after the 1st session of the intervention demonstrated that treatment by the both MT and PMR was associated with short-term reduction in pain unpleasantness (MT from 4.20 to 2.51; PMR from 5.63 to 3.25, $p=.002$ ) and pain intensity (MT from 4.58 to 2.48; PMR from 4.98 to 3.93, $p=.001$ ). There was no time by type-of-intervention interaction effects, indicating that relaxation training and massage therapy were not significantly different in effectiveness. Comparing VAS pain ratings taken before the 1st and 6th interventions demonstrated a reduction of pain unpleasantness ( $p=.02$ ) and pain intensity ( $p=.01$ ) over time. Neither intervention had a significant long-term impact on the Sickness Impact Questionnaire and the McGill Pain Questionnaire scores
Odebiyi, 2007 <sup>34</sup>	RCT	Hip pain	NR	Clinical presentation, VAS	Sodium salicylate Iontophoresis	10	100	10 treatments lasting 20 min over 5 weeks + Usual Care—conventional physiotherapy and regular medications	5 weeks	Yes	10	100	Conventional physiotherapy and regular medications	Mann Whitney U test showed that there was a statistically significant difference between the pre- and posttreatment VAS scores (pain intensity) of the participants in the study group (-2.83) ( $p<.05$ ) while there was no significant difference in the pre- and posttreatment VAS scores (pain intensity) of the participants in the control group (0.00) ( $p>.05$ ). The results also showed that there was a statistically significant difference only in the posttreatment values between the study and control groups (-1.17 vs. -3.88) ( $p<.05$ ). Paired t-test showed that there was a statistically significant difference ( $p<.05$ ) between the pre- and posttreatment range of motion (ROM) values of participants in the study group (13.21), while there was none in the participants in the control group (-0.95) ( $p>.05$ ). Also, there was a statistically significant difference only in the posttreatment ROM values ( $p<.05$ ) between the study and control groups (-0.76 vs. 9.08)

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/ medication	Duration of treatment	Secondary/ control arm	N of patients	% of patients	Control treatment	Reported results
Crawford, 2006 <sup>86</sup>	R, Obs	Postoperative pain	NR	NR	Patient-controlled analgesia of morphine after laparoscopic cholecystectomy (both groups)	12	(100% had pain)	Total post-operative morphine consumption in the sickle group (1.58±0.78 mg/kg) was more than double than that in the nonsickle group (0.65±0.32 mg/kg) ( <i>p</i> <.005)	NR	Patients without SCD	10	100% had pain	Postoperative morphine	Mean pain scores in sickle children in the first 24 h after surgery (5.3±1.5) were significantly greater than those in nonsickle patients (3.9±1.5) ( <i>p</i> <.05). The proportion of patients requiring patient-controlled analgesia (PCA) for >48 h was significantly greater in the sickle group (42% vs. 0%) ( <i>p</i> <.05). The mean duration of PCA use in the sickle group (51±25 h) was more than double than that of the nonsickle group (21±11 h) ( <i>p</i> <.005). Postoperative morphine consumption among sickle patients who had received opioid analgesia within 1 mo before surgery ( <i>n</i> =6) (1.8±0.9 mg/kg) was approximately 28% greater than that for sickle children not treated with opioids before surgery ( <i>n</i> =6) (1.4±0.6 mg/kg). The duration of postoperative hospital stay in sickle patients (3.4±1.6 d) was more than double than that for nonsickle patients (1.5±0.5 d) ( <i>p</i> <.005). The time from admission to hospital until surgery was also significantly greater among sickle (3.8±4.3 d) compared with nonsickle patients (0.4±0.8 d). There was no perioperative mortality
Bodhise, 2004 <sup>169</sup>	P, Obs	Chronic pain associated with avascular necrosis (AVN) (particularly of the low back and hip)	NR	Clinically	Deep tissue/deep pressure MT technique, including neuromuscular trigger point therapy with acupressure	5	100	Deep tissue/deep pressure MT technique, including neuromuscular trigger point therapy with acupressure	NR	No	NA	NA	NA	Significant changes were noted in each patient. The pain score (or numeric pain index, NPI), the tension and profile of mood score (TPMS), and the activities of daily living (ADL) showed significant improvement after completion of therapy (NPI score premean=9.6±0.80; postmean=2.8±0.75; TPMS premean=9.4±1.2, postmean=2.2±0.4; ADL premean=3.8±0.4, postmean=1.8±0.75). Days spent in the emergency room (ER) and/or hospital were significantly less after MT (premean=6.2 d, postmean=3.2 d). Moreover, opioid consumption also decreased after therapy (from 5/5 patients needing daily opioid use to 4/5 patients not needing any opioid use). The patients reported a sense of relaxation, with pain and tension relief and an increase in their ADL that persisted for up to 24–48 h or longer postmassage. The majority of patients did not need to take opioid analgesics for 24 h following the neuromuscular trigger point procedure

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/ medication	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Chaplin, 1989 <sup>173</sup>	P, Obs	Recurrent painful sickle cell crises	NR	Clinical presentation	Prophylaxis mini-dose heparin	4	100	Heparin sodium injections USP (derived from porcine intestinal mucosa and containing 20,000 USP U/mL)	12–36 mo	Yes, comparison	4	100	No heparin prophylaxis	No treatment-related complications occurred requiring discontinuation of heparin. Thrombocytopenia was not observed. There was no evidence of progressive osteopenia. All patients improved while receiving heparin; 1 moderately, 3 markedly. Cumulative data (8.7 patient yr on heparin, 12 control yr) revealed a 73% reduction in days of hospitalization per year and 74% reduction in h spent in ERs per year during heparin administration. Pretreatment pain patterns recurred when heparin was discontinued
Dinges, 1997 <sup>177</sup>	P, Obs	VOC pain	NR	Pain diaries (morning and evening entries) measuring pain, medication, school/ work attendance and sleep	After: analgesics + self-hypnosis	37	100	Training in self-hypnosis (weekly sessions for the first 6 mo, then biweekly for 6 mo and then once every 3 weeks for 6 mo)	18 mo	Before: conventional analgesics	37	100	Prescribed pain medications (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids)	SUMMARY: Self-hypnosis was successfully integrated into SCD home pain management program and was able to reduce the frequency, but not severity or pain medication requirements, of SCD pain episodes
Gill, 2000 <sup>181</sup>	P, Obs	Acute and chronic pain	NR	NR	NA	34	100	Daily diary about pain response	14 d	No	NA	NA	NA	As pain levels increased, children were more likely to use narcotic medications and health care services, although overall health care utilization during the 2-week period tended to be relatively infrequent. On average, children considerably reduced school, household, and social activities when in pain. Moreover, parents and adolescents generally agreed on daily pain response, especially for salient events such as health care visits
Alam, 2004 <sup>237</sup>	Case report/ case series	Painful crisis in pregnancy	Pain was localized to her lower limbs and back and was deep in nature. Hemoglobin was 7.5 g/dL	VAS	Intravenous (IV) dextrose 5% and oxygen supplementation. Morphine was started with a bolus 3 mg IV and then infusion was given at the rate of 2 mg/h (0.04 mg/kg/h) with an infusion pump	1	100	Broad-spectrum antibiotics were empirically administered. 2 U of packed red blood cells (PRBCs) were transfused	3 d	No	NA	NA	NA	There was good response to the dose of morphine, and was reduced to 1 mg/h (0.02 mg/kg/h) after 24 h. she was pain-free after 3 d of treatment. she was given tablet diclofenac sodium, 50 mg 8 hourly, for 2 d and then discharged from the hospital

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Chaplin, 1980 <sup>279</sup>	Case report/ case series	Prevention of chronic pain crisis	NR	Clinical	Aspirin and dipyridamole	3	100	Each patient took 0.65 mg aspirin and 50 mg dipyridamole bid	24 mo on treatment	No	NA	NA	NA	During the treatment period, patients were either asymptomatic or mildly symptomatic for 85% of the time, compared to 73% while off treatment; and while on treatment, patients were hospitalized 4% of the time, compared to 9% while off treatment. However, this was not significant when corrected for observation period. While on therapy, patients' hospitalizations were shorter and prescription drug usage was lower
Kleinman, 1981 <sup>370</sup>	Case report/ case series	Recurrent VOCs	NR	Clinically	Erythrocytapheresis	4	100	Red cell exchange (RCE) transfusion to maintain sickle cell hemoglobin (HbS) <30%	4–18 mo	No	NA	NA	NA	No prolongation in symptom-free intervals between crises was demonstrated
Powers, 2002 <sup>444</sup>	Case report/ case series	Pain	NR	NR	Children and parents received intensive pain management skills training (nonpharmacological and pharmacological pain management strategies)	3	100	Pain management skills training	NR	No	NA	NA	NA	Participant showed improvement in coping and daily functioning
Sacerdote, 1999 <sup>465</sup>	Case report/ case series	Pain crisis	NR	NR	Pentoxifylline	1	100	The patient was started on pentoxifylline 400 mg orally 3 times daily after meals. After several years of therapy, the dosage was increased to 400 mg 4 times daily for another 3 mo	108 mo	No	NA	NA	NA	Pain crises decreased from 6 to 0/yr, hemoglobin level rose from 8.4 g/dL to 11.4 g/dL, hematocrit rose from 24.8% to 34.8%, lactate dehydrogenase level decreased from 375 IU/L to 322 IU/L, and total bilirubin level decreased from 1.8 mg/dL to 1.6 mg/dL. Mean corpuscular hemoglobin increased from 21.6 pg to 30 pg, and mean corpuscular hemoglobin concentration increased from 24.1 g/dL to 34.5 g/dL. The patient has had no pain crises for the past 9 yr except for 1 episode that did not require hospitalization when she stopped taking the pentoxifylline for 6 weeks. Conjunctival and palmar pallor were absent, and the systolic ejection murmur had resolved. Increase of the dosage of pentoxifylline to 400 mg 4 times daily did not appreciably change any clinical or laboratory parameter after 3 mo

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Shaiova, 2004 <sup>476</sup>	Case report/ case series	NR	NR	Clinical presentation	A long-acting opioid (methadone or controlled-release oxycodone), in conjunction with a short-acting opioid for breakthrough pain (oral transmucosal fentanyl citrate (OTFC), or short acting oxycodone)	3	100	Case 1: 240 mg methadone every 6 h and uses 1,600 µg OTFC for breakthrough pain crises Case 2: Controlled-release oxycodone 160 mg twice/d with short-acting oxycodone 25 mg every 3 h as needed for breakthrough pain crises Case 3: 400 µg/h transdermal fentanyl with 1,600 µg OTFC for breakthrough pain	NA	No	NA	NA	NA	Reduced pain frequency and hospital admissions for all patients

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Description of treatment/ medication	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Shulman, 1995 <sup>486</sup>	Case report/ case series	Pain crisis	NR	Clinical presentation	Hydroxyurea (HU), erythropoietin	1	100	HU 1 g q d (20 mg/kg) on d 1–4 and 50,000 U of erythropoietin (1000 U/kg) on d 5–7 of each week. 1 mo later, erythropoietin and HU doses were reduced to 15,000–20,000 U 3 times per week and 15 mg/kg 4 times/week, respectively. Starting 5 mo after that, erythropoietin and HU were given at slightly higher doses of 20,000 U 3 times/week, and 20 mg/kg 4 times per week, respectively	9.5 mo	No	NA	NA	NA	The patient obtained no benefit from erythropoietin and HU despite an increase in hemoglobin F (HbF) to 15.6%. There was worsening of the back pain after erythropoietin and HU that may be related to marrow expansion
Smith, 2005 <sup>492</sup>	Case report/ case series	Chronic pain in multiple bones, and AVN of her left shoulder	NR	NR	Intrathecal drug delivery system (IDDS) implantation	1	100	Her intrathecal dose of morphine was 11.99 mg/d, which was increased to 13.2 mg/d after 3 d. Her discharge medications included only sustained-release oxycodone (Oxycontin™) 160 mg every 8 h and morphine 30 mg every 4 h as needed	NR	No	NA	NA	NA	The patient reported marked improvements in sedation, anorexia, constipation, as well as increased mobility. 2 weeks later, she discontinued her sustained-release oxycodone. She no longer uses her cane, and this relatively normal activity has persisted for 8 mo, and she has had no hospitalizations for crisis or chronic pain

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Spector, 1978 <sup>497</sup>	Case report/ case series	Pain after a successful renal transplantation	NR	NR	Treatment included prolonged bed rest and parenteral meperidine	1	100	Transfusions of 2 U of buffy coat-poor packed cells were given at a 4–5 week intervals for 6 mo	6 weeks	No	NA	NA	NA	After she stopped the transfusions, the pain returned, so prophylactic transfusions were reinstated, and at the 8 mo followup she had only experienced 1 mild painful crisis
Tinti, 2010 <sup>510</sup>	Case report/ case series	Apathy, depression, frequent fatigue, and constant, generalized pain	NR	NR	Physiotherapy	1	100	To improve the patient's lung capacity and to relieve her pain, physiotherapy was proposed. A kinesiotherapy/a quatic rehabilitation plan was developed; it consisted of exercise in warm water, stretching, aerobics, and relaxation	5 weeks, 2x a week=10 sessions	No	NA	NA	NA	The pain experienced by the patient was reduced after the 1st therapy session, and her quality of life also improved. Only mood did not change from pre- to posttreatment. The maximum inspiratory pressure was 76.7 and 79.2 cm water (H2O), before and after treatment, respectively. The maximum expiratory pressure was 81.3 and 85.4 cm H2O, before and after treatment, respectively
Williams, 2007 <sup>528</sup>	Case report/ case series	Chronic pain and anemia	Documented approximately 1 emergency room visit for pain control, as well as intravenous fluids (IVFs) every 2 mo for the previous year	Angiography	Coumadin and clopidogrel, hydroxyurea	1	100	Trandolapril 1 mg orally daily was given	Continues to take medication	No	NA	NA	NA	She was pain-free at discharge and remained on trandolapril 1 mg daily at bedtime. Except for a 3-d period when she visited a colder climate and developed joint and chest pain, she used no pain medication for 6 mo while she was on the trandolapril. As a test, and during a period of sustained warm weather, the trandolapril was discontinued. After 2 weeks, however, she again developed joint pain. Trandolapril was resumed and 15 tablets hydrocodone/acetaminophen were provided. She has had no pain and has taken no pain medications for >12 mo now. She continues on trandolapril 1 mg nightly
Zeltzer, 1979 <sup>537</sup>	Case report/ case series	Pain	NR	Clinical presentation	Self-hypnosis	2	100	Self-hypnosis	8 mo, 4 mo respectively	No	NA	NA	NA	Reduction in (1) frequency and intensity of pain crises; (2) need for heavy analgesia; (3) frequency of ER visits; (4) frequency; and length of hospitalization for pain

**Table 10. Hepatobiliary Complications Incidence and Outcomes**

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
AL-Mulhim, 2002 <sup>62</sup>	R, Obs	Acute cholecystitis	NR	Abdominal ultrasonography (US), laparoscopy	Laparoscopic cholecystectomy (LC) (a closed technique was used to create pneumoperitoneum and to introduce the subumbilical port. A forward-viewing (0°) laparoscope was used in all cases)	35	100	Upon admission, the patients were well hydrated, given nothing orally, and had intravenous (IV) antibiotics started and continued for a minimum of 48 h after the surgical procedure. Preoperative blood transfusion (sickle cell-free) was given in 27 cases (77.1%) but not postoperatively and partial exchange transfusion was given in 8 cases (22.9%)	NA (surgery)	No	NA	NA	NA	Conversion to open cholecystectomy was required in 2 cases (5.7%), as the bleeding from the cystic artery could not be controlled in 1 case and in the other because the anatomy as Calot's triangle could not be visualized because of dense adhesion. Aspiration of the gallbladder was done in 20 cases (57%). Postoperative endoscopic retrograde cholangiopancreatography (ERCP) was done for 1 patient who developed postoperative biliary collection owing to a slipped clip of the cystic duct. A Redivac drain was used in 26 cases (74.3%) and was removed on the 1st postoperative morning round. In 6 (23%) cases, this was up to 48 h. In 13 cases (37.1%) it was necessary to enlarge the epigastric incision to deliver the inflamed gall bladder, and these cases did not differ in complications or length of stay (LOS) or duration of operation. In this series, there was an epigastric superficial wound infection that subsided with postoperative antibiotic therapy. Postoperative chest infection was noticed in 3 cases and was treated by antibiotic, mucolytic agent, steam inhalation, and chest physiotherapy; and 1 case had a lower limb vaso-occlusive crisis (VOC). There was no mortality

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Al-Salem, 1995 <sup>63</sup>	R, Obs	Cholelithiasis	NR	Clinically; all children had experienced recurrent episodes of abdominal pain that was localized to the right-upper quadrant (RUQ). Abdominal US revealing gallbladder stones and in 4 patients common bile duct (CBD) stones	Presurgery transfusion, cholecystectomy, and postsurgery intravenous fluids (IVFs) and morphine	22	100	Postoperatively, all patients received IVFs at a rate of 1.5 times maintenance until they had adequate oral intake and were maintained on a morphine infusion (10 µg/kg • h) for 24–48 h for analgesia All patients with an admission hemoglobin <10 g/dL (20 of 22 children) underwent preoperative transfusion to increase the level to 10–12 g/dL and the hematocrit to 30–40%. They were transfused with packed erythrocytes 3 mL/kg multiplied with (hemoglobin desired minus hemoglobin on admission)	NR	No	NA	NA	NA	No patient developed a painful VOC, but 2 developed mild acute chest syndrome (ACS) 1 had bleeding from the splenic bed and 1 developed minor wound infection. All the patients recovered well with no mortality
Al-Salem, 2000 <sup>68</sup>	R, Obs	Cholelithiasis	Symptomatic biliary colon in the majority of patients (very few asymptomatic)	Abdominal imaging (mainly US)	Surgery	31	100	Laparoscopic cholecystectomy (LC)	Mean operation time 104.3 min, mean hospital stay 3.5 d	No	NA	NA	NA	LC children with sickle cell disease (SCD) seems to be effective and safe (mean operation time 104 min, hospital stay 3.5 d, only 2 required conversion to open procedure)

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Bhattacharya, 1993 <sup>73</sup>	R, Obs	Cholelithiasis	Not defined	Clinical exam/investigations	Cholecystectomy preceded by transfusion	22	100	14 patients underwent immediate preoperative automated red cell exchange (RCE). Median volume of packed red blood cells (PRBCs) exchanged was 28.1mLKg. 8 other patients underwent sequential transfusion (3 after an exchange for an acute pulmonary VOC). They received a median of 26.9 mL PRBCs/kg	For sequential transfusion: 2–8 weeks preoperatively	No	NA	NA	NA	Following sequential transfusion the median Hb was 11.8 g/dL (range, 9–15.7) and the median sickle cell hemoglobin (HbS) was 19% (range, 5–32%) at the time of surgery. All patients received extended antigen-matched blood. Complications of preoperative transfusion were minor and included 2 febrile/allergic reactions and 1 mild superficial catheter-induced phlebitis. 12 cholecystectomies were performed electively, whereas 10 were done on an emergent/semielective basis with 2 of these patients septic from acute cholecystitis. There were no intraoperative complications. There were no apparent sickle-related vaso-occlusive events (VOEs) and no delayed complications including retained CBD stones
Curro, 2006 <sup>87</sup>	R, Obs	Cholelithiasis	NR	Abdominal US	Prophylactic cholecystectomy	24	100	NA	NA	Comparison: Symptomatic patients operated on after onset of biliary colic, and symptomatic patients who underwent emergency admission for acute cholecystitis and/or choledocholithiasis	12, 6	100	Laparoscopic cholecystectomy in group B and emergency LC in group C	Elective LC in asymptomatic children (group A) was safe with no major complications reported. In children who refused surgery (groups B and C), 4 sickle cell crises, 4 acute cholecystitis, and 2 choledocholithiasis were observed, and all these complications were related to waiting. 2 sickle cell crises occurred in symptomatic children waiting for surgery during biliary colic. The risk of emergency admission in children with cholelithiasis and chronic hemolytic anemia (CHA) awaiting surgery was found to be high: 28% of the children admitted in emergency after a mean of 32 mo (range, 22–36). Morbidity rate and postoperative stay increased when children with hemoglobinopathies underwent emergency LC

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Curro, 2007 <sup>88</sup>	R, Obs	Acute cholelithiasis	NR	Abdominal US, magnetic resonance cholangiopancreatography	Elective LC was performed on Group 1 (asymptomatic children)	16	100	IV antibiotics started 2 h before surgery and continued for 24 h after the procedure. Simple transfusion before surgery was considered as beneficial in 2 children of the elective group to raise the hemoglobin above 10 g/dL and to decrease the HbS below 50%	NR	Comparison Symptomatic patients	10	100	Emergent LC was performed within 72 h since occurrence of biliary symptoms—Prophylactic erythrocyte transfusion or partial exchange transfusion was adopted in all emergent children considering the higher risk of intraoperative bleeding and hypoxia—IV antibiotics started soon after admission and continued for 48–72 h after the procedure	Group 1: No major complications were reported in all 16 elective LC (group A). 1 child developed wound infection and another child had fever for 2 d. No transfusions were necessary postoperatively. The mean postoperative stay was 3 d (range, 2–4 d) Group 2: The correlation between cholecystectomy performed in asymptomatic children (group A) and cholecystectomy performed in symptomatic children (group B) showed significant difference in the outcome. Significant differences were found in operative time (mean 65 min vs. mean 90 min), group A and group B, respectively, morbidity rate (12.5% vs. 50%), postoperative stay (mean 3 d vs. mean 7.4 d), and total hospital stay (mean 4 d vs. mean 9 d)
Duncan, 1992 <sup>91</sup>	R, Obs	Cholecystitis, choledocholithiasis	NR	Abdominal US, intraoperative cholangiogram	Cholecystectomy 12 cases, cholecystectomy + exploration of CBD 5 cases, cholecystectomy + exploration of CBD and choledochoduodenostomy 3 cases	12	100	NR	10.9 d average postoperative stay	No	NA	NA	NA	Postoperatively, 5 patient had unexplained prexia >100°F, 4 developed ACS with serious morbidity in 2

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Gholson, 1995 <sup>99</sup>	R, Obs	Cholelithiasis, choledocholithiasis	Gallstones and CBD stones	Abdominal US and ERCP	Surgery	8	100	Endoscopic sphincterotomy, LC	NA	No	NA	NA	NA	All 8 patients underwent LC, which was successful and uncomplicated except for 1 patient. Although the patient did well following endoscopic ductal clearance, dense pericholecystic adhesions were present, which precluded the LC. The patient then had open cholecystectomy followed by a stormy postoperative course due to a right subcostal abscess that required percutaneous drainage, and that was the only postoperative complication
Gibson, 1979 <sup>100</sup>	R, Obs	Cholelithiasis	NR	Oral cholecystogram, abdominal x ray, abdominal US, laparotomy	Elective cholecystectomy and transfusion	16	66	14/16 patients received preoperative transfusions. 2 patients had admission hemoglobin levels of 10.6 and 11.0 g/100 mL	NR	No	NA	NA	NA	There were a total of 11 complications in 6 patients (37% of patients). Complications included wound infection (2 patients); subphrenic abscess; pneumonia (2), incisional hernia, aplastic crisis, seizure, retained CBD stone and urinary tract infection. 1 patient had a concomitant splenectomy and died from intervascular coagulation and postoperative hemorrhage

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Leandros, 2000 <sup>14</sup>	R, Obs	Cholelithiasis	NR	NR	LC. Before cholecystectomy, all except 3 patients in each group were given blood transfusions, hydrated IV at 1.5 times the maintenance rate on the night before operation, and given a single dose of an antibiotic prophylactically at induction of anesthesia	41	100	Blood transfusions	NA	Comparison: Patients with open cholecystectomy	41	100	Open cholecystectomy. Before cholecystectomy all except 3 patients were given blood transfusions, hydrated IV at 1.5 times the maintenance rate on the night before operation, and given a single dose of an antibiotic prophylactically at induction of anesthesia	After completing the preoperative transfusion regimen the mean preoperative hemoglobin concentration was 116 g/L and 118 g/L in open and LC group, respectively. The mean operation time was 81.4 min (range 55–125) in the open group and 64.2 min (range 50–90) in the LC group; the difference was significant ( $p < .01$ ). The mean hospital stay was 2.7 d (range 2–5) in the LC group and 5.6 d (3–9) in the open group ( $p < .01$ ). Patients who had open operations were more likely than patients treated laparoscopically to require postoperative analgesia (10/41, 24% compared with 2/41, 5%) ( $p = .02$ ). Conversion to open cholecystectomy was necessary in 2 patients (5%), 1 for inflammation and adhesions that hampered dissection in Calot's triangle, and the other because of bile duct injury, shown by an operative cholangiogram. In the LC group there were 2 (5%) postoperative complications, while in the open group there were 8 (20%). The intra-abdominal bleeding in 1 patient resulted in an exploratory laparotomy to control the bleeding. Postoperative ileus was defined by symptoms (constipation, abdominal distension, vomiting, and hiccups); physical signs (silent abdomen on auscultation); and radiographic findings (air-fluid levels). A higher rate of complications was found in the open group than in the LC group ( $p = .04$ ). No patients experienced a VOC, and there were no deaths in either group. No long-term biliary complications were seen in any of the patients during a mean followup period of 11.7 months (range 6–15)

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Meshikhes, 1998 <sup>118</sup>	R, Obs	Gallstones	NR	NR	LC	71	100	Mean operation time was 80 min (range: 40–270); 4 cases were converted to open cholecystectomy. 55 patients received preoperative blood transfusion—simple transfusion in 42 patients and exchange in 13	NA (surgery)	No	NA	NA	NA	There were 10 postop complications (6 respiratory, 3 wound related, 1 VOC); there was 1 mortality due to VOC
Plummer, 2006 <sup>123</sup>	R, Obs	Chronic cholecystitis	Patients had CBD stones	ERCP	LC	16	100	Laparoscopic cholecystectomy	NA (surgery)	No	NA	NA	NA	There were 4 cases of life-threatening postoperative ACS leading to demise in 1. 1 patient developed a painful crisis and 1 a wound infection. Postoperative hospitalization period ranged from 1 to 13 d (mean 5.5 d)
Rambo, 1986 <sup>126</sup>	R, Obs	Cholelithiasis, choledocholithiasis	NR	Oral cholecystogram, abdominal US	Elective cholecystectomy, transfusion	11	(100% cholelithiasis; 27% also had choledocholithiasis)	9/11 patients had preoperative transfusion	NA (surgery)	No	NA	NA	NA	There were 2 complications: 1 patient developed pneumonia and 1 patient a retained CBD stone
Rudolph, 1992 <sup>130</sup>	R, Obs	Cholelithiasis	NR	Abdominal US, oral cholecystogram (1 patient)	Cholecystectomy, transfusion	14	100	Preoperative transfusion or exchange transfusion was undertaken in 12 (86%) of the 14 patients. After an average transfusion of 3.3 U, the mean hemoglobin was improved to 10.9 g/dL	NA	No	NA	NA	NA	Preoperative transfusion or exchange transfusion was undertaken in 12 (86%) of the 14 patients. After an average transfusion of 3.3 U, the mean hemoglobin was improved to 10.9 g/dL. The 2 patients who did not undergo a transfusion had preoperative hemoglobins over 10.5 g/dL
Seguier-Lipszyc, 2001 <sup>136</sup>	R, Obs	Cholelithiasis	NR	Abdominal US	LC	29	100	IV pain-killing drugs (paracetamol) for a mean time of 1.5 d. In 26 of 29 patients, an automated RCE was planned at a mean time of 7.5 preoperative d	NA (surgery)	No	NA	NA	NA	4 patients developed hyperthermia around the 2nd postoperative d, but it resolved spontaneously. There were no deaths during the followup period, and no VOCs were noted during the hospital stay. In the followup period, there were no bile duct injuries or complications related to the LC surgery

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Tagge, 1994 <sup>145</sup>	R, Obs	Cholelithiasis	Not defined	Clinical exam/ Investigations	Cholecystectomy: open	8	100	NR	Average operative time: 2.4 h	Yes laparoscopic	22	100	Laparoscopic	Total operative length was comparable between the 2 groups, but the LC patients' postoperative LOS was half that of the open cholecystectomy patients (2.1 vs. 4.6 d). To date there have been no bile duct complications in the LC group. Thus LC has proven to be a safe and efficacious technique in this high-risk population
Ware, 1988 <sup>153</sup>	R, Obs	Cholelithiasis	NR	US, abdominal x ray	Elective cholecystectomy	27	100	NR	NA (surgery)	No	NA	NA	NA	There were no VOs nor any other perioperative morbidity or mortality. 4 mo after cholecystectomy, 1 boy had a small bowel obstruction requiring surgical re-exploration
Ware, 1992 <sup>154</sup>	R, Obs	CBD stones	NR	Abdominal US, intraoperative cholangiogram, liver function tests (LFTs)	Cholecystectomy + CBD exploration	9	100	NR	NR	No	NA	NA	NA	Procedures were successful, CBD stones removed from all 9 patients. There were no significant complication
Winter, 1994 <sup>157</sup>	R, Obs	Gallbladder sludge and/or gallstones	Not clearly defined	US following clinical exam	Cholecystectomy	17	100	NR	4–10 mo	No	NA	NA	NA	Each of the 17 patients in the study eventually had gallstones identified and each underwent cholecystectomy after appropriate preoperative preparation
Al-Abkari, 2001 <sup>163</sup>	P, Obs	Gallbladder cholelithiasis	Gallbladder pigment stones	Abdominal US	LC on patients with SCD	36	100	Patients with hemoglobin less than 10g/dl were transfused with red blood cells to 10g/dl. Deep venous thrombosis prophylaxis and prophylactic antibiotics was given to all. Sickle cell disease patients were preoxygenated with 100% oxygen for 5min before the endotracheal intubations	NA	Patients without SCD	111	100	LC	There were no mortalities in both groups. Most of patients with SCD were relieved of their symptoms of gallstones. Incidence of choledocholithiasis was higher in the SCD group and was managed successfully by ERCP and endoscopic sphincterotomy

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Bond, 1987 <sup>170</sup>	P, Obs	Gallstones	Calculi were diagnosed if highly reflective structures, with or without acoustic shadowing, were detected within the lumen of the gallbladder	9 patients were diagnosed via the US study	Cholecystectomy, transfusion, IV hydration, and postoperative oxygen	29	100	Exchange transfusion in 28/29 patients	NA	No	NA	NA	NA	Postoperative complications, including acute sickle crisis (2 patients) and chest infection (4 patients), occurred in 10 of 28 (36%) patients. When the preoperative HbS (or HbSC) concentration was reduced by transfusion to below 40%, infectious complications and sickle crises occurred in only 3 of 19 patients, compared with 5 of 6 patients in whom the HbS concentration was above 40% (Fisher's exact test, $p=.01$ ). The most serious complication was a biliary stricture in a 10-yr-old boy, which later required bypass surgery. Postoperative followup of >1 yr (range 18 mo to 12 yr) was possible in 14 patients. 8 remained free of pain, but 4 had abdominal pain during crises that was clearly different from their previous pain from gallstones. 2 patients reported episodes typical of biliary colic, but both had normal findings on US examination and liver function testing
Meshikhes, 1995 <sup>197</sup>	P, Obs	Symptomatic gallstones secondary to SCD	Not defined	Clinical exam/ Investigations	LC	30	100	LC	NA	No	NA	NA	NA	24 patients (80%) had a previous history of abdominal sickle cell crises. The preoperative hemoglobin F (HbF) and HbS levels ranged from 18 to 33% and from 66 to 77.2%, respectively. The hemoglobin level ranged from 8.6 to 12 g% (mean 9.7 g%). Blood transfusion was given preoperatively to 19 patients (63%) and 3 patients needed perioperative transfusion. The mean operative time was 75 min (range 60–100 min). 1 of the 4 emergency cases was converted to open cholecystectomy due to difficult anatomy and inability to grasp a thick-walled, distended gallbladder. 2 patients developed minor chest infections and 1 had an acute VOC on the 5th postoperative d and died despite the appropriate treatment (morbidity 6.6%, mortality 3.3%). The median hospital stay was 2 d (range 1–5 d)

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Seleem, 2005 <sup>209</sup>	P, Obs	Cholelithiasis (gallstones identified)	NR	Clinical exam/ investigations	Surgical	12	100	Mini-laparoscopic cholecystectomy (MLC)	NA	No	NA	NA	NA	The mean operating time was 46.5 min (range: 35–65 min). Intraoperative cholangiogram failed in 2 children due to narrow cystic ducts. The mean hospital stay was 2.1 d (range: 2–4 d). No patient required intra-abdominal drain. The mean followup period was 13.4 mo (range: 4–24 mo). The only postoperative complication was deep jaundice 1 mo postoperatively due to cholestasis, and this responded to medical treatment. None of the children had recurrent abdominal pain after MLC
Ware, 1992 <sup>154</sup>	P, Obs	Cholelithiasis	NR	Clinical exam/ investigations	LC	9	100	Prior to cholecystectomy, each patient received erythrocyte transfusion that increase the hemoglobin concentration to 10-12 g/dL and hemoglobin A to at least 70% of the total hemoglobin mass. All patients were hydrated intravenously at a rate of 1.5 times maintenance beginning 12 h before cholecystectomy or cholangiopancreatography	Unclear	No	NA	NA	NA	9 young patients with sickle hemoglobinopathies successfully underwent LC; no complications resulted from the procedure. The mean postoperative hospital stay was 1.6 d. This technique appears to be a safe and efficacious procedure in children with sickle hemoglobinopathies who require cholecystectomy for cholelithiasis

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Duncan, 2000 <sup>224</sup>	R-P, Obs	Gallstones	NR	History of recurrent RUQ pain, abdominal US	Cholecystectomy, transfusion, IV crystalloids and perioperative antibiotics	27	100	11 cholecystectomies were elective, and 16 were emergencies. IV crystalloids were administered to all patients 12–24 h prior to surgery at approximate rate of 31/m <sup>2</sup> /24 h. All patients received perioperative antibiotics. 4 of the 27 patients received preoperative transfusions. Patients were transfused if they had a hemoglobin level >1 g/dL below their steady state. Transfusion of these patients raised preoperative hemoglobin to approximately 10g/dL	NR	No	NA	NA	NA	There was 1 case of wound infection. Retained CBD calculi were detected in 2 cases. In 6 cases there was onset of dyspnea and the appearance of new lung infiltrates on plain chest x ray indicating ACS within 24–48 h postanesthesia. In 5 of 6 patients, ACS responded well to simple transfusion, oxygen and antibiotics. 1 of 6 patients developed multi-organ system failure and died 5 d postsurgery
Ahmed, 2006 <sup>230</sup>	Case report/case series	Diffuse cholangiopathy of both extrahepatic and intrahepatic bile ducts	NR	Abdominal US, ERCP	Fat-soluble vitamin supplements and ursodeoxycholic acid	1	100	NR	NR	No	NA	NA	NA	2 yr later, she was readmitted with increasing jaundice and abdominal pain. A repeat ERCP at this stage showed stricture of the extrahepatic duct, along with multiple stones in the dilated intrahepatic ducts. A pigtail stent was placed and balloon dilatation was performed. She remains stable with underlying chronic liver disease 5 yr and 3 mo since the diagnosis of cholangiopathy

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Ahmed, 2007 <sup>231</sup>	Case report/case series	Acute hepatic sequestration	At presentation, the child was febrile to 39.1°C with an oxygen saturation of 98% on room air by pulse oximetry. The physical examination showed erythema of the oropharynx, and notably no hepatomegaly was appreciable by either the admitting or the in-patient physician	An abdominal US showed massive hepatomegaly (14-cm vertical span), thickened gall bladder wall, and edema of the bowel loops	The patient needed cardiorespiratory support in addition to repeated transfusions of PRBC, platelets, and fresh frozen plasma (FFP)	1	100	Morphine sulfate was given via IV and acetaminophen orally. Hemoglobin level was 7.1 g/dL, hematocrit was 21.6%, total white blood cell (WBC) count was 16,700/mL, and platelet count was 115,000/mL. Ceftriaxone 50 mg/kg was given via IV after blood cultures were collected.  PRBC transfusion; the hemoglobin levels dropped rapidly after each transfusion	18 h	No	NA	NA	NA	After 14 h of incubation, the blood culture grew gram-positive diplococci, later identified as Streptococcus pneumoniae serotype 13. Although the hemoglobin level seemed to plateau above 12 g/dL, the patient's condition worsened progressively with maximal cardiorespiratory support, massive hepatomegaly (12 cm below the costal margin in the mid-clavicular line), and a very tense abdominal wall. He died 18 h after admission
Ariyan, 1976 <sup>233</sup>	Case report/case series	Cholecystitis, cholelithiasis	NR	Abdominal x ray, IV cholangiogram with tomographic cuts	Cholecystectomy, blood transfusion	1	100	PRBCs	NR	No	NA	NA	NA	Symptoms resolved, no jaundice, painful episodes became mild and infrequent
Al-Hawsawi, 2001 <sup>240</sup>	Case report/case series	Acute splenic sequestration crisis (ASSC)	Defined as a decrease of at least 2 g/dL from the steady-state hemoglobin concentration, evidence of increased erythropoiesis such as markedly elevated reticulocyte count and acutely enlarging spleen	Based on cellulose acetate electrophoresis at alkaline pH 8.4	All patients received blood transfusion at presentation and 3 patients had splenectomy at 2 yr of age	10	100	NR	NR	No	NA	NA	NA	4 patients had recurrence, and there was no mortality

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AL-Malki, 2004 <sup>244</sup>	Case report/case series	Perforation of the common hepatic duct	NR	Laparotomy	Repair of the perforation with absorbable suture and placement of a T-tube	1	100	NA	NA	No	NA	NA	NA	The patient improved his total, and direct bilirubin declined to normal
Al-Suleiman, 2006 <sup>249</sup>	Case report/case series	Acute fulminant cholestatic jaundice	NR	LFTs, coagulation studies, abdominal US	IVF, broad spectrum antibiotics, vitamin K, FFP, blood exchange	3	100	NR	15–23 d	No	NA	NA	NA	Symptoms resolved
Baichi, 2005 <sup>256</sup>	Case report/case series	Sickle cell intrahepatic cholestasis (SCIC)	An unusually severe form of hepatic crisis characterized by the acute onset of hepatomegaly, extreme hyperbilirubinemia, coagulopathy, and acute liver failure	Clinical exam/investigations	Liver transplantation	1	100	NR	35 d	No	NA	NA	NA	Patient expired
Baichi, 2005 <sup>256</sup>	Case report/case series	Sclerosing cholangitis	Theoretically, repeated intrahepatic sickling could lead to hypoxia and ischemia with ductal changes resulting in secondary cholangitis	Clinical exam/investigations	Liver transplantation	1	100	NR	85 d	No	NA	NA	NA	Patient expired

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Bandyopadhyay, 2008 <sup>261</sup>	Case report/case series	Sickle cell hepatopathy	Hepatopathy characterized by variable hyperbilirubinemia and either mild or severe hepatic dysfunction, with patients potentially presenting with abdominal pain, nausea, fever, jaundice, and transaminase elevation	Abdominal US, liver biopsy	NR	1	100	NR	NA	No	NA	NA	NA	The findings of the biopsy (mild to moderate necrosis, mild spotty necrosis, sinusoidal dilatation, mild to moderate inflammation, and widening of the portal area with cholestasis) along with the presentation were consistent with the final diagnosis of sickle cell hepatopathy
Bell, 2005 <sup>264</sup>	Case report/case series	Hemolytic anemia and hepatitis	NR	Chest radiograph, physical exam, lab tests	Antibiotics, epinephrine, mannitol and bicarbonate, analgesics, O <sub>2</sub> , hydration	1	100	Ceftriaxone, hydromorphone. Later, antibiotics were broadened—azithromycin, vancomycin, amikacin, and meropenem were added to the antibiotic regimen. Altogether, 5 U of PRBCs were transfused	19 d	No	NA	NA	NA	The patient's renal function did not improve despite continuous venovenous hemodiafiltration. Despite ongoing resuscitative efforts over the next few days she exhibited progressive renal, liver, and respiratory failure. On hospital d 19, she suffered a cardiac arrest and could not be resuscitated

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Betrosian, 1996 <sup>267</sup>	Case report/case series	Reversible acute liver failure	Marked hyperbilirubinemia, prolonged prothrombin time, encephalopathy and modest transaminase elevations are the most notable features of liver failure	Abdominal US, elevated LFTs, bilirubin	Transfusion, lactulose, neomycin, antibiotics	1	100	Lactulose (30 mL every 4 h) and neomycin (500 mg every 6 h) were administered via nasogastric tube. He was treated with broad spectrum antibiotic cefuroxime. 2 units of packed erythrocytes and 4 U of FFP were given for the 1st d. After patient achieved a hematocrit of 25%, transfusion of erythrocytes was stopped. After patient stabilized, FFP transfusion was provided for 6 following d	NR	No	NA	NA	NA	48 h after admission, the patient became alert and oriented. By the 3rd hospital d, his hemodynamic condition was stable and urine output increased to 40 mL/h. On physical examination, the liver flap was gone and the liver size had decreased to 4 cm over the right costal margin. Bilirubin, hepatic enzymes, and prothrombin time declined substantially, and arterial ammonia level was within normal limits. A liver biopsy was performed on the 21st hospital d. Kupffer cells were swollen with phagocytosed sickle red cells. The sinusoids were dilated with aggregates of sickle red cells. Cholestasis and dilated canaliculi that contained bile plugs were present. There were no signs of congestion, parenchymal necrosis, acute or chronic inflammation or evidence of nodular regeneration and cirrhosis
Bonatsos, 2001 <sup>269</sup>	Case report/case series	Cholelithiasis	NR	Elevated LFTs, abdominal US	LC	13	100	The day before the operation, all patients received 5% dextrose with 26 mmol/L of potassium chloride (KCl) via IV; this amounted to 1.5 times their calculated fluid requirements. Patients with an Hb of <10 g/dL (independent of the HbS percentage) were transfused with PRBCs on an outpatient basis 10–15 d before surgery	Acute	No	NA	NA	NA	All patients underwent a successful LC. None of them experienced perioperative hypotension, hypoxia, or hypothermia, or required transfusion during or after surgery. Postoperatively, 1 patient developed pyrexia and a superficial wound infection in the subumbilical port site. None of the patients experienced VOC or other SCD-related complications (ACS, cerebrovascular accident. There were no CBD injuries or deaths. 9 patients (69%) were discharged on the 2nd postoperative d
Chuang, 1997 <sup>281</sup>	Case report/case series	Autoimmune liver disease	NR	Clinical exam, investigations	All cases received immunomodulator and steroids. Cases 1 and 3 also received ursodeoxycholic acid	3	100	All cases received immunomodulator and steroids. Cases 1 and 3 also received ursodeoxycholic acid	NR	No	NA	NA	NA	2 patients had autoimmune hepatitis and have responded to immunosuppressive therapy, and 1 had primary sclerosing cholangitis and is stable with therapy

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Costa, 2006 <sup>286</sup>	Case report/case series	Intrahepatic cholestasis	Marked hyperbilirubinemia with acute hepatic failure and is frequently accompanied by renal dysfunction.	US/Abdominal computed tomography (CT) confirmed hepatomegaly and ascites as well as hepatic nodularity	Initial management consisted of IV saline, vitamin K, PRBCs, and FFP. Despite an initial clinical improvement with the lowered HbS level, his condition continued to deteriorate. He received aggressive supportive care in the intensive care unit with mechanical ventilation	1	100	Broad-spectrum antibiotics Exchange transfusion was initiated within 12 h of admission due to his multiorgan failure, particularly hepatic dysfunction. 5 U of PRBCs were exchanged in 1 session. Pre- and postexchange transfusion hemoglobin electrophoresis demonstrated a decline in HbS from 58% to <15%	26 d	No	NA	NA	NA	Due to unresponsive cholestasis, a trial of ursodeoxycholic acid was attempted without benefit to the bilirubin levels. 26 d after his initial admission, the patient succumbed to multiorgan failure. The day prior to his death, the HbS level was 12%
Cross, 2007 <sup>288</sup>	Case report/case series	Sickle hepatopathy causing decompensated cirrhosis	NR	The CT imaging confirmed US findings of ascites and splenomegaly, and the liver had an irregular contour with left and caudate lobe hypertrophy and atrophy of the right liver. Arterial phase images showed patchy enhancement consistent with ischemia or necrosis, but the portal venous system and hepatic artery were patent	Fluconazole and tazobactam/piperacillin venovenous hemofiltration noradrenaline	1	100	In view of his progressive clinical deterioration and worsening hepatic synthetic function, he was listed for liver transplantation. He had an episode of Staphylococcus aureus bacteremia. He was commenced on fluconazole and tazobactam/piperacillin. He developed Grade 2 hepatic encephalopathy, and was intubated and ventilated because of respiratory failure. He was started on continuous venovenous hemofiltration for anuric renal failure, and required inotropic support with nor-adrenaline	31 d	No	NA	NA	NA	His condition failed to improve and because of refractory sepsis he became too unwell for liver transplantation and was removed from the waiting list. He developed a worsening coagulopathy (international normalized ratio (INR) >5) and a sudden escalation in his aspartate aminotransferase (AST) (4,500 IU/L). There was further escalation of noradrenaline requirements, and he became hyperlactemic (lactate 11: normal range <2.5). He died on the 31st d of his admission

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Delis, 2006 <sup>295</sup>	Case report/case series	Intrahepatic cholestasis	NR	Elevated LFTs and bilirubin	Exchange transfusion	1	100	Exchange transfusion of 3 U PRBCs was administered to reduce the HbS	NR	No	NA	NA	NA	A 43-yr-old white woman with sickle cell anemia (SCA) underwent colon resection for cancer of the rectum. 1 yr later a metastasis was noted in segment VIII of the right liver lobe. The patient underwent a formal right lobectomy with minimal blood loss using a radiofrequency cool-tip device for parenchymal transection after extrahepatic vessel ligation. On the 1st postoperative d, she developed a high bilirubin (4.63 mg/dL) with cholestatic enzyme elevation (ALP (alkaline phosphatase) 203 IU/L, GGT (gamma-glutamyl transpeptidase) 404 IU/L) with mild increase in the HbS level (36.7%). Constant pulse oxygen documentation and maintenance of the pH toward an alkalotic state using IV bicarbonate had been routinely performed in the early postoperative period. A decline in LFTs and bilirubin levels toward normal was noted the following day and remained until discharge
Durand, 2009 <sup>303</sup>	Case report/case series	SCIC	NR	RUQ pain, hepatomegaly, and extreme hyperbilirubinemia	Transfusion, IVF, and analgesia	1	100	Emergency exchange transfusion of 7 U PRBCs	7 d	No	NA	NA	NA	Symptoms resolved and patient discharged in 5 d, had 2 recurrences over the next 8 mo
Emre, 2000 <sup>308</sup>	Case report/case series	SCIC	NR	Clinical exam/investigations	Liver transplant	1	100	Liver transplant	6 mo	No	NA	NA	NA	Although the allograft functioned well initially; the patient developed veno-occlusive disease and required repeat transplantation at 5 mo after transplant. Histologic examination of the explant revealed occlusion of the terminal hepatic venules due to fibrosis and PRBCs. Repeat transplant was complicated by thrombosis of the intrahepatic portion of hepatic artery and sepsis. Patient died of sepsis after a 3rd transplant

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Gilli, 2002 <sup>326</sup>	Case report/ case series	Sickle cell intrahepatic cholestasis (SCIC)	Unusually severe form of hepatic crisis marked by the sudden onset of severe right upper quadrant pain, progressive hepatomegaly, coagulopathy with hemorrhage, and extreme hyperbilirubinemia with poor prognosis	Liver biopsy	Liver transplant	1	100	Liver transplant	NR	No	NA	NA	NA	Patient recovered
Hillaire, 2000 <sup>342</sup>	Case report/ case series	Cholangiopathy and intrahepatic stones	NR	Duplex Doppler US	Laparotomy and extraction of intrahepatic stones	1	100	Regular blood transfusions	NR	No	NA	NA	NA	Patient died of multiorgan failure
Hochberger, 1983 <sup>345</sup>	Case report/ case series	Cholelithiasis	NA	Double dose cholecystography	Cholecystectomy + incidental appendectomy + blood transfusion	1	100	PRBCs 10 mL/kg	7 d	No	NA	NA	NA	Patient did well postoperatively; followup examination has revealed that the patient no longer has RUQ pain or intolerance to fatty food
Horn, 1987 <sup>347</sup>	Case report/ case series	Sickle cell hepatopathy	NR	Clinical presentation, LFTs	Exchange transfusion	1	100	3 partial exchange transfusions over 3 d	3 d	No	NA	NA	NA	Patient recovered and was discharged after being scheduled for a liver biopsy and an ERCP but never returned for these procedures

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Irizarry, 2006 <sup>353</sup>	Case report/case series	SCIC and cholelithiasis	SCIC is clinically recognized by sudden onset of RUQ pain, progressive hepatomegaly, mild elevation of transaminases, coagulopathy, and extreme hyperbilirubinemia. This condition is usually accompanied by renal insufficiency. Whereas total bilirubin normally ranges from 3 to 10 mg/dL in sickle cell patients, total bilirubin can be as high as 276 mg/dL during SCIC. This extreme direct hyperbilirubinemia is the hallmark of SCIC	Abdominal US, CT, HIDA (hepatobiliary iminodiacetic acid) scan	Blood transfusion, IVF hydration, empiric IV antibiotic therapy (ceftriaxone), vitamin K, FFP, cryoprecipitate, and LC with concomitant appendectomy and right inguinal herniorrhaphy	2	100	Multiple blood transfusions (14 U) for Case 1 and exchange transfusion for Case 2	NR	No	NA	NA	NA	<p>Case 1: 11 d following surgery he developed a stroke involving the right thalamus, occipital and parietal lobes. An extensive thrombophilia evaluation was unremarkable. He was discharged with outpatient rehabilitative services and serial blood transfusions to maintain his HbSS fraction &lt;30%. His total bilirubin was 9.1 mg/dL with direct fraction of 1.5 mg/dL. Due to the thromboembolic sequelae, a future bone marrow transplant is being considered</p> <p>Case 2: He did well for 17 mo until he was readmitted with periumbilical pain, increasing jaundice, and epistaxis. His PT was &gt;40 s, PTT &gt;150 s, total bilirubin 86 mg/dL, direct bilirubin 48.9 mg/dL, and HbSS fraction of 60%. Prompt treatment with exchange transfusion and IV hydration led to a quick recovery</p>

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Jeng, 2003 <sup>367</sup>	Case report/case series	Chronic hepatic sequestration	NR	U/S, clinical presentation. Hepatomegaly that is responsive to exchange transfusion along with negative viral serologies	Hydroxyurea (HU)	1	100	The patient was started on an initial dose of 15 mg/kg/d of HU, which was escalated to a dose of 30 mg/kg/d over a 6-mo period. Because of limited availability while the patient was in Jamaica, HU therapy was periodically interrupted	60 mo	No	NA	NA	NA	After the initiation of HU therapy, the patient experienced a hematologic response with an increase in hemoglobin concentration from 6.5 g/dL at the initiation of therapy to 8.9 g/dL at 36 mo and 8.2 g/dL at 60 mo. Mean corpuscular volume increased from 88 fL prior to HU therapy to 124 fL at 36 mo and 118 fL at 60 mo. HbF increased from 2.9% at initiation of therapy to 15.5% at 36 mo and 10% at 60 mo. 6-mo: Clinical examinations were performed approximately every 6 mo at our institution by the same health care provider and revealed gradual resolution of hepatomegaly. The liver edge was 6–7 cm below the middle of the RCM (right costal margin) prior to the start of therapy, 5 cm after 18 mo, 2 cm at 36 mo and 1 cm at 60 mo. Although a liver biopsy was not performed prior to beginning HU, a liver biopsy obtained after 6 mo demonstrated moderate to severe sinusoidal dilatation with sickled red blood cells (RBCs), cholestasis, Kupffer cell hyperplasia, and erythrophagocytosis. 30-mo: a 2nd liver biopsy revealed a decrease in sinusoidal congestion, sickled RBCs, and Kupffer cell hyperplasia compared with the previous biopsy. Quantitative CT scans of the abdomen demonstrated decreases in liver volume from 7,600 mL before treatment to 2,500 mL at 30 mo and 2,400 mL at 36 mo. No significant changes in hepatic enzyme levels occurred. The total bilirubin concentration decreased from 3.7 mg/dL at the initiation of HU therapy to 1.6 mg/dL at 36 mo and 2.4 mg/dL at 60 mo; the concentration of lactate dehydrogenase decreased from 2,594 U/L at the initiation of HU therapy to 1,393 U/L at 36 mo and 1,228 U/L at 60 mo

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Karaunatilake, 2009 <sup>359</sup>	Case report/case series	Intrahepatic cholestasis	NR	Liver biopsy	Partial blood-plasma exchange transfusion	1	100	Partial blood-plasma exchange transfusion: 1 U of whole blood was removed and replaced with FFP and 1 U of cross-matched blood. This was done 5 times in 24 h	24 h	No	NA	NA	NA	Asterixis disappeared within 24 h of exchange. By d 6, his total bilirubin had decreased to 359 µmol/L. After 4 weeks, his bilirubin was 137 µmol/L
Khurshid, 2002 <sup>366</sup>	Case report/case series	Intrahepatic cholestasis	NR	Unclear	Initial treatment included IVFs, empirical antibiotic coverage (ampicillin/sulbactam and ciprofloxacin). outpatient medications included benazepril, furosemide, and folic acid	1	100	Exchange transfusion (3 U of PRBCs) was begun with a target reduction of HbS to <30%. The patient responded to multiple exchange transfusions with a subsequent decrease in his HbS levels to 24%. After developing cardiac complications, he continued exchange transfusions and needed further PRBC transfusions (5 U) as well as 2 FFP U	<1 mo	No	NA	NA	NA	Patient was gradually improving and was eventually discharged
Lacaille, 2004 <sup>380</sup>	Case report/case series	Acute hepatic crisis	NR	Abdominal US, blood tests	2 children were treated with hyperhydration (31cm <sup>3</sup> /m <sup>2</sup> normal saline), 2 received a blood transfusion (including patient 5), and 2 an exchange transfusion	6	100	Exchange transfusion was chosen for patients 1 and 6 in view of their very high level of bilirubin. Exchange transfusion was planned for patient 5, but he died a few hours after admission of multiorgan failure	3–60 d	No	NA	NA	NA	Patient 5 died of multiorgan failure. In the 5 surviving children, the symptoms resolved in a few days to 2 weeks. Liver test results returned to their previous level in <3 mo. The patients have not experienced another episode of hepatic crisis
Lama, 1993 <sup>382</sup>	Case report/case series	Hepatic abscess	NR	Abdominal US	Percutaneous drainage under US guidance, IVFs, antibiotics, analgesics, blood transfusion	1	100	Percutaneous drainage under US guidance, IVFs, antibiotics, analgesics, blood transfusion	10 d	No	NA	NA	NA	The child's general condition improved dramatically over the next 2 d. The fever subsided, the liver regressed to 2 cm, and the tenderness disappeared

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Lang, 1995 <sup>383</sup>	Case report/case series	Persistent cholangitis, biliary cirrhosis, coagulopathy, failure to thrive	Not defined	Clinical exams/investigations	Liver transplantation	1	100	Desferoxamine, ceftriaxone ampicillin, clotrimazole, vitamin K, A, E and D supplementation, ursodeoxycholic acid, cholestyramine and antibiotics	60 d	No	NA	NA	NA	Immediate graft function was good in the patient with normalization of prothrombin time to 13.7 s within 3 d of surgery. Total bilirubin dropped from 41.7 to 13.5 mg/dL by the 7th d. An episode of acute rejection on the 6th postoperative d was treated with monoclonal OKT3. The patient was discharged home on the 36th postoperative d. The patient has normal LFTs, gained weight, and resumed normal activities 2 yr later
Lebensburger, 2008 <sup>387</sup>	Case report/case series	Biloma and pneumobilia	Bilomas are fluid-filled cysts located outside the biliary system, which commonly develop from a bile leak	CT scan, ERCP	A 5-cm stent was placed in the CBD below the insertion of the cystic duct, and within 2 d the bilious drainage had decreased significantly	1	100	Ceftazidime, vancomycin, and metronidazole erythrocyte transfusion (10 mL/kg)	2 d	No	NA	NA	NA	The catheter was removed and the patient was discharged from the hospital. 2 weeks later, he underwent an LC; he has had no further abdominal symptoms since that time
Lee, 1996 <sup>388</sup>	Case report/case series	Hepatic and pulmonary sequestration	On admission patient was pyrexia, tachycardic and jaundiced, hemoglobin was 5.6 g/dL	Chest radiograph, physical examination	Assisted ventilation on the 15th d after admission	1	100	Ceftazidime transfused with 4 U of blood	20 d	No	NA	NA	NA	Her condition gradually worsened over 20 d in the hospital and she eventually died
Lerut, 1999 <sup>391</sup>	Case report/case series	Liver parenchymal necrosis due to intrahepatic sickling	Not clearly defined	Clinical exam/investigations	Broad spectrum antibiotic therapy and supportive management	1	100	Hydroxyurea, immunosuppression (cyclosporine, azathioprine and low-dose steroids), and antibiotics	3.5 mo	No	NA	NA	NA	Liver biopsy was performed 30 mo after transplantation showed presence of sinusoidal fibrosis in the presence of atypical portal lymphocytic infiltrate. 39 mo after transplant, patient's liver function is normal; her condition, however, is impaired by multiple infarctions of femoral, tibial, calcaneal, talar, and cuboidal bones
Liberman, 1997 <sup>394</sup>	Case report/case series	CBD stones	NR	Abdominal US	LC + exploration of the CBD + intraoperative angiogram	1	100	PRBCs once	NR	No	NA	NA	NA	Operation was successful; the patient was seen a week after surgery. He was doing well
Malone, 1988 <sup>405</sup>	Case report/case series	Cholecystectomy, cholelithiasis	NR	Abdominal US, Technetium-99m scan	Cholecystectomy + transfusion	12	100	10 mL/kg/transfusion session, and 2 sessions over 2–3 weeks of PRBCs	Mean hospitalization 6.3 d	No	NA	NA	NA	Recurrent abdominal pain resolved shortly after surgery in all patients

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Mekeel, 2007 <sup>410</sup>	Case report/case series	Intrahepatic cholestasis, hepatic sequestration and hepatitis C	NR	NR	Liver transplantation	3	100	Steroid	NA	No	NA	NA	NA	All 3 patients developed mild to moderate biopsy-proven acute rejection within 3 mo of transplant. All 3 cases were successfully treated with a standard steroid pulse and taper. The patient with hepatitis C virus infection as an indication for transplantation has developed mild recurrent hepatitis C infection. Only 1 child, who was transplanted for intrahepatic cholestasis, suffered from recurrent disease and chronic graft failure. He later died from cerebral complications of SCD. 1 child has developed narcotic addiction and depression related to his pain crises. 1 child developed insulin-dependent diabetes mellitus from the immunosuppressive regimen. 1 child suffered from recurrent seizures and cerebral infarcts secondary to SCD. This child also had chronic graft dysfunction from recurrent disease as mentioned, and he suffered a seizure, fell, and died from the resultant subdural hematoma 6 yr after transplantation
Meshikhes, 1996 <sup>412</sup>	Case report/case series	Cholecystitis + appendicular mass	NR	Abdominal US	LC and appendectomy	1	100	Exchange transfusion preoperatively to reduce the level of HbS to <50%	3 d	No	NA	NA	NA	Surgery was successful
Middleton, 1984 <sup>413</sup>	Case report/case series	Hepatic biloma	An expanding intrahepatic bile-filled cyst	Abdominal US	Needle aspiration	1	100	Needle aspiration	NR	No	NA	NA	NA	Cyst decreased in size after 6 mo followup
Mishra, 1992 <sup>415</sup>	Case report/case series	SCD hepatopathy	NR	Hepatomegaly, jaundice, elevated LFTs, liver biopsy	NR	3	100	NR	NR	No	NA	NA	NA	SCD hepatopathy was diagnosed after ruling out secondary causes of liver disease. All 3 patients recovered though hepatomegaly persisted in 2 of 3 cases

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
O'Callaghan, 1995 <sup>432</sup>	Case report/ case series	Cholestasis	NR	Abdominal US, ERCP	Antibiotics and vitamin K and an exchange transfusion	1	100	He was therefore started on a regular exchange transfusion program to maintain the HbS concentration at <20%	36 mo	No	NA	NA	NA	He was therefore started on a regular exchange transfusion program to maintain the HbS concentration at <20%. After this his clinical condition returned to normal, bilirubin concentrations remained at <200 µmol/L, the AST returned to steady state values (<50 IU/1), serum albumin increased to 40–45 g/L and the prothrombin time remained normal without vitamin K. His weight, which had dropped by 5 kg to the 25th centile over the 3 mo of his acute illness, began to rise and had returned, without nutritional supplementation, to the 75th centile after 9 mo. Liver biopsy at 8 mo showed histological recovery. About 1 yr after initial presentation, after a period of erratic attendance at hospital, his HbS concentration rose to 56%. His original symptoms of fever, severe jaundice, RUQ pain associated with dark urine, pale stools, and hepatomegaly returned. His only treatment was prophylactic penicillin V and folic acid. Biochemical profile showed raised bilirubin at 736 g/mol/1; AST 73 IU/1; alkaline phosphatase 391 IU/1. The prothrombin time was prolonged at 18 s but the hemoglobin was stable at 9.6 g/dL. Although his AST continued to rise, reaching a peak of 430 IU/1, again this relapse rapidly responded to exchange transfusion. He continues, nearly 3 yr after presentation to require regular exchange transfusions to control the hyperbilirubinemia

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Ross, 2002 <sup>459</sup>	Case report/case series	Intrahepatic cholestasis	NR	Liver biopsy, abdominal magnetic resonance imaging (MRI), abdominal US	Cyclosporine, prednisone, and mycophenolate mofetil	1	100	Cyclosporine, prednisone, and mycophenolate mofetil	NA	No	NA	NA	NA	In Nov. 1998, patient underwent a combined liver and kidney transplantation. The patient was discharged on posttransplant d 33. In Feb. 2000, the patient presented with a rising bilirubin. ERCP revealed a CBD stricture and stones. The stones were removed in Mar. and a biliary stent was again left in place. In Sept. 2000, the patient was readmitted for elective stent change. During the procedure for an elective stent change, suffered a cardiopulmonary arrest, and died
Rossof, 1981 <sup>460</sup>	Case report/case series	Intrahepatic sickling crisis	NR	Clinical presentation, LFTs, liver biopsy	Bed rest, IVFs, analgesics, ampicillin, intermittent nasal oxygen, partial exchange transfusion	1	100	Bed rest, IVFs, analgesics, ampicillin, intermittent nasal oxygen, partial exchange transfusion	NR	No	NA	NA	NA	Patient resolved completely after 18 mo of 1st admission total bilirubin was 1.1, SGOT (serum glutamic oxaloacetic transaminase) 14 U, hematocrit 31, 5% reticulocyte
Savafi, 2006 <sup>468</sup>	Case report/case series	Chronic liver disease	NR	Abdominal US, liver biopsy, upper gastrointestinal system endoscopy, echocardiography	HU	1	100	HU	NR	No	NA	NA	NA	Following the exclusion of autoimmune hepatitis, the patient was diagnosed with sickle cell-related chronic liver disease. Patient was started on HU to decrease severity of hemolysis
Sawke, 2009 <sup>469</sup>	Case report/case series	Cholelithiasis	NR	Abdominal US	NR	1	100	NR	NR	No	NA	NA	NA	Patient's abdominal US demonstrated cholelithiasis and splenomegaly. She was advised to consult a tertiary care center hematologist for advanced management

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Shao, 1995 <sup>477</sup>	Case report/case series	SCIC	SCIC is characterized by the acute onset of hepatomegaly, modest elevation of transaminases, extreme hyperbilirubinemia, coagulopathy, and acute liver failure	Clinical presentation (abdominal pain, fever), abdominal US	Cholecystectomy	2	100	Broad-spectrum antibiotics. Patient 1: Received 2 U of PRBCs postcholecystectomy. Patient 2: When severe epistaxis persisted, a decision was made to perform exchange transfusion using PRBCs and FFP. Postexchange, all hematological parameters improved (hemoglobin 8.6 g/dL, PT 14.2 s)	<1 mo	No	NA	NA	NA	Patient 1 died following surgery due to intraperitoneal hemorrhage. Patient 2 had a favorable outcome and is currently well
Sheehy, 1980 <sup>481</sup>	Case report/case series	Intrahepatic cholestasis	NA	Abdominal US, Technetium-99m colloid liver spleen scan, LFT	Partial blood-plasma exchange transfusion	1	100	Partial blood-plasma exchange transfusion. 1 unit of whole blood was withdrawn and replaced with 1 U of FFP (200 mL) and 1 U of typed and cross-matched PRBCs, (250 mL). This was done 8 times in 24 h. During the next 2 d, the patient received 1 U of PRBCs and 2 more U of FFP	6 d	No	NA	NA	NA	In 6 d, his total serum bilirubin level decreased to 16 mg/dL and the prothrombin and partial thromboplastin times became normal
Shulman, 1971 <sup>485</sup>	Case report/case series	Pyogenic hepatic abscess	NR	Exploratory laparotomy	Cephalothin 80 mg/kg/d	1	100	Cephalothin 80 mg/kg/d	36 d	No	NA	NA	NA	Symptoms resolved
Solanki, 1979 <sup>495</sup>	Case report/case series	Chronic cholecystitis in 7 patients, biliary obstruction in 3 patient	Not defined	Clinical exam/investigations	Cholecystectomy	10	100	NR	NR	No	NA	NA	NA	All 10 patients recovered. Transfusions were given preoperatively and with attention to oxygenation and fluid and electrolyte balance. There were few complications, none serious
Stephan, 1995 <sup>502</sup>	Case report/case series	Fulminant liver failure	NR	LFTs, abdominal US	Packed cell then partial exchange transfusion	1	100	Packed cell then partial exchange transfusion	7 d	No	NA	NA	NA	Patient completely recovered after partial exchange transfusion
Svarch, 1986 <sup>506</sup>	Case report/case series	Acute cholestasis	NR	Clinical presentation, LFT, abdominal US	Plasma exchange	1	100	Fresh plasma exchange of 600 mL on 2 occasions	NR	No	NA	NA	NA	Complete recovery immediately after plasma exchange, jaundice decreased, and neurological signs improved

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Transfusion/Medication details	Duration of treatment	Secondary/control arm	N of patients	% of patients	Control treatment	Reported results
Tiftik, 2004 <sup>509</sup>	Case report/case series	SCIC	NR	Liver biopsy, abdominal US	Therapeutic erythrocytapheresis	1	100	A mean of 4.2 U of RBCs were exchanged per procedure (range 3–7 U). Mean RBCs volume exchanged was 1.3 (range 1.1–2.0). Mean duration of the procedures was 70 min	11 mo	No	NA	NA	NA	HbS was maintained at a level of ≤30% and, postapheresis, hematocrit was kept at a level of <30%. The exchange procedures were extremely well-tolerated by the patient and adverse effects were limited to symptoms of hypocalcaemia and transfusion reactions
Vecchio, 2001 <sup>516</sup>	Case report/case series	Gallbladder lithiasis	NR	Abdominal US	5 patients out of 7 had preoperative transfusion. LC was completed.	7	100	5 patients out of 7 needed preoperative transfusion	Acutely	No	NA	NA	NA	LC in patients can be performed safely without increasing risk of complications if appropriate monitoring and management in the preoperative, intraoperative, and postoperative periods are achieved
Vicari, 2008 <sup>517</sup>	Case report/case series	Choledocholithiasis	NR	Clinical presentation, abdominal US, cholangio-MRI	Laparotomy was performed. Operative cholangiography showed numerous calculi in choledocho duct. Choledocholithotomy of multiple pigment stones combined with T-tube drainage was performed	1	100	Cefepime(for bronchopneumonia)	Acutely	No	NA	NA	NA	1 d after surgery, the patient developed left bronchopneumonia, which was treated with cefepime. The subsequent course was marked by ACS and sepsis. Multiorgan failure and death occurred 14 d after laparotomy

**Table 11. Priapism Incidence and Outcomes**

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Serjeant, 1985 <sup>43</sup>	RCT	Stuttering priapism: Stuttering attacks of priapism that are typically painful, recurrent, short lived (characteristically 2–6 h), and nocturnal	Patient reported	Stilboestrol	11	100	5 mg daily, orally	2 weeks followed by 2 more weeks if no response to treatment in the first 2 weeks	No stilbestrol (n=4)	Analysis of the 1st treatment period (during which no tablet was taken by 4 of the 11 patients) showed no significant treatment effect. However, analysis of initial, crossover and repeat measurements in the 9 patients who completed the trial showed that attacks of priapism ceased with stilboestrol ( $p=.031$ , Fisher's exact test)
Adetayo, 2009 <sup>57</sup>	R, Obs	Priapism	NR	Surgery: Ebbehøj technique of cavernosaglandular shunt. If this did not result in immediate complete detumescence, the procedure was completed on the other side	54	100	35 patients were treated surgically as follows: Presurgery, all patients started on medical treatment of intravenous fluids (IVFs), generous analgesics, sedatives. Postoperatively, the patient was given analgesics, sedatives, and IVF for 24 h and antibiotics when indicated. 19 patients were treated conservatively (those who refused surgery) by IVFs, generous analgesics, sedatives, and, when indicated, blood transfusion	NR	Conservative management (those who refused surgery), n=19	For the surgery group: The potency rate postsurgery was 70.3%, with 2/35 patients (6%) developing recurrence of priapism in the immediate postoperative period. 3/35 patients (8.6%) developed recurrence priapism over the followup period. For the conservatively managed group: The potency rate posttreatment was 47.3%
Adeyokunnu, 1981 <sup>58</sup>	R, Obs	Priapism: Persistent, painful and pathological erection of the penis	NR	40 patients received conservative, medical management, while the remaining 5 had surgery	45	100	All medically managed patients were given analgesics, sedation, tranquilizers and IVFs	NR	NA	1 patient died in a hemolytic crisis 2 mo after recovery from his episode of priapism. 4 patients had recurrent episodes of priapism. All the remaining 28 medically managed patients remained well for at least 1 yr after their episodes of priapism. Among the 5 surgically managed patients, the outcome was good in only 1, and 1 other patient died on the 2nd postoperative d

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Dunn, 1995 <sup>92</sup>	R, Obs	Priapism	Clinical presentation, penile scintigraphy with Technetium-99m-pertechnetate	Admission, intravenous (IV) hydration, exchange transfusions for those who fail to respond after 24–48 h, intracorporeal blood gas with corporeal aspiration/ irrigation and intracorporeal injection of epinephrine if priapism persisted after transfusion, glans cavernosa shunt (Winter procedure) if the problem still persisted	13 (15 incidents)	100	Partial or reconstituted packed red cell exchange (RCE) transfusion	NR	NA	5 patients had stagnant patterns in scintigraphy. 4 of them responded to analgesics and IV hydration. 4 of 8 patients with stagnant pattern did not require any aggressive interventions such as corporeal aspiration/irrigation, intracorporeal epinephrine or glans-cavernosa shunt. It was concluded that whereas the constant scintigraphic finding appeared to be a favorable indicator for conservative treatment, the stagnant finding was apparently noncontributory. In addition, no correlation was found between these 2 patterns and the subsequent sexual potency of these patients
McCarthy, 2000 <sup>17</sup>	R, Obs	Priapism	Clinical presentation	Exchange transfusion	7	100	Automated RCE transfusion, exchanging 60–70% of the patients' red blood cells (RBCs) and resulting in sickle cell hemoglobin (HbS) levels <30%	Acutely	NA	Only 1 patient experienced detumescence 8 h postexchange; however, he had a history of "stuttering" priapism. Otherwise, the exchange was not successful in treating the patients' priapism and they all required decompression procedures

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Muneer, 2009 <sup>121</sup>	R, Obs	Priapism: Unwanted persistent erection of >6 h duration without sexual stimulation; can be classified as being either ischemic, nonischemic, or recurrent (stuttering)	Clinical presentation	The drugs utilized in the 51 patients not affected by sickle cell disease (SCD) were procyclidine (dose 5 mg nocte—20 mg bd), pseudoephedrine (60 mg tds), cyproterone acetate (CPA; 50 mg nocte—100 mg tds), goserelin (3.6 mg subcutaneous injection), digoxin (500 µg daily), and sildenafil (50 mg nocte). Etilefrine (25—200 mg) was exclusively used in patients with known SCD. Surgical options were utilized in patients whose priapism episodes were not controlled by the drug regimens above or in those individuals presenting with an acute prolonged ischemic priapism. Surgical interventions are (corporal blood aspiration alone with or without additional instillation of the alpha adrenergic agonist phenylephrine and a shunt procedures)	60	100	Procyclidine (dose 5 mg nocte—20 mg bd), pseudoephedrine (60 mg tds), CPA (50 mg nocte—100 mg tds), goserelin (3.6 mg subcutaneous injection), digoxin (500 µg daily), and sildenafil (50 mg nocte). Etilefrine (25—200 mg) was exclusively used in patients with known SCD	All patients had at least a 6-week trial of 1 pharmacotherapy and when unsuccessful they were changed to 1 of the alternative drugs	NA	Analysis of the outcomes of both medical and surgical interventions has shown that the use of hormone analogues such as CPA is the most efficacious treatment option as it allows a successful control of their erections without a significant loss of libido in 86% of patients. The most successful surgical option was the insertion of a penile prosthesis

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Rachid-Filho, 2009 <sup>125</sup>	R, Obs	Priapism: Recurrent priapism was considered as an occurrence of at least 2 episodes a week, with 40 min duration	NR	Finasteride	35	100	All 35 patients started the treatment with 5 mg/d finasteride. Dose was decreased over the initial 40 d, from 5 mg/d to 3 mg and then to 1 mg	120 d	NA	5 groups (G) were created based on the number of recurrences in 1 mo: G0=no recurrence, G1=1–15 recurrences, G2=16–30 recurrences, G3=31–45 recurrences, G4=>45 recurrences. After 120 d of the study, with patients receiving 1 mg/d finasteride for the last 40 d, we observed that 16 patients (46%) were in G0, 16 (46%) in G1, and 3 patients needed dose increase to 3 mg (n=1) and 5 mg (n=2) because of recurrence of frequent priapism episodes. On d 1 of treatment, the mean of recurrent episodes was 22.7 and on d 120, it was 2.1. The difference of the mean of recurrences between d 1–40 was 10.7 episodes, that of d 40–80 was 8.2 episodes, and that of d 80–120 was 1.5 episodes. 12 of 16 patients in G1 had <5 episodes/mo at the end of the study
Mantadakis, 2000 <sup>192</sup>	P, Obs	Priapism: A sustained, unwanted, and painful erection usually unrelated to sexual activity	Clinical presentation	Procedure	15 (39 procedures)	100	Penile aspiration and epinephrine irrigation	Acutely	NA	The procedure was successful in producing immediate detumescence on 37 of 39 occasions (95% efficacy, 95% confidence intervals (CI): 81–99%). No serious immediate or long-term side effects were observed. None of the patients who demonstrated detumescence required hospitalization. The 2 patients whose priapism persisted after aspiration and irrigation presented with episodes lasting >24 h. All evaluable patients whose priapism resolved after aspiration and irrigation self-reported normal erectile function at a median of 40 mo (range, 3–58 mo) after the last procedure

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Al Jam'a, 1998 <sup>234</sup>	Case report/ case series	Priapism: A sustained, often painful penile erection that is not associated with sexual desire	Clinical presentation	Hydroxyurea (HU), hydralazine, piracetam and pentoxifylline, repeated penile aspirations and partial exchange blood transfusion	1	100	A dose of 1,000 mg of HU daily was started and was increased to 1.5 g daily after 4 weeks Partial exchange blood transfusion	7 mo with HU	NA	He was admitted to the urology ward and started on IVFs. Detumescence spontaneously occurred overnight, and the patient was discharged home. He was readmitted to the hospital in Apr. 1995 for a similar episode of priapism 9 h in duration. Initial conservative measures with hydration and analgesia failed, and repeated penile aspirations were attempted by the urologist and partial exchange blood transfusion was given. This episode subsided but he continued to have recurrent stuttering priapism. The patient received hydralazine, piracetam and pentoxifylline, but the episodes continued to recur during the next 6 mo. We decided to include him in our trial of HU. A dose of 1,000 mg of HU daily was started and was increased to 1.5 g daily after 4 weeks. He did not report further significant episodes of priapism for 7 mo. HU was interrupted for 3 mo by the patient and the episodes recurred, but they were much milder. After resuming the treatment no further episodes were reported
Baruchel, 1993 <sup>262</sup>	Case report/ case series	Priapism: Painful persistent penile erection	Clinical presentation	Hydralazine	1	100	Hydralazine hydrochloride 10 mg with each episode	NR	NA	Pain relief in 15–30 min and complete detumescence in 45 min, no need for hospitalization, analgesics, or regular exchange transfusion
Burnett, 2006 <sup>272</sup>	Case report/ case series	Priapism: An obscure erectile disorder in which prolonged penile erection occurs uncontrollably and often painfully without sexual purpose	NR	Phosphodiesterase type 5 (PDE5) inhibitors: sildenafil, tadalafil (long acting)	3	100	Sildenafil: 25–50 mg oral. Tadalafil: 5 mg oral morning dose	5–14 mo	NA	Long-term PDE5 inhibitor treatment alleviated priapism recurrences. Patients retained erectile function

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Colombani, 2000 <sup>284</sup>	Case report/ case series	Persistent priapism: Persisting priapism after 24 h of medical treatment	NR	Oxygen therapy, hyperhydration and analgesics	6	100	Because of severe pain, marcain 91 was administered through peridural injection and for 2 other cases, morphinics were used	NR	NA	In 2 cases, priapism regressed 6 h after admission to the unit (after 30 h of medical treatment). As for the other cases, surgical intervention proved necessary considering the absence of detumescence after the 48th hr. In 2 cases, a draining of the corpus cavernosus, with physiological saline solution was added. In 3 cases, detumescence was observed between the 4th and the 6th hr. In each of the cases we noticed no recurrence. Case 3 presented a cerebrovascular accident (CVA) 10 d after the priapism regression. The 5 other cases have normal erections
Costabile, 1998 <sup>287</sup>	Case report/ case series	Priapism: Patient had history of nocturnal prolonged erections, lasting between 2 and 3 h and occurring 4– 5 times/week	NR	Pseudoephedrine, imipramine, aspirin and leuprolide	1	100	Initial treatment with pseudoephedrine, imipramine, and aspirin did not decrease the frequency or severity of the episodes, so he was started on monthly intramuscular (IM) injections of leuprolide 7.5 mg	NR	NA	Cessation of prolonged erections came after 1 mo. His libido and sexual function remained normal. On followup 18 mo later, he had no recurrence of prolonged erections and his sexual function was intact
Dahm, 2002 <sup>291</sup>	Case report/ case series	Recurrent priapism	Patient reported	Antiandrogen, Bicalutamide	2	100	50 mg daily, later 50 mg every other day	Variable	NA	Symptoms resolved in both cases after taking the prescribed treatment drug

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Davila, 2008 <sup>294</sup>	Case report/ case series	Priapism: A painful penile erection of >3 h duration	Clinical presentation	Phenylephrine injections-intracavernous cava	1	100	500 µg/mL, repeated every 3 min for a total of 4 mL	Acutely	NA	A penile block was attempted at first without success. Following the phenylephrine injections, detumescence was finally achieved after last injection. The patient complained of a sudden headache immediately following this last injection, his blood pressure (BP) increased to 180/100. A head computed tomography (CT) was obtained and came suspicious for CVA. Patient was admitted and a followup CT the next day confirmed a small subarachnoid hemorrhage within the sulcus in the left frontotemporal region. The patient's headache gradually diminished and he remained neurologically intact and was discharged without further complications
Douglas, 1990 <sup>300</sup>	Case report/ case series	Priapism: Major attacks of priapism lasting >24 h and their outcome is determined by age of patient, attacks after age 15 yr being generally followed by complete impotence	Clinical exam/ investigations	Penile prosthesis	5	100	Case 1: cannulation and irrigation of the corpora, then 4 yr later a Small-Carrion prosthesis was inserted. Case 2: a Small-Carrion prosthesis was inserted, and followed by 4 further procedures to reposition the left prosthesis Case 3: a Small-Carrion prosthesis was inserted, which was removed and reinserted and functioned for 2 yr Case 4: a Small-Carrion prosthesis was inserted, although the patient was troubled by premature ejaculation Case 5: a Small-Carrion prosthesis first and then a Pearman prosthesis	Periodically	No	Reasonable sexual function was achieved with penile prosthesis in all 5 patients though some required repositioning of the same
el Mauhoub, 1991 <sup>305</sup>	Case report/ case series	Priapism: An abnormally prolonged penile erection, unaccompanied by sexual desire, usually painful and not relieved by coitus	Clinical presentation	Transfusion	1	100	Transfusions of 300 mL of whole blood and 200 mL of packed red blood cells (PRBCs)	4 d	No	Relief of pain promptly followed transfusion. The penis became soft 1 d after transfusion, and the penile hematoma resolved spontaneously after a few days. There was no recurrence

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El Morsi, 1973 <sup>306</sup>	Case report/ case series	Priapism: Prolonged and sustained erection of the penis, which may occur without sexual stimulation	Clinical presentation	Small incision in the corpora cavernosa	5	100	Sedatives and female hormone (did not work)	NR	No	Condition completely resolved
Enwerem, 1992 <sup>310</sup>	Case report/ case series	Priapism: A painful and persistent penile erection	Clinical exam/ investigations	Conservative measures	2	100	Bed rest, sedation, analgesics, hydration, and vitamin therapy	Variable	No	Both patients responded to treatment promptly and were relieved of symptoms in the next 7–10 d
Fich, 1981 <sup>314</sup>	Case report/ case series	Priapism	Clinical presentation	Blood transfusion	1	100	5 U of PRBCs	7 d	No	Priapism completely subsided at the 7th d following transfusion
Gbadoe, 2001 <sup>321</sup>	Case report/ case series	Priapism: A painful vaso-occlusive episode (VOE) complication of SCA, presented as stuttering priapism, acute priapism, or acute priapism complicating stuttering priapism	NR	Etilefrine injections, and later on oral	11	100	Treatment of acute priapism consisted of intracavernous injections of 5 mg (0.5 mL) of undiluted etilefrine when priapism had been present for <6 h, or intracavernous injections proceeded by drainage of blood in more prolonged priapism. To prevent relapse, we used 0.25 mg/kg twice/d of oral etilefrine for 1 mo. Stuttering priapism was treated with oral daily administration of 0.5 mg/kg etilefrine for 1 mo. This was given in the evening to patients with nocturnal priapism; 0.25 mg/kg twice/d was given for priapism, which occurred both during the day and night. These patients also self-administered (or parent-administered) intracavernous injections to reverse painful VOE lasting >1 h	1–7 mo	No	5 patients with acute priapism were given intracavernous etilefrine with a delay ranging from 4 to 28 h. This procedure was successful in producing immediate detumescence in all children after a single injection. No patients treated for prevention of acute priapism relapsed. After 1 mo of treatment, attacks decreased in 1 patient with stuttering priapism, while 4 others remitted. 3 of the latter relapsed 2 weeks to 2 mo later, but prolonged remission was achieved in all after 1–7 mo of treatment. No serious immediate or long-term side effects were observed, either with intracavernous injections or oral etilefrine. 1 patient experienced agitation, which ceased after dosage reduction
Gradisek, 1983 <sup>331</sup>	Case report/ case series	Priapism: Sustained painful penile erection unaccompanied by sexual desire	Clinical presentation	Procedure	1	100	Aspiration of blood from corpora cavernosa bilaterally	NR	No	Complete detumescence achieved, normal erectile capacity reported 5 mo later

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Hamre, 1991 <sup>337</sup>	Case report/ case series	Major priapism: A prolonged episode lasting >1 d that required hospitalization and treatment with an operation and/or transfusions. Minor priapism was defined as isolated or infrequently recurrent episodes of <3 h duration. Stuttering priapism refers to multiple, brief (<3 h) episodes several times a week for ≥4 weeks	NR	Transfusion and/or surgery	Reviewed: 305, Personal cases: 11	100	NR	NR	No	7 cases resolved without treatment, 1 patient had surgery when conservative treatment failed, 3 had transfusions

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Huffman, 2000 <sup>351</sup>	Case report/ case series	Recurring priapism (prevention)	Clinical presentation	Bicalutamide, phenylpropanolamine, chlorpheniramine, phenylpropanolamine, and chlorpheniramine	1	100	Initial: Bicalutamide (50 mg po qd), phenylpropanolamine (75 mg po bid), chlorpheniramine (12 mg po bid). Substitution: phenylpropanolamine 75 mg and chlorpheniramine 8 mg, 1 po bid	NR	No	The patient subsequently stopped using bicalutamide due to impotence (despite good libido), yet remained priapism-free with phenylpropanolamine=chlorpheniramine alone. He later substituted Contac (phenylpropanolamine 75 mg=chlorpheniramine 8 mg, 1 po bid) for Ornade as a matter of availability, and continued to remain priapism-free for 3 weeks. The patient's compliance then wavered, and a major episode of priapism ensued in the absence of any medication at all. He was hospitalized again, though he refused angiography in fear of the potential for impotence associated with the procedures that might have followed. He underwent corporal irrigations phenylephrine injections daily, and bicalutamide and phenylpropanolamine=chlorpheniramine were restarted. Relief of priapism was noted by d 5 when the patient was discharged. The patient remained priapism-free and had painless intercourse regularly while using phenylpropanolamine=chlorpheniramine at home for 8 mo until he presented to the emergency department (ED) in sickle cell crisis. In the ED the patient's Casodex=Ornade protocol was discontinued, and he subsequently developed priapism. The patient regained his priapism-free state when Casodex and Ornade (or Contac) were continued

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Karayalcin, 1972 <sup>360</sup>	Case report/ case series	Priapism: Persistent, painful, abnormal erection of the penis without sexual desire and not relieved by intercourse	Clinical presentation	Analgesia, blood transfusion, IV urea, and aspiration of corpora cavernosa	5	100	Demerol, generally 75 mg every 6 h Partial exchange transfusion (1 patient); 2 U of PRBCs (1 patient)	NR	No	Partial (1 patient) to complete improvement (4 patients) occurred in 3–20 d with conservative treatment. Long-term followup: 1 patient lost to followup, 3 patients were potent and had had no recurrences and 1 patient has had several recurrences and only semierrection
Kinney, 1975 <sup>367</sup>	Case report/ case series	Priapism: A persistent painful erection, unaccompanied by sexual desire	Clinical exam/ investigations	Hydration, analgesics, antibiotics, transfusion, surgery	4	100	NR	Variable	No	All 4 patients recovered with appropriate treatment and had favorable outcomes
Kleinman, 1980 <sup>368</sup>	Case report/ case series	Priapism	Clinical presentation	Exchange transfusion	1	100	Exchange transfusion with 7 U of saline washed PRBCs	NR	No	Within 24 h patient had significant detumescence and complete resolution by 48 h. The platelet count dropped to 383,000/μL but rose to 1,100,000/μL by d 8 postpheresis with wound infection (from previous cavernosum drainage). The patient was discharged 11 d after transfusion with normal penile size and urological function but partial impairment of sexual function
Kleinman, 1981 <sup>370</sup>	Case report/ case series	Priapism	Clinical presentation	Erythrocytapheresis	3	33	RCE transfusion (otherwise not specified)	Acute	No	All patients treated with erythrocytapheresis for acute complication responded favorably with resolution of symptoms within 24–48 h
Koirala, 2009 <sup>374</sup>	Case report/ case series	Risperidone-induced priapism	Clinical presentation	Procedure	1	100	IVFs, exchange transfusion, corporal aspiration with phenylephrine irrigation. A 2nd exchange transfusion was administered due to the presence of >30% HbS, but fever and leukocytosis continued; blood cultures revealed no growth. Ultrasonogram (US) documented decreased penile blood flow. A Winter shunt did not provide improvement. 3 d later, a T-shunt procedure and antibiotic coverage reduced the pain and swelling. Exchange transfusion, twice	NR	No	The T-shunt procedure and antibiotic coverage reduced pain and swelling and was followed by recovery of erectile function

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Levine, 1993 <sup>392</sup>	Case report/ case series	Priapism	Clinical presentation	Goserlin acetate for the 1st 6 mo, stopped for 6 weeks then leuprolide reinstated, for another 6 mo + transfusion in the 1st hospitalization period	1	100	Goserlin dose NR, Leuprolide 5.25 mg IM monthly injection+ flutamide acetate 125 mg 3 times daily for 4 weeks 3 U of PRBCs	12 mo	No	On monthly followup, the patient reported no attacks of priapism and no drug side effects, but he reported decreased libido and sexual fantasies
Liu, 2003 <sup>396</sup>	Case report/ case series	Priapism: Persistence of erection that does not result from sexual desire and fails to subside despite orgasm	Clinical presentation	Ephedrine injections, corpora aspiration	3	100	Ephedrine injections, corpora aspiration	NR	No	All patients were successfully treated with low dose antiandrogens without major side effects
Maconochie, 1988 <sup>402</sup>	Case report/ case series	Priapism	Clinical presentation	Exchange transfusion	1	100	1,250 mL of whole blood	8 d	No	A slight improvement in the degree of erection occurred over the following 2 d, but it was a full 8 d before the erection subsided
McHardy, 2007 <sup>408</sup>	Case report/ case series	Priapism	Clinical presentation	Morphine infusing at 40 µg·kg <sup>-1</sup> ·h <sup>-1</sup>	1	100	Epidural analgesia: After the patient was transferred to the procedure room, the patient was sedated with propofol 40 mg, and sedation was maintained with propofol by infusion at a rate of 200 µg/kg/min. A lumbar epidural was sited using a midline approach and the epidural space identified by loss of resistance to saline at the L3/4 interspace with an 18-gauge Tuohy needle. A test dose of 2 mL of 0.25% bupivacaine with 1:200,000 mg epinephrine was administered without complication. A further 10 mL of 0.25% bupivacaine with 1:200,000 mg epinephrine was then given via the epidural catheter	3 d	No	15 min after the procedure, the patient reported no pain, and there was no penile tenderness on examination. The morphine infusion was continued for the chest crisis and an infusion of bupivacaine 0.125% without opioid was commenced. The priapism gradually resolved over the next 16 h. There was no worsening or recurrence of the priapism
Monga, 1996 <sup>418</sup>	Case report/ case series	Priapism: A prolonged painful erection of the penis that is not associated with sexual desire	Clinical presentation	Procedure	7	100	Excision of fibrotic cavernosal sinusoidal tissue and placement of a malleable prosthesis (n=6) and a 1-stage penile reconstruction using a forearm free-flap and a 2-piece inflatable penile prosthesis for the autoamputation case (n=1)	NA	No	All patients in the series were reported to be currently potent. Due to infection, 1 patient required removal and subsequent reinsertion of his prosthesis and another required revision
Noe, 1981 <sup>429</sup>	Case report/ case series	Priapism	NR	Shunting procedure	5	100	Each child undergoing the treatment received initial metabolic support, including hydration and analgesics, after 24 h vigorous transfusion therapy was given	NR	No	Following the shunting procedure, each child experienced immediate detumescence and was discharged from the hospital an average of 3 d postoperatively. No complications were observed in any patient

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Ramos, 1995 <sup>448</sup>	Case report/ case series	High-flow priapism: Priapism associated with SCD has classically been described as a low-flow state; sludging of sickled RBCs presumably causes impedance of penile venous outflow	Patient report/ clinical exam	IV hydration, alkalization, transfusion followed by arterial embolization in case 1. Case 2 refused arterial embolization. PRBCs	2	100	IV hydration, alkalization, transfusion followed by arterial embolization in case 1. Case 2 refused arterial embolization. PRBCs	Unclear	No	Case 1: The patient has had no further episodes of priapism at 4 mo. Case 2: No relief after operative intervention and arterial embolization was refused, case lost to followup
Rifkind, 1979 <sup>452</sup>	Case report/ case series	Priapism	Clinical presentation	RBC exchange pheresis	1	100	RBC exchange	15 d (hospitalization)	No	Within 24 h of exchange, there was a pronounced decrease in penile turgidity, with return to normal size within 4 d. The patient remains asymptomatic 6 mo after discharge
Saad, 2004 <sup>464</sup>	Case report/ case series	NR	Clinical presentation	HU	5	100	Following HU protocol, the initial dose of HU was 10 mg/kg/d, given once/d, and was increased by 5 mg/kg/d every 8 weeks until the patient presented no priapism at all	4+ mo	No	As the HU dosage increased, the number or length of priapism episodes decreased. 1–2 mo after the maximal dose was introduced the episodes disappeared. In 2 patients, we were forced to administer >30 mg/kg of HU to abort the episodes, and in another, the necessary dose was 25 mg/kg. All patients had normal sexual activity, that is, they were capable of achieving intercourse on demand
Shah, 2004 <sup>475</sup>	Case report/ case series	Priapism: Persistent, usually painful erection not necessarily associated with sexual stimulation or desire	Clinical presentation	A right saphenocorporal shunt was carried out. This failed to achieve complete detumescence; hence, a saphenocorporal shunt was performed on the contralateral side. Broad-spectrum antibiotics and analgesia	1	NA	A right saphenocorporal shunt was carried out. This failed to achieve complete detumescence; hence, a saphenocorporal shunt was performed on the contralateral side. Broad-spectrum antibiotics and analgesia	8 d	No	The treatment was successful in producing a completely flaccid penis. The 4-mo period of followup has been uneventful. A Doppler examination 4 mo after the operation showed that the shunts were no longer patent. The patient is having normal erections
Slayton, 1995 <sup>491</sup>	Case report/ case series	Priapism: Abnormal penile erection which is painful and persists in spite of the lack of sexual stimulation	Clinical presentation	Medical	2	100	Case 1: Terbutaline 5 mg twice daily, 10 mg nifedipine every 6 h, diethylstilbestrol every 12 h, blood transfusion. Case 2: IVFs, meperidine, and oxygen	NR	No	Priapism resolved

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Upadhyay, 1998 <sup>512</sup>	Case report/ case series	Priapism	Clinical presentation	Procedure	1	100	Insertion of an inflatable penile prosthesis	NR	No	He consequently maintained potency and remains free of priapitic episodes
Virag, 1996 <sup>519</sup>	Case report/ case series	Priapism: Patients had frequent episodes of stuttering priapism and acute episodes lasting >3 h	Clinical presentation	Etilefrine	6	100	Oral therapy was prescribed for adults and children over 12 yr of age. Etilefrine was given according to the circadian rhythm of stuttering episodes: twice/d (morning and evening) (15 mg) if the episodes occur throughout the day or night; only in the evening (30 mg) if the stuttering episodes are nocturnal and early morning. The self-administered intracavernous injection technique was 1 used routinely in a program for the treatment of impotence with intracavernous vasoactive medications. Patients were taught to inject themselves with 6 mg of undiluted etilefrine (0.6 mL of 10 mg/mL solution) with a 1 mL syringe and 30-gauge needle in the lateral aspect of either corpus. Self-administered intracavernous injection is recommended if a stuttering episode lasts >1 h or if the patient awakes with a painful pulsatile erection	When there were no further stuttering priapism episodes, generally after 3–4 weeks, patients stopped oral treatment. They were advised to restart as soon as stuttering priapism recurred	No	2 patients used self-administered intracavernous injection: patient 1 constantly and patient 4 occasionally for acute priapism events occurring because he had not restarted oral therapy despite the recurrence of stuttering priapism. Patients 2 and 6 are totally dependent on oral therapy, not having stopped since inclusion in the study. 3 patients are partially dependent, with periods of therapy alternating with periods without therapy. Patient 5 has not used the treatment for 4 mo
Walker, 1983 <sup>522</sup>	Case report/ case series	Priapism	Clinical presentation	Erythrocytapheresis	5	100	Automated RCE transfusion by continuous-flow and semicontinuous-flow procedures	During hospitalization	No	All 5 patients demonstrated clinical signs of improvement within 2–3 d after RCE and 3 experienced rapid and marked improvements. The other 2 patients showed only gradual, mild improvement related possibly to the existence of corpus cavernositis as a complication to priapism. Of those 2, 1 eventually required creation of a corpus cavernosum-spongiosum shunt and irrigation of the corpora to remove blood clots, which was required to bring about complete resolution of the priapism
Winter, 1979 <sup>529</sup>	Case report/ case series	Priapism	Clinical presentation	Procedure	5	100	Modification of creation of fistulas between glans penis and corpora cavernosa	NR	No	4 patient had success with no recurrence for up to 2 yr, 1 patient was not cured and had to have shunt between corpus cavernosum and spongiosum

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Yang, 1990 <sup>534</sup>	Case report/ case series	Priapism: A common and distressing problem in male patients with sickle cell	Clinical presentation	Surgery	1	100	Corporectomy	NA	No	Patient presented with severely painful priapism. He continued to require IV morphine and was kept on a transfusion program to maintain HbS <30%. After 1 mo of hospitalization with vigorous therapy, it was believed that all medical and surgical options had been exhausted and the corporectomy was suggested to the patient. The procedure was performed after 6 weeks of hospitalization. Post-surgical course was uneventful. The penis was markedly reduced in size and flaccid and the patient was discharged 2 weeks later and had been pain-free for >1 yr

**Table 12. Pulmonary Hypertension Incidence and Outcomes**

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/ medication details	Duration of treatment	Secondary/ control arm	N of patients	% of patients	Control treatment	Reported results
Barst, 2010 <sup>6</sup>	RCT	Pulmonary hypertension (PHTN): Pulmonary arterial hypertension (PAH) (precapillary PH) included patients with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and pulmonary vascular resistance (PVR) ≥160 dyn/s/cm. PHTN (mixed vasculopathy) included patients with either PCWP ≤15 mmHg and PVR ≥100 dyn/s/cm and <160 dyn/s/cm, or PCWP 16–25 mmHg and PVR ≥100 dyn/s/cm	Pulmonary artery catheterization (PAC) swan-ganz pressure readings	Bosentan	11	100	Either 125 mg bid or 62.5 mg bid	4 mo	Placebo	15	100	Placebo: Either 125 mg bid or 62.5 mg bid	No significant differences between the 2 groups were reported
Castro, 2003 <sup>80</sup>	R, Obs	PHTN: Mean pulmonary artery pressure >25 mm Hg by PAC	PAC	Cardiac catheterization	20 (Patients with PHTN)	100	Cardiac catheterization	Acutely in hospital	Patients without PHTN	14 (patients without PHTN)	100	Cardiac catheterization	Mortality with PHTN vs. without was 55% vs. 21%; those with PHTN tended to be older. Each increase of 10 mmHg in mean pulmonary artery pressure was associated with a 1.7-fold increase in the rate (hazards ratio) of death (95% confidence interval (CI)=1.1–2.7; p=.028). The median survival for patients with PHTN was 25.6 mo, whereas for patients without PHTN the survival was still >70% at the end of the 119-mo observation period (p=.044)
Minniti, 2009 <sup>119</sup>	R, Obs	PHTN: The diagnosis of PHTN was definitively established by right-heart PAC, with a pulmonary artery mean pressure >25 mmHg	Echocardiography, right-heart PAC, 6-min walk test	Endothelin receptor (ETR) blocking therapy (either bosentan and ambrisentan)	14	100	ETR blocking therapy: The starting dose of bosentan was 62.5 mg twice/d for 4 weeks, increased to 125 mg twice/d if no side effects were noted. The starting dose of ambrisentan was 5 mg once daily for 4 weeks, increased to 10 mg once. (9 patients received hydroxyurea (HU) and patients' transfusion regimen or HU therapy was initiated at least 3 mo before starting ETR blocking therapy and was not modified during the ETR blocking therapy. 5/12 patients received a blood transfusion (packed red blood cells (PRBCs) every 3–4 weeks) to maintain hemoglobin S (HbS) level <40%	Mean: 8.5 mo	No	NA	NA	NA	Summary: This is a retrospective case series of ETR blocking agents in patients with SCD with clinically significant PHTN. It found that ambrisentan and bosentan doses were well tolerated, with most adverse events mild in severity, despite the baseline anaemia and end organ damage. Only 2 patients required discontinuation of therapy with that specific ETR blocking agent and switching to the other one. In this small study, the treatment-associated improvement in 6-min walk distances was 11%

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/ medication details	Duration of treatment	Secondary/ control arm	N of patients	% of patients	Control treatment	Reported results
Ataga, 2006 <sup>167</sup>	P, Obs	PHTN: A subject was classified as having PHTN if his/her pulmonary artery systolic pressure exceeded the upper limits of normal in the reference ranges. Subjects with evidence of PHTN were further classified into categories of mild (higher than the upper limits of normal and up to 44 mmHg), moderate (45–74 mmHg) or severe ( $\geq 75$ mmHg) PHTN	Transthoracic Doppler echocardiography	NR	43	100	NR	NR	No	NA	NA	NA	93 subjects were included in the mortality analysis. The mean duration of followup for subjects who had PHTN ( $n=36$ , 39%) was $2.4\pm 1.6$ yr, with a mean followup duration of $2.7\pm 1.6$ yr for patients without PHTN ( $n=57$ , 61%). At the time of this report, 10 of the 93 study subjects had died (11%). PHTN was strongly associated with an increased risk of death (relative risk (RR), 9.24; 95% CI: 1.2–73.3). There were no differences in the risk of death when different degrees of PHTN were compared (mild, moderate, or severe)
El-Beshlawy, 2006 <sup>178</sup>	P, Obs	PHTN and diastolic dysfunction: Diastolic dysfunction was defined as evidence of abnormal left ventricular relaxation, filling, diastolic distensibility, or diastolic stiffness	Echocardiography	L-carnitine	37	100	L-carnitine given orally at a dose of 50 mg/kg/d	6 mo	No	NA	NA	NA	There was a significant decrease in transfusion requirements from $3.7\pm 2.4$ U during the 6 mo preceding the treatment to $0.96\pm 0.66$ U after treatment. The mean number per 6 mo of vaso-occlusive crises (VOC) recorded also decreased from $1.22\pm 0.75$ to 0 after treatment. Diastolic function significantly improved after treatment for 6 mo with a statistically significant decrease in both the electromagnetic wave (E wave) velocity from $83.3\pm 22.8$ to $72.1\pm 12.6$ m/s ( $p=.024$ ), and Doppler ratio of early-to-late transmitral flow velocity (E/A ratio) from $1.6\pm 0.32$ to $1.3\pm 0.24$ ( $p=.001$ )

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/ medication details	Duration of treatment	Secondary/ control arm	N of patients	% of patients	Control treatment	Reported results
Machado, 2005 <sup>191</sup>	P, Obs	PHTN: Tricuspid regurgitant jet velocity of $\geq 2.5$ m/s (corresponding to an estimated pulmonary artery systolic pressure of $\geq 30$ – $35$ mmHg)	Transthoracic echocardiogram (TTE)	Sildenafil	12	100	When the hemoglobin and fetal hemoglobin (HbF) levels had been stable for at least 4 weeks, oral sildenafil was initiated at a dose of 25 mg 3 times daily. The dose was increased by 25 mg 3 times daily every 2–4 weeks as tolerated to a maximum dose of 100 mg 3 times/d (100 mg 4 times/d was used in 1 patient)	Mean: 6 mo	No	NA	NA	NA	Hemoglobin and HbF levels did not change after sildenafil therapy was initiated ( $p > .05$ ), enabling the assessment of sildenafil-dependent changes in exercise capacity. Further, lactate dehydrogenase levels did not change with after sildenafil therapy was initiated ( $354 \pm 52$ IU/L presildenafil vs. $348 \pm 53$ IU/L, $p = .5$ ), suggesting that the hemolytic rate did not change with sildenafil therapy. Although the PHTN was only mild, all patients had significant impairment in exercise capacity, as evidenced by a low 6-min walk distance. Therapy with sildenafil decreased the estimated pulmonary artery systolic pressure ( $50 \pm 4$ to $41 \pm 3$ mmHg; difference $-9$ mmHg, 95% CI: $0.3$ – $17$ , $p = .047$ ), and increased the 6-min walk distance ( $384 \pm 30$ to $462 \pm 28$ m; difference $78$ m, 95% CI: $40$ – $117$ , $p = .003$ ). Sildenafil produced sustained reductions in pulmonary artery pressures over time, as measured by tricuspid regurgitant jet velocities. In addition, sildenafil therapy significantly decreased plasma N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) levels [BNP (pg/mL): $559 \pm 333$ – $111 \pm 28$ , $p = .002$ ], further suggesting that the improvement in exercise capacity was related to an improvement in pulmonary pressure and right ventricular function

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/ medication details	Duration of treatment	Secondary/ control arm	N of patients	% of patients	Control treatment	Reported results
Morris, 2003 <sup>199</sup>	P, Obs	PHTN: Estimated pulmonary artery pressures of >30 mmHg by echocardiogram (or tricuspid regurgitant jet velocity of >2.5 m/s), >2 mo of duration, not associated with acute chest syndrome (ACS)	Echocardiography	L-arginine-HCl	10	100	Oral L-arginine-HCl at a dose of 0.1 g/kg tid for 5 d	5 d	Healthy volunteers	10	0	None	Oral arginine produced a 15.2% mean reduction in estimated pulmonary artery systolic pressure (63.9±13 to 54.2±12 mmHg, $p=.002$ ) after 5 d of therapy in 10 patients. 1 noncompliant patient was the only 1 who failed to show improvement. Tricuspid regurgitant velocity was obtained >2 mo after arginine therapy in the 9 compliant patients and demonstrated mixed results. 4 patients demonstrated persistent improvement in pulmonary artery systolic pressure, 4 reverted to pretreatment levels, and 1 patient actually worsened. 2 of the patients that had persistent improvement were started on transfusion therapy, and 1 of them continued L-arginine therapy. Arginase activity was elevated almost twofold ( $p=.07$ ). Plasma L-arginine levels were low in patients with PHTN compared with normal control subjects (50.8±19 vs. 114±27 $\mu\text{m}$ , $p<.0001$ ) but were similar to levels found in sickle cell patients at steady state who did not have PHTN
Pashankar, 2009 <sup>542</sup>	P, Obs	PHTN: Defined as pulmonary artery pressures >30 mmHg corresponding to a tricuspid regurgitant jet velocity $\pm 2\text{AE}5$ m/s, in the absence of any structural obstruction to pulmonary blood flow. Mild PHTN was defined as peak tricuspid regurgitant jet velocity of $2\text{AE}5\text{--}2\text{AE}9$ m/s, and moderate PHTN was defined as a peak tricuspid regurgitant jet velocity (TRJV) $\geq 3$ m/s	Echocardiography	HU	18	100	After the initial screening echocardiogram, patients had a cardiopulmonary evaluation including pulmonary function test (PFT) and polysomnography to evaluate for the presence of nocturnal hypoxemia and/or obstructive sleep apnea. If identified, appropriate intervention was instituted. Patients not receiving HU were offered treatment with HU. Echocardiograms were repeated every 6–12 mo, when patients were in steady state and at least 2 weeks after admission for VOC	19–31 mo	No	NA	NA	NA	Tricuspid regurgitant velocity (TRV) normalized in 8 patients by 12–18 mo; 4/8 patients were on HU at the time of initial echocardiogram, which was continued. 10 patients had persistent elevation of TRV on repeat echocardiogram. 1/10 patients was on HU at the time of initial echocardiogram
Singh, 2008 <sup>490</sup>	Case report/ case series	PHTN with chronic hypoxemia	NR	HU	3	100	Started at 15 mg/kg/d and increased in 5 mg/kg increments every 8 weeks to a maximum dose of 26–30 mg/kg/d	20–24 mo	No	NA	NA	NA	Partial to complete reversal of hypoxemia

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/ medication details	Duration of treatment	Secondary/ control arm	N of patients	% of patients	Control treatment	Reported results
Taylor, 2008 <sup>508</sup>	Case report/ case series	PHTN	Color flow Doppler from echocardiogram, computed tomography angio, right heart cath	Continuous intravenous epoprostenol therapy	1	100	Continuous intravenous epoprostenol therapy	NR	No	NA	NA	NA	Summary: The diagnostic impression was severe progressive PHTN secondary to sickle cell disease and inoperable, presumed chronic small vessel pulmonary emboli
Villa-vicencio, 2008 <sup>518</sup>	Case report/ case series	PHTN and elevation of TRJV	Chest x ray, echocardiogram	Oxygen, red cell transfusion, diuretics, and steroids	1	100	4.5 mo from presentation, the TRJV remained elevated and a transcranial Doppler ultrasound showed a mean flow of 178 m/s in the left middle cerebral artery. Therapy was commenced with monthly minor antigen-matched, red cell transfusions. 10 mo from presentation, a TRJV could not be detected and arginine was discontinued. Due to difficulty suppressing hematopoiesis, transfusion therapy was intensified 1 mo later, from 15 cm <sup>3</sup> /kg of red cells every 4 weeks to every 3 weeks. Oxygen, red cell transfusion, furosemide, bronchodilators, and nasal steroids were administered and at discharge, he was receiving 0.75 L oxygen continuously to maintain pulse oximetry>90%	Around 17 mo; followup was at 29 mo	No	NA	NA	NA	16.5 mo from presentation, the TRJV was again undetectable, the patient appeared well, and his mother ended transfusion therapy. About 2 mo later, he presented with fatigue, chest pain, hepatomegaly, and a room air pulse oximetry of 80%. He was again treated with oxygen, red cell transfusion, diuretics, and steroids. After catheterization, sildenafil (20 mg 3 times daily) was added to the treatment regimen. Because of persistent elevation in TRJV and an electrocardiogram showing left ventricular hypertrophy with mild biatrial and left ventricular dilation, sildenafil was subsequently increased to 30 mg 3 times daily. 29 mo from presentation, 10 mo from relapse, the patient appeared clinically well, but he had persistent mild biatrial dilation, left ventricular end-diastolic dilation (6.13 cm), and a TRJV unchanged from the time of right heart catheterization with a persistently elevated Nterminal probrain natriuretic peptide. He had development of a red cell auto-antibody (e) but continued with transfusions every 3 weeks

**Table 13. Splenic Complications Incidence and Outcomes**

Study label	Design	Specific Complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment*	Secondary/control arm	Reported results
Al Jama, 2002 <sup>60</sup>	R, Obs	Massive splenic infarction	Splenic infarction involving more than half the size of the spleen	Clinical suspicion, confirmed by ultrasound (US) or computed tomography (CT)	Varied; conservative management to surgery	8	100	Intravenous fluids (IVFs), analgesia, blood transfusions	Acutely	No	All patients were managed conservatively with IVFs, analgesia and blood transfusions when necessary. 2 patients required splenectomy during the same admission because of suspicion of secondary infection and abscess formation, while a 3rd patient had splenectomy 2 mo after the attack because of persistent left upper quadrant (LUQ) abdominal pain. All patients survived. 2 patients subsequently developed autosplenectomy, while the remaining 3 continued having persistent but asymptomatic splenomegaly
Al-Salem, 1996 <sup>61</sup>	R, Obs	Acute splenic sequestration crisis (ASSC)	The onset of acute anemia, splenomegaly, and evidence of active bone marrow activity	NR	Splenectomy and transfusion	19	100	Preoperative pneumococcal vaccine and antibiotics. Preoperative blood transfusion	NA	No	All patients recovered rapidly. The only immediate postoperative complication was bleeding from the splenic bed in 1 patient. With followup between 6 mo to 5 yr, 5 patients required readmission for acute chest syndrome (ACS), osteomyelitis, septicemia, and vaso-occlusive crisis (VOC). 2 patients developed gallstones
Al-Salem, 1996 <sup>64</sup>	R, Obs	ASSC	ASSC is divided into major and minor attacks. The minor attacks are characterized by moderate increase in splenic size associated with a decrease of hemoglobin level of 2–3 g/dL, while major attacks are associated with a greater drop in hemoglobin level sometimes reaching a hemoglobin level of <2 g/dL	Clinical exam/ investigations	Surgery	21	48.8	Splenectomy	Acutely	No	Collective results reported for 43 patients: On subsequent followup, which ranged from 8 to 69 mo (mean, 3.2 yr), 7 patients required readmissions: 3 suffered repeated attacks of VOC; 1 developed osteomyelitis and ACS; 1 developed a central nervous system (CNS) infarction with transient left hemiparesis; and 2 developed septicemia, 1 due to B-hemolytic streptococci 4 mo postoperatively and the other due to <i>Salmonella</i> 8 mo postoperatively

\* When the exact time in hospital was not clear in the articles and the treatment was short or one-time, “acute” or “acutely” were used as the “Duration of treatment.”

Study label	Design	Specific Complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment*	Secondary/control arm	Reported results
Al-Salem, 1996 <sup>64</sup>	R, Obs	Splenic sequestration	Splenomegaly with accompanying anemia, as judged by the transfusion requirements exceeding 250 mL/kg of packed red blood cells (PRBCs) per yr or when the fall of hemoglobin had exceeded a frequency of 0.5 g or more per week, platelet count below 100,000/mm <sup>3</sup> , or leukocyte count below 4,000/mm <sup>3</sup> , either singly or in combination	Clinical exam/investigations	Surgery	9 (with major acute splenic sequestration crises)	100	Splenectomy	Acutely	10 patients with minor splenic sequestration crises	Postoperatively, all patients recovered rapidly, except one had bleeding from the splenic bed requiring reoperation. 6 mo to 5 yr followup showed 5 patients had readmissions due to ACS, osteomyelitis, salmonella septicemia. And 2 patients developed gallstones
Al-Salem, 1996 <sup>64</sup>	R, Obs	Splenic abscess	NR	Clinical exam/investigations	Surgery	7	16	Splenectomy	Acutely	No	1 patient developed bleeding from the splenic bed that required reoperation. 2 other patients developed minor wound infections, 1 of whom suffered adhesive intestinal obstruction following splenectomy for splenic abscess
Al-Salem, 1998 <sup>65</sup>	R, Obs	Splenic abscess	NR	Abdominal US, CT, needle aspiration (to differentiate between splenic abscess and infarct)	Splenectomy, antibiotics, and pneumococcal vaccine	10	100	Presurgery, patients received antibiotics and 0.5 mL prophylactic pneumococcal vaccine	NR	No	A notable feature during surgery was the presence of dense adhesions between the spleen, anterior abdominal wall, diaphragm, left lobe of liver, splenic flexure of the colon, and greater omentum in most of the cases. The histopathology of the resected spleens showed hemorrhage and engorgement of sinusoids by sickled red blood cells (RBCs) and large areas of infarction with abscess formation and hemosiderin deposition. In the patient, there was cavitation and formation of a tract leading to a splenic capsule and the abscess. Postoperatively, all the patients recovered with no mortality. 2 patients developed mild wound infection. 1 patient developed adhesive intestinal obstruction, and 1 patient developed hematoma at the site of splenectomy, which required evacuation

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Al-Salem, 1999 <sup>66</sup>	R, Obs	Splenic sequestration (64.6%, n=73). 50 patients had minor recurrent splenic sequestration crises (MRSSC), major splenic sequestration crises (MSSC, 20%, n=23), hypersplenism (23%, n=26)	MRSSC: A moderate increase in splenic size along with a decrease in hemoglobin level of 2–3 g/dL. MSSC: A greater decrease in hemoglobin level sometimes to <2 g/dL with splenomegaly	Hypersplenism: (a) presence of splenomegaly with accompanying anemia as judged by transfusion requirements exceeding 250 mL/kg of PRBCs per yr, or (b) the decrease of hemoglobin exceeding a frequency of 0.5 g/week, and (c) a platelet count <100,000/mm <sup>3</sup> or a leukocyte count <4,000/mm <sup>3</sup> , either singly or in combination	Surgery	113	100	Splenectomy	Acutely	No	Splenectomy was beneficial in reducing transfusion requirements. Postsplenectomy transfusion requirements were nonexistent in 21 (81%) of 26 patients who had splenectomy due to splenomegaly, 1 patient received 5 transfusions in 6.5 yr, 3 patients received 3–4 transfusions every yr for 6 yr and 1 patient continued to receive monthly transfusions. It was also curative for patients with splenic abscess and massive splenic infarction. 24 patients with sickle cell disease (SCD) had splenectomy and cholecystectomy caused by concomitant gallstones. There was no mortality and postoperative morbidity was 7% and on followup ranging from 8 mo to 8.8 yr, complication developed in 6 other patients
Buchanan, 1989 <sup>77</sup>	R, Obs	Functional asplenia and splenic autoinfarction	NR	Radionuclide spleen scanning and quantitation of pocked erythrocytes	Intensive transfusion	5	100	Group 1: PRBCs transfusions to maintain a sickle cell hemoglobin (HbS) level <20%. Group 2: PRBCs transfusion that is less intensive with the HbS level usually ranging between 30 and 40%	Mean: 6.8 yr and 3.9 (groups 1 and 2)	Less intensive transfusion (n=7)	The 5 patients on intensive transfusion had normal or increased splenic size and function (normal scan and normal or minimally elevated pocked erythrocyte count). The patients in group 2 had abnormal splenic function (absent radionuclide uptake and elevated pocked erythrocyte count)
Kinney, 1990 <sup>111</sup>	R, Obs	Splenic sequestration	A fall in the hemoglobin concentration >2 g/dL below the patient's baseline concentration, in association with an enlarged spleen and evidence of bone marrow erythroid activity	Clinical exam, lab data	Prompt splenectomy	4	100	Group 1: Surgery (4 patients) Group 2: Observation (no therapy, 7 patients) Group 3: Transfusion program aimed to reduce HbS level to <30% (12 patients)	Acutely	Careful observation + short-term transfusion program (n=7+12)	Risk for recurrent splenic sequestration was similar in groups 2 and 3. It was concluded that a short-term transfusion program to prevent recurrent splenic sequestration was of limited benefit and comparable to observation

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Leshner, 2009 <sup>115</sup>	R, Obs	ASSC	NR	NR	Antibiotics, surgery	52	100	Penicillin, splenectomy	Mean length of hospital stay was 3.7 d	No	Laparoscopic and open splenectomy was performed in 30 (56.6%) and 22 children (43.8%), respectively. 3 patients died, but no mortality was because of surgery itself, there were a total of 353 hospital readmissions after splenectomy. The average number of admissions before splenectomy (mean ± standard deviation (SD), 3.0±2.8; range, 1–18) was significantly lower than the number of admissions after splenectomy (6.6±8.6; range, 0–28) ( $p=.007$ ). Most readmissions were for febrile episodes, with the remainder for ACS or pain crisis
Powell, 1992 <sup>124</sup>	R, Obs	ASSC	ASSC represents an uncommon complication of SCD and its variants, but with infections accounts for majority of deaths in sickle cell patients in the 1st decade of life. A child with a major crisis presents with symptoms of acute anemia, splenomegaly, and evidence of an active bone marrow response. Severe crisis can present with acute circulatory collapse or result in sudden death	Clinical exam/ investigations	Surgery	8	100	Splenectomy	Mean postoperative course=4.87 d	No	Over a 6-yr period 12 patients ranging in age from 5-1/2 mo to 7 yr presenting with ASSC were treated. 11 had homozygous SCD (HbSS) and the other had sickle-thalassemia. 1 patient died of acute circulatory collapse. 8 patients underwent splenectomy after a major episode of sequestration with no serious infectious complications up to 5 yr following splenectomy. 3 patients with minor episodes have been followed with no recurrences. To foster early detection of this potentially lethal complication of SCD, an educational program in our Comprehensive Sickle Cell Center instructs the parents to examine the spleen and bring their child in for evaluation if the spleen enlarges. A newly developed videotape describes the common symptoms of ASSC and illustrates the technique of palpating the spleen. With early detection of SCD by neonatal screening and the educational program, the morbidity and mortality from this complication of SCD can be reduced
Rao, 1985 <sup>127</sup>	R, Obs	ASSC	NR	Splenomegaly, spleen scan	Transfusion	2	18	Partial exchange transfusion, 1 patient	NR	No	1 patient died before any resuscitative measures could be provided. The 2nd patient was transferred from another hospital in a comatose state, was revived and received partial exchange transfusions, but remained in a coma and died of aspiration pneumonia 3 weeks later

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Rao, 1985 <sup>127</sup>	R, Obs	Subacute splenic sequestration	Significant increase in spleen size over that found on previous examinations; drop in hemoglobin/hematocrit by at least 25% of patient's baseline values; drop in platelet count to <100,000/mm <sup>3</sup> ; elevation in reticulocyte count to over patient's baseline; and absence of other explanations for such hemoglobin changes	Most infants presented with pallor and slight irritability. 6 patients had splenic function as evidenced by normal or decreased uptake on Technetium-99m sulfur colloid scan. The spleen was not visualized in 5/11 patients. There was no evidence of hypersplenism on any of the other spleen scans	Transfusion and pneumococcal vaccine	11	100	All patients older than 2 yr received 1 dose of pneumococcal vaccine while on the transfusion. During hospitalization, 5 children received an initial partial exchange transfusion and 6 received a simple transfusion of washed PRBC. The 11 children were then placed on a short-term periodic transfusion program for a 1–3 yr period. Washed PRBC transfusions were given every 3–4 weeks to maintain hemoglobin around 12 g/dL and the reticulocytes <2%	1–3 yr	No	Within 48 h of initial transfusion, the spleen reduced to baseline palpability in 9/11 patients and in 2/11, there was significant reduction in size. On the periodic transfusion program, 4/11 patients developed minor blood group allosensitization but continued. After 5–6 mo of periodic transfusions, discontinuation attempts were made. 3/11 patients have not had recurrence of splenomegaly/sequestration since discontinuing. 7/11 patients had recurring significant sequestration with discontinuation and 4/7 had acute sequestration and required splenectomy. 1 patient continues transfusion. All 11 children are alive
Rezende, 2009 <sup>129</sup>	R, Obs	ASSC	Defined as an episode of ASSC entered on the medical record by the hematologist in charge of the child's followup	NR	Surgery	48	34.9	51 splenectomies were indicated for the 89 children who had ASSC; 48 were actually performed. In 2 cases, the procedure was not authorized by the family. The patients remained under clinical observation and did not have new episodes of ASSC	NA	Clinical observation (n=166)	In the study population (n=255), 19 deaths occurred; 7 of them associated with infections, 5 due to ASS, 4 of unknown cause, 2 of "respiratory failure," and 1 in a state of coma (possibly a cerebrovascular accident). Mortality rate at 2 yr of age was 5.1% (95% confidence interval (CI)) 2.4–7.8
Salamah, 1989 <sup>131</sup>	R, Obs	ASSC	A sudden and rapid enlargement of the spleen, secondary to the massive pooling of RBCs in the splenic sinusoids in a functioning spleen	Fever, abdominal discomfort, splenomegaly, splenic tenderness, severe anemia	Transfusion	17	100	All children were given incremental PRBC transfusion, up to hemoglobin of 12 g/dL	NR	No	The spleen started to decrease in size a few hours after transfusions and was not palpable 2–3 d after admission. After ASSC, 6 children received transfusion with washed PRBCs every 3–4 weeks when indicated. None of these children developed recurrent attacks. 4 of the 11 children who were not receiving repeated transfusions developed recurrent attacks (36%). 4 children underwent splenectomy within 1 yr of initial ASSC diagnosis because of recurrent attacks and development of hypersplenism

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Sandoval, 2002 <sup>132</sup>	R, Obs	Recurrent splenic sequestration and/or symptomatic cholelithiasis/cholecystitis	NR	NR	Surgery	13	100	Laparoscopic splenectomy/cholecystectomy 12 patients received PRBCs	Once	No	The median operative time was 150 min, and the median hospitalization was 3 d. 4 patients suffered postoperative complications (2 with ACS, 1 with recurrent abdominal pain, and 1 with priapism). The patient with abdominal pain was found to have a retained stone in the common bile duct, which was retrieved via endoscopic retrograde cholangiopancreatography and sphincterotomy. All complications resolved with medical management. No patient has had any long-term postoperative complications during a median followup time of 19 mo. 2 patients have required hospitalizations for recurrent VOCs, and 1 patient has required 2 admissions for postsplenectomy fever. In neither case did the patient with fever appear ill, and her hospital course was uneventful
Subbannan, 2009 <sup>142</sup>	R, Obs	Acute splenic complications requiring splenectomy, including splenic infarction, hypersplenism, and sequestration, subcapsular bleeding	NR	NR	Surgery	12	9.6	Splenectomy	Acutely	Patient with sickle hemoglobin C disease (HbSC) who did not have splenectomy (n=112)	Group 1: Presplenectomy: Median hemoglobin 7.2 g/dL; median platelet count 146×10 <sup>9</sup> /L; palpable spleen 66% (8/12 patients); median HbS %: 47.4%; median hemoglobin C (HbC) %: 45.7%; median hemoglobin F (HbF) %: 1.4%; median total bilirubin (mg/dL): 1. Postsplenectomy median hemoglobin 11.4 g/dL; median platelet count 416×10 <sup>9</sup> /L; median HbS %: 48.5%; median HbC %: 46.3%; median HbF %: 2%; median total bilirubin (mg/dL): 1. Group 2: palpable spleen %: 16% (18/112); median hemoglobin 12.5 g/dL; median platelet count 275×10 <sup>9</sup> /L; median HbS %: 47.7%; median HbC %: 46.7%; median HbF %: 1.8%; median total bilirubin (mg/dL): 1; mortality rate: 4% (5/112)

Study label	Design	Specific Complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment*	Secondary/control arm	Reported results
Svarch, 1996 <sup>143</sup>	R, Obs	Recurrent splenic sequestration	ASSC is defined as a fall in the hemoglobin concentration of >2 g/dL, referred to as the patient baseline concentration in association with an enlarged spleen and evidence of bone marrow erythroid activity	NR	Partial splenectomy	25	100	After Jan. 1989, children under the age of 5 and patients of all ages with a partial splenectomy (for 3 yr) received prophylactic antibiotics. All patients received preoperative transfusions of PRBCs in order to raise the hemoglobin level to 10 g/dL	Acutely	No	Clinical severity varied widely between ASSC episodes but all required hospital admission and at least on PRBC transfusion. The most frequently associated clinical problems were: upper respiratory infection in 11 patients, fever of unknown origin in 5, and cardiac failure in 3. Comparisons of hematological baseline studies before and after surgery showed significant increases in total hemoglobin, WBC, and platelet counts. No difference was found between the percentages of pitted RBCs before and after partial splenectomy. Mean levels of Immunoglobulin M (IgM) before and after surgery were not significantly different (0.42±0.78 g/L vs. 1.53±0.36 g/L). The postoperative gammagraphy showed the presence of the splenic remnant in 10 of the 15 children. There were no significant differences between the number of pitted red cells in the patients in whom splenic uptake was observed in a Technetium-99m sulfur colloid study (4.03%) compared with the ones in whom such uptake did not occur (5.36%). Surgery was uneventful in all patients and no episode of ASSC has been observed during the post-surgical followup period. No cases of pneumococcal septicemia or meningitis have occurred. 2 children experienced pneumonia with complete recovery
Svrach, 2003 <sup>144</sup>	R, Obs	ASSC	ASSC is defined as a fall in the hemoglobin level >2 g/dL from the baseline concentration, associated with an enlarged spleen and evidence of bone marrow erythroid activity	Splenic function was also evaluated by radionuclide scan with the Technetium-99m sulfur colloid	Partial splenectomy and prophylactic antibiotics	50	100	Prior to Jan. 1989, no prophylaxis was given. Afterwards, oral penicillin was given to all patients for 3 yr after the operation	Acutely	No	Immediate postoperative morbidity was limited to fever in 10 patients, wound infections in 5 patients, and pneumonia in 3 patients. There was a significant reduction in requirements for blood transfusions (from mean of 6.25–1.12) and a decrease in the number of hospitalizations (from 5.77 to 3.21). The postoperative spleen scans showed the presence of splenic remnant in 13 of 20 children. No recurrence of ASSC occurred after the operation. There were also increases in hemoglobin levels (from 6.0 g/dL to 7.7 g/dL) and platelet counts (from 228.0 to 408.5×10 <sup>9</sup> /L). The level of pitted RBCs decreased to 3.7%

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Grover, 1990 <sup>182</sup>	P, Obs	ASSC	Severe anemia associated with sudden enlargement of the spleen and an active bone marrow. Criteria for the diagnosis of ASSC were a rapid drop of hemoglobin/hematocrit by >30% of the baseline; sudden and significant enlargement of the spleen, at least twice the baseline; and elevation of reticulocyte count above the baseline	Clinical exam	Long-term transfusion therapy for children under the age of 5 yr and splenectomy for children aged 5 yr and older	15	100	PRBCs; frequency not specified	1 yr for patients receiving transfusion therapy	No	5 patients had splenectomy after the 2nd episode. The mean pit count during long-term transfusion therapy in 9 patients was 2.2±0.77% (range, 0–8%). During long-term transfusion therapy, HbS levels fell from a mean value of 90±1.33% (range, 80–95%) to 25.20±1.80% (range, 14.3–40%). The mean serum ferritin level of 7 of the 9 patients after long-term transfusion therapy was 261±112 ns/mL (range, 63–10). All patients are living and well after a followup period of 10 mo to 10.5 yr (mean period of 8.4 yr, 98.3 patient-yr)
Santos, 2002 <sup>207</sup>	P, Obs	Functional asplenia	No definition was provided	Liver/spleen scintigraphy	Hydroxyurea (HU)	21	100	Starting dose 15 mg/kg once daily. Increased by 5 mg/kg/d every 8 weeks up to a maximum dose of 30 mg/kg daily, unless toxicity was present	Unclear	No	Imaging prior to treatment demonstrated functional asplenia in 9 HbSS patients and 1 hemoglobin S beta-zero (HbSβ <sup>0</sup> ) patient and impaired splenic function in 5 HbSS patients and 6 HbSβ <sup>0</sup> patients. After treatment, splenic function improved in 10 patients, remained unchanged in 8, and worsened in 3
Topley, 1981 <sup>217</sup>	P, Obs	ASSC and hypersplenism	Fall in hemoglobin concentration of at least 2 g/dL, associated with evidence of marrow activity and an acutely enlarging spleen	Clinical presentation, complete blood count (CBC)	Simple blood transfusion, splenectomy	52	24	NR	NR	NA	12% mortality in the 1st episode. 14 patients experienced 2 episodes and 5 patients, 3 episodes with mortality rates of 21% and 20% respectively. Of the 4 children surviving 3 episodes of ASSC, 3 have had impalpable spleens for at least 1 yr at ages 55, 62, and 66 mo, and 1 child of 21 mo has been a persistent defaulter. 4 patients had splenectomy after the 1st episode and 2 after the 2nd episode
Badaloo, 1996 <sup>222</sup>	R-P, Obs	Hypersplenism	The diagnosis of hypersplenism was based on a spleen enlarged 4 cm or more below the left costal margin and a hemoglobin level <6.5 g/dL on at least 2 occasions 3 mo apart	Clinical exam/investigations	Surgery	6	100	Splenectomy	Acutely	No	After splenectomy protein turnover fell significantly by 30% and resting metabolic rate (RMR) by 34 kJ/kg/d. Mean weight velocity, which was below normal before surgery, z=-2.3, improved significantly after surgery, z=0.7, (p=.03). Height velocity increased in 2 children, but the mean height velocity did not change following splenectomy. The reduction in protein turnover was estimated to account for 62% of the fall in RMR

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Wright, 1999 <sup>227</sup>	Case-control	ASSC and chronic hypersplenism	A sudden increase in splenic size (usually $\geq 3$ cm below costal margin), a fall in hemoglobin (usually $< 4.5$ g/dL), an increase in reticulocyte count, and decrease in splenomegaly after transfusion or spontaneous resolution of the attack. Hypersplenism: combination of splenomegaly (often $> 6$ cm below the costal margin), low hemoglobin (usually $< 6$ g/dL), and high reticulocytes sustained for periods $> 3$ mo	NR	Splenectomy	130	100	Splenectomy was performed for the prevention of recurrent ASSC in 46 (35%) patients, usually after 2 attacks, and for relief of hypersplenism in 84 (65%) patients, usually after an observation period of 6 mo	NA	130 control patients	Mortality (9 and 12 deaths) and bacteremic episodes (10 and 12 episodes) did not differ between the splenectomy and control groups respectively. Painful crises were more common in the splenectomy group than in the control group (odds ratio (OR): 1.47, 95% CI: 1.10, 1.98) but did not differ between splenectomy indications. ACS was more common in the splenectomy group than in the control group (OR: 1.88, 95% CI 1.25, 2.84) and was more common in the ASSC group than in the hypersplenism group ( $p=.01$ ). Febrile events did not differ between the groups or between the indications for splenectomy
Adekile, 1999 <sup>228</sup>	Case report/case series	Acute splenic infarction	NA	Abdominal CT and US	Conservative	1	100	IVFs, intravenous (IV) ceftriaxone, analgesics	1 week	No	Patient recovered
Al Jama, 2002 <sup>50</sup>	Case report/case series	Massive splenic infarction	Splenic infarction involving more than half of the size of the spleen	Clinical presentation, US, CT scan	Conservative and surgical	8	100	IVF, analgesics and blood transfusion all patients, antibiotics 7 of them, splenectomy in 3	NR	No	All patients survived, 2 patients require splenectomy during the same admission. A 3rd patient required splenectomy 2 mo after the attack. 2 developed autosplenectomy in 2 and 5 yr, after attack. The remaining 3 patients continue to have persistent but asymptomatic splenomegaly for 6 mo, 1 yr, and 4 yr after the attack
Al-Salem, 1994 <sup>248</sup>	Case report/case series	Splenic abscess	NR	US and CT scan of the abdomen	Splenectomy	4	100	Penicillin, gentamycin, metronidazole NR	NR	No	All patients made rapid recovery following splenectomy
Al-Tawfiq <sup>250</sup>	Case report/case series	Splenic abscess	NR	Chest x ray, respiratory examination, CT	Antibiotics, surgery	1	100	NR	12 d	No	The patient was started on ceftriaxone 1 g IV daily and clindamycin 600 mg IV q 6 hourly. 12 d later, he underwent splenectomy without complications. The patient was treated for an additional 12 d and was discharged in good condition

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Alvarado, 1988 <sup>251</sup>	Case report/ case series	Splenic infarction	NR	Chest roentgenogram, abdomen CT scan, abdomen US	Intravenous fluids, analgesics, and parenteral antibiotics	1	100	He was started on IVFs, analgesics and parenteral antibiotics (ampicillin and erythromycin)	8 d	No	On the 5th hospital d, the patient was afebrile and his pain had diminished, the hemoglobin was 12.3 g/dL. The patient steadily improved and was discharged home 8 d after admission; 4 weeks later the spleen was palpable at the left costal margin, repeat CT scan was normal
Aslam, 2005 <sup>253</sup>	Case report/ case series	ASSC	VOC within the spleen and splenic pooling of RBCs produces a marked fall in hemoglobin concentration with a rapidly enlarging spleen and persistent reticulocytosis. Pathologically, there is entrapment of the sickled RBCs in the splenic sinusoids and infarction of the spleen	LUQ tenderness, massive splenomegaly, severe anemia, thrombocytopenia, abdominal CT with oral contrast	Fluids and transfusion	1	100	PRBC transfusion	NR	No	Patient had a progressive downhill course and was intubated for respiratory distress and hemodynamic compromise. A repeat hemoglobin level after transfusions was 10.0 g/dL, with a progressive decrease of the platelet count to 68,000/mm <sup>3</sup> . During the course of the illness, levels of hepatic transaminases progressively increased (aspartate transaminase, 3640 U/L; alanine transaminase, 2310 U/L; alkaline phosphatase, 397 U/L) with predominantly conjugated hyperbilirubinemia (total bilirubin 2.8 mg/dL, direct bilirubin 2.4 mg/dL). The patient's renal function also deteriorated, with serum creatinine concentration increasing from 1.4 mg/dL at presentation to 2.6 mg/dL with severe oliguria. An echocardiogram obtained in the meantime showed evidence of right ventricular pressure overload. Despite intensive resuscitative efforts for 36 h, the patient developed cardiac arrest and could not be revived
Ballester, 1979 <sup>260</sup>	Case report/ case series	Splenic pain	NA	CBC, abdominal x ray, spleen scan	Transfusion, surgery	1	100	Exchange transfusion, splenectomy, incidental cholecystectomy	17 d hospitalization	No	Patient completely recovered after surgery
Berry, 1991 <sup>266</sup>	Case report/ case series	ASSC and complete infarction	NR	Clinically, abdominal US	Transfusion, surgery	1	100	Exchange transfusion and splenectomy	NR	No	After transfusion, the patient's condition deteriorated with his temperature rising to 41.5 °C, his LUQ pain increasing, and his leukocyte count rising to 37.9×10 <sup>9</sup> /L. Splenectomy was done on d 19. The spleen weighed 950 g and was totally infarcted. The patient's recovery was prompt and complete. The non-Q wave myocardial infarct occurred at the time of splenic sequestration and may have contributed to the clinical state
Berry, 1991 <sup>266</sup>	Case report/ case series	ASSC and complete splenic infarction	NR	Abdominal US, liver-spleen scan with Technetium-99m sulphuris colloid	Transfusion, surgery	1	100	Transfusion (1st admission), antibiotics (1st admission), splenectomy (2nd admission)	NR	No	The patient's 1,250-g spleen was removed and was totally infarcted. After the operation, he rapidly improved. Throughout his 2nd hospital admission, Howell-Jolly bodies were noted on his peripheral blood smear. They were not seen on a retrospective review of peripheral smears from his earlier hospital admission

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Casey, 1994 <sup>276</sup>	Case report/case series	ASSC	Entrapment of sickled erythrocyte and platelets within the spleen leading to worsening of anemia and thrombocytopenia	CBC, abdominal US	Transfusion	1	100	200 mL PRBCs once	3 d	No	Symptoms resolved, patient discharged the 3rd d
Cavenagh, 1994 <sup>277</sup>	Case report/case series	Splenic sepsis	NR	Case1: Abdominal US Case 2: US, CT abdomen	Exchange transfusion, IV antibiotic, splenectomy	2	100	Exchange transfusion, IV antibiotic, splenectomy	NR	No	Both patients showed complete recovery
Doodnath, 2010 <sup>299</sup>	Case report/case series	ASSC	NR	Vomiting, diarrhea, and abdominal pain	Laparoscopic splenectomy	1	100	He was on the blood transfusion program and transfused every 4 weeks	He had 8 blood transfusions prior to surgery	No	There were no postoperative complications, and he was discharged home 2 d after the procedure, reviewed 3 weeks after discharge, and was well
Ferster, 1993 <sup>313</sup>	Case report/case series	Splenic reticuloendothelial dysfunction	NR	NR	Bone marrow transplant (BMT)	3	100	BMT	NR	No	All 3 patients had loss of reticuloendothelial splenic function, as assessed by the presence of abundant Howell-Jolly bodies on blood smears and absence of Technetium-99m splenic uptake. After BMT, Howell-Jolly bodies disappeared from blood smear, whereas Technetium-99m isotopic scan found normal isotope uptake
Geola, 1978 <sup>323</sup>	Case report/case series	Splenic sequestration crisis (SSC)	NR	CBC, Technetium-99m colloid liver spleen scan	Blood transfusion	1	100	PRBCs, 5 U over 6 h	NR	No	The splenic uptake progressively increased as visualized on both anterior and posterior views. In addition, there was a progressive decrease in the size of the spleen. On the 2nd scan, there were several areas of decreased uptake within the spleen, with a gradual progressive return to a homogeneous uptake pattern on the subsequent scans. This indicated gradual return of function associated with a decrease in the size of the spleen

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Huang, 2003 <sup>350</sup>	Case report/case series	Splenomegaly	NR	Physical examination	HU	1	100	1,000 mg/d	10 mo	No	At the time of HU initiation, her spleen was not palpable. 6 weeks later, HbF increased to 2.2%, but platelet count decreased to 86×10 <sup>9</sup> /L. In May 2001, HU was held due to worsening thrombocytopenia. Her platelet count went down to 33×10 <sup>9</sup> /L. 2 weeks later the platelet count recovered to 105×10 <sup>9</sup> /L. HU was restarted at 1,000 mg/d, which was later increased to 1,500 mg/d, 5 d/week, and 1,000 mg/d, 2 d/week. In Sept. 2001, routine followup physical examination revealed a palpable spleen (4 cm below the left costal margin). Abdominal US showed a homogeneous enlarged spleen. The spleen measured 18.2 cm longitudinally. Clinically, her splenomegaly continued to worsen, associated with early satiety, nausea, and LUQ abdominal pain. In Dec. 2001, her spleen was 8 cm below the left costal margin with tenderness on palpation. She underwent splenectomy in Jan. 2002. The spleen measured 24×13×8 cm and weighed 1,100 g. Histopathologic examination revealed an enlarged, congested spleen with numerous Gamma-Gandy bodies and many sickle RBCs within the sinusoids. The patient recovered well from surgery and her thrombocytopenia resolved. She was restarted on HU. She has tolerated the medication well without cytopenia complications and her clinical condition improved
Idowu, 1998 <sup>352</sup>	Case report/case series	Hemoglobinopathy	NR	The need for surgery was determined by the increasing need for blood transfusions, specifically SSC and hypersplenism	Splenectomy	6	83.3	Splenectomy	Average hospital stay was 6.3 d	No	The blood transfusion rate was decreased significantly postoperatively in 5 patients. Postoperative morbidity was limited to pneumonia, and the mortality rate was 0. Conclusion: Partial splenectomy is a safe and effective procedure in children <4 yr of age with hemoglobinopathies. The procedure as described yields minimal blood loss and retains immune competence
Kar, 2008 <sup>358</sup>	Case report/case series	Splenic calcification and bone marrow infarction	NR	Abdominal US and CT, trephine bone marrow biopsy	3 U of transfusion, broad spectrum antibiotics	1	NA	Transfusion, broad spectrum antibiotics	2 weeks of antibiotics	No	Fever subsided after 2 weeks
Koduri, 2006 <sup>372</sup>	Case report/case series	ASSC	NR	LUQ tenderness, splenomegaly, an otherwise unexplained drop in hemoglobin	Transfusion, splenectomy, and conservative management	9	100	6 patients were transfused with packed erythrocytes (3–6 U)	NR	No	2 patients failed to respond to transfusion of packed erythrocytes and required urgent splenectomy. There was 1 fatality: a 76-yr-old woman, who died 36 h after admission. There was no recurrence of ASSC in 5 patients followed for 2, 3, 16, 18, and 21 yr, respectively

Study label	Design	Specific Complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment*	Secondary/control arm	Reported results
Koduri, 2006 <sup>373</sup>	Case report/case series	ASSC	It is characterized by a sudden enlargement of the spleen due to trapping of a significant proportion of the blood volume, rapid drop in the hematocrit with hypovolemia, and thrombocytopenia	LUQ pain, exacerbation of anemia	Transfusion, splenectomy, and cholecystectomy	1	100	Over 2 d, he was transfused with 7 U of packed erythrocytes and 15 U of platelets. His hematocrit was 30%, and the platelet count was 62×10 <sup>9</sup> /L posttransfusion. He continued to have severe abdominal pain and tenderness. He was preoperatively transfused with 4 more U of packed erythrocytes	Splenectomy and cholecystectomy were done on the 6th hospital d	No	The spleen weighed 795 g and the cut surface was diffusely reddish purple with indistinct trabeculae and white pulp. There were no areas of splenic infarction. Microscopic examination showed markedly congested red pulp with pooling of sickled erythrocytes and scattered small aggregates of normoblasts. At discharge on the 10th hospital d, his hemoglobin was 13.5 g/dL, leukocytes were 11.5×10 <sup>9</sup> /L, and platelets were 362×10 <sup>9</sup> /L
Moll, 1996 <sup>417</sup>	Case report/case series	Splenomegaly and SSC	NR	CBC, Technetium-99m labeled sulfur colloid liver spleen scan	Surgery	1	100	Splenectomy	Acutely	No	12 mo after splenectomy the patient is asymptomatic, hemoglobin is 12.6 g/dL
Nouri, 1991 <sup>431</sup>	Case report/case series	ASSC, hypersplenism, and hypersplenism + ASSC	A fall in the hemoglobin concentration of >2 g/dL, with evidence of marrow compensation, and an acutely enlarged spleen. A definition of hypersplenism includes: (1) a chronically enlarged spleen >4 cm below the left costal margin; (2) a hemoglobin concentration <65 g/L; (3) >15% reticulocytes; and (4) a platelet count <200×10 <sup>9</sup> /L	ASSC (8%), hypersplenism (42%), and ASSC + hypersplenism (50%)	Partial splenectomy, polyvalent pneumococcal vaccine, and postsurgery penicillin	12	100	Presurgery polyvalent pneumococcal vaccine and postsurgery penicillin	Acutely	No	Surgery was uneventful in 11 patients. A bilateral pneumonia occurred in 1 patient on the 3rd postoperative d and the patient recovered with antibiotic treatment. A reduction of blood requirements (HbSS from 2.1 to 0.62 and hemoglobin S thalassemia (HbS-thal) disease from 4.2 to 0.21/yr) and a decrease of the number of hospitalizations/ patient/yr (HbSS 4.7–1.5 and HbS-thal from 2.4 to 0.37) were observed after splenectomy. No recurrence of hypersplenism or ASSC occurred. Mean hemoglobin concentrations and leucocyte and platelet counts were significantly increased after splenectomy (p<.001). Platelet count immediately after surgery was 540 (273) × 10 <sup>9</sup> /L. No thrombosis occurred and platelets returned to normal in all patients within 1 yr. No severe infection was observed during the followup period. Mean residual splenic size was 4.6 cm in patients; mean splenic size before surgery was 13 cm. Mean IgM concentrations did not differ before and after splenectomy
Okoro, 1989 <sup>433</sup>	Case report/case series	Hypersplenism	Hypersplenism is diagnosed on the basis of repeated episodes of acute hemolysis, thrombocytopenia, reticulocytosis, and splenomegaly	NR	Surgery	4	100	Splenectomy	Acutely	No	For all 4 patients, pretransfusion hemoglobin levels were very low (range: 2.6–4.2 g/dL) and despite repeated transfusions remained very low (range: 2.7–5.8 g/dL). None of the 4 patients has developed hemolytic crisis postsplenectomy. Over followup period, patients have presented with bone pains, abdominal pain crisis, and thrombotic crisis

Study label	Design	Specific Complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment*	Secondary/control arm	Reported results
Orringer, 1991 <sup>436</sup>	Case report/ case series	Splenic infarction and ASSC	Sudden splenic enlargement that can result in the entrapment of a major portion of the circulating RBCs	CBC, abdominal CT, Technetium -99m sulfur-colloid liver-spleen scan	Surgery	2	100	Splenectomy	Acutely	No	Complete recovery
Ouyang, 2008 <sup>437</sup>	Case report/ case series	Massive splenic infarct	NR	CT abdomen	IVF, morphine	1	100	IVF, morphine	2 d	No	Symptoms resolved
Pappo, 1989 <sup>439</sup>	Case report/ case series	SSC	NR	Lab data, medical presentation	Transfusion	1	100	2 U PRBCs acutely	4 d	No	Resolution of complication after transfusion
Rao, 1979 <sup>450</sup>	Case report/ case series	ASSC	NR	Clinical presentation, CBC and peripheral blood smear, autopsy	Oxygen, aspirin, IVF	1	100	Compatible blood could not be obtained immediately because of the presence of strong irregular antibodies with AB-ve blood group	3 d	No	Patient died of cardiac arrest
Rivera-Ruiz, 2008 <sup>455</sup>	Case report/ case series	ASSC	ASSC is the sudden impounding of RBCs by the spleen, characterized by the rapid fall in hemoglobin concentration, rise in reticulocyte count, and splenomegaly	Abdominal CT	Narcotic treatment, RBC transfusion therapy with 4 PRBCs, splenectomy	1	100	RBC transfusion therapy with 4 PRBCs	NR	No	Despite aggressive narcotic treatment of back pain, the pain continued to increase, and in spite of RBC transfusion therapy with 4 PRBCs, the patient's hemoglobin progressively dropped to a level of <4 mg/dL over the course of 3 h, with evolving thrombocytopenia (<50×10 <sup>9</sup> /L). The patient was immediately transferred to an intensive care unit (ICU). At the ICU, the patient exhibited altered mental status and worsening gas exchange. Airway protection with intubation and mechanical ventilation were initiated. As the patient was rapidly deteriorating, an emergent splenectomy was performed, confirming the findings of the CT scan. Intraoperatively, the spleen was friable with specific infarction sites. Postoperatively, the patient developed multisystem organ failure with systemic inflammatory response syndrome. After extensive management and rehabilitation, the patient recovered every organ function and, 6 mo later, has resumed his normal activities

Study label	Design	Specific Complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment*	Secondary/control arm	Reported results
Roshkow, 1990 <sup>458</sup>	Case report/case series	ASSC	ASSC is diagnosed clinically by sudden splenic enlargement accompanied by a rapid fall in hematocrit	Abdominal US, abdominal CT, magnetic resonance imaging (MRI)	Transfusion and splenectomy	1	100	Exchange transfusion	Was performed 14 d after the acute episode	No	The spleen weighed 880 g. The capsule was intact. The cut surface showed multiple irregular areas of yellow discoloration that corresponded to the focal lesions seen on the images. At histologic examination, these areas were hemorrhagic infarcts, approximately 10–14 d old. Congestion was noted, and the sinusoids were packed with sickled erythrocytes
Sarma, 1989 <sup>467</sup>	Case report/case series	ASSC	NR	CBC, peripheral blood smear, clinical presentation (enlarged spleen)	IVFs, IV chloramphenicol and ampicillin, and 4 U of PRBCs	1	100	2 U of PRBCs on admission, 2 U during the course of hospitalization of 6 d	7 d	No	At the time of discharge she was afebrile, anicteric, and her hematological and biochemical values were back to her steady state, and the spleen was not palpable. She remained well during 12 mo followup
Shao, 1996 <sup>478</sup>	Case report/case series	ASSC	ASSC is characterized by a sudden decrease in hemoglobin concentration and marked splenomegaly	Abdominal US, CBC	Transfusion, mechanical ventilation, hemodialysis	1	100	Aggressive transfusion therapy was initiated immediately, with 8 U of packed erythrocytes infused during the first 24 h. The coagulopathy was treated with infusion of both fresh frozen plasma and cryoprecipitate	<1 mo	No	Because of respiratory failure, the patient was intubated and placed on mechanical ventilation. Aggressive transfusion therapy was initiated immediately, with 8 U of packed erythrocytes infused during the first 24 h. The coagulopathy was treated with infusion of both fresh frozen plasma and cryoprecipitate. Despite the massive fluid volumes she received, patient remained oliguric. By the 2nd hospital d, her serum creatinine concentration increased to 3.6 mg/dL, and a chest radiograph revealed the new appearance of bilateral, diffuse, pulmonary infiltrates. Hemodialysis was begun to remove excess fluid and to correct the metabolic acidosis. During the next 4 d, the patient's hemoglobin stabilized in the range of 10 g/dL, her platelet count normalized, the coagulopathy resolved, and the liver enzymes declined. Her urine output increased, her creatinine concentration decreased, and the hemodialysis was discontinued. The patient continued to improve, and she was discharged from the hospital on d 14. When last seen, 4 mo later after the acute episode, the patient had returned to school and was doing well
Sharma, 2009 <sup>479</sup>	Case report/case series	Spontaneous splenic rupture	There was no history of trauma or any disease process to precipitate splenic rupture	LUQ tenderness, abdominal US	Surgery	1	100	Subcapsular splenectomy, starting from near the diaphragm, was performed so as to avoid inadvertent iatrogenic trauma to neighboring structures	NA	No	Patient made an uneventful recovery

Study label	Design	Specific Complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment*	Secondary/control arm	Reported results
Shoemaker, 2004 <sup>484</sup>	Case report/case series	Acute splenic rupture	NR	Abdominal CT, diagnostic peritoneal lavage	Transfusion, surgery	1	100	He received 2 U of PRBCs perioperatively. Splenectomy and cholecystectomy were performed	He was in the ICU for 2 d and was transferred to a pediatric ward for 5 d	No	His examination was remarkable for mild chest pain with deep breathing and palpation. No splenomegaly was appreciated. At presentation his hemoglobin was 9.2 g/dL. He was given ceftriaxone and azithromycin and discharged to home with followup the next day. In the hematology clinic the next day, he reported left upper back and shoulder pain. He was afebrile and his physical examination was normal, to include no splenomegaly. Hemoglobin was 8.0 g/dL He was given morphine for pain control and was to return the next day for a preplanned transfusion. Later that evening he returned to the emergency room with worsening pain, this time more located in the abdominal LUQ. As of July 2004, he has had no problems, continues to receive transfusions every 3 weeks, and is doing well, including no progression of CNS disease
Sorrells, 1998 <sup>496</sup>	Case report/case series	ASSC	The diagnosis of ASSC is based on at least 2 g/dL fall in hemoglobin concentration, an enlarging spleen, and evidence of marrow activity	Splenomegaly, acute drop in hemoglobin	Surgery	16	100	Splenectomy	NA	No	Infection rates were similar before and after splenectomy for sequestration
Vishwanathan, 1984 <sup>520</sup>	Case report/case series	Salmonella splenic abscess	NA	Lump on examination, pus on aspiration of the lump, plain x ray	Emetine, metronidazole, tetracycline, gentamycin, chloramphenicol, blood transfusion	1	100	2 weeks 4 U of transfusion once	4 weeks	No	Uneventful recovery, no recurrence of abscess after 3 mo
Wang-Gillam, 2004 <sup>524</sup>	Case report/case series	ASSC	Severe left hip pain, tachypnea, tachycardia, diaphoresis, hypoxia, and jaundice	CT, physical exam, lab tests, chest radiograph	Elective laparoscopic splenectomy 1 mo after 1st admission (see results)	1	100	IVF and analgesics were administered upon admission. By d 5, his hemoglobin decreased from 13.5 g/dL to 7.5 g/dL. He received 3 U of PRBC and was started on broad-spectrum antibiotics after blood cultures were drawn (after d 5)	NR	No	With supportive care, the patient gradually improved. His clinical deterioration was attributed to an ASSC, and he was re-hospitalized the next month for an elective laparoscopic splenectomy. Pathologic examination of the spleen was consistent with ASSC: the spleen weighed 900 g (the average adult spleen weighs 150 g), <sup>7</sup> and histologic examination revealed multiple areas of infarction
Wethers, 1987 <sup>526</sup>	Case report/case series	An elevated pit count correlating to abnormal splenic function	Not defined	Clinical exam/investigations	Transfusions	2	100	Case 1: Exchange transfusion, once. Case 2: Partial exchange transfusions, 2		No	In both patients, the spleen function as measured by the pit count (vesiculated or pitted RBCs) was restored to normal range after transfusion in spite of both patients developing transfusion reactions to the exchange transfusions

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Wetton, 1995 <sup>527</sup>	Case report/case series	Splenic infarction	NR	Histology, CT scan findings	Splenectomy	1	100	NR	Acutely	No	Not described
Yates, 2009 <sup>535</sup>	Case report/case series	Simultaneous ASSC and transient aplastic crisis	NR	CBC, clinical presentation	PRBCs transfusion, case 5 PRBCs + splenectomy	5	100	Cases 1 and 2: 2 blood transfusions. Case 3: 45 mL/kg PRBCs and platelets. Case 4: 40 mL/kg of PRBC and underwent erythrocytapheresis. Case 5: 22 mL/kg of PRBCs	NR	No	All patients made full recovery without complications

**Table 14. Avascular Necrosis Incidence and Outcomes**

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Acurio, 1992 <sup>56</sup>	R, Obs	Avascular necrosis (AVN) of the hip	The small blood vessels of the femoral head, with its specific blood supply and lack of collateral circulation, are particularly liable to occlusion by sickled cells. Local thrombosis gives a further reduction of the oxygen tension, resulting in increased sickling. This vicious circle of continued hypoxia and sickling eventually produces infarction, necrosis, femoral head collapse, and joint destruction	Clinical exam/ investigations	Surgery	25	100	Total hip arthroplasty	NR	No	The mean age of the 10 women and 15 men at the onset of hip symptoms was 25 yr, and at surgery 30 yr (16–45); 66% had either homozygous sickle cell disease (HbSS) or hemoglobin S thalassemia (HbS-thal) disease, 20% sickle cell trait, and the remainder sickle cell disease (SCD). The mean followup was 8.6 yr (2–18). 14 (40%) of the arthroplasties had been revised at a mean of 7.5 yr after the primary procedure and 9 other hips were either radiographically and/or symptomatically loose. The overall complication rate was 49% and the infection rate 20%. The risk-to-benefit ratio of hip arthroplasty in sickle cell hemoglobinopathy is high
Bishop, 1988 <sup>54</sup>	R, Obs	AVN of the hip	Not defined	Clinical exam/ investigations	Surgery	11 (13 hips)	100	Total hip arthroplasty	NR	No	4 patients had a revision and 3 had a resection arthroplasty. 4 had a serious infection postoperatively. Both acute and late complications were numerous. Harris Hip Scores (HHS) ranged from 73 to 82 points and each patient reported a marked relief of preoperative pain
Clarke, 1989 <sup>52</sup>	R, Obs	AVN of the hip	NR	Clinical presentation, hip x ray	Surgery	15	100	Total hip arthroplasty	NR	No	Of the 17 replacements with followup for over 2 yr, 7 were primary operations, and 10 were revisions. Revision had been performed at an average of only 43 mo, 7 for loosening and 3 for secondary bacterial infection. In the 13 hips, which had had a cemented replacement, the prognosis was uniformly bad, and 9 of the 10 revision arthroplasties had previously had cemented arthroplasties
Ebong, 1977 <sup>53</sup>	R, Obs	AVN of the hip	NR	Clinical presentation, x rays	Conservative management	22	100	All patients were treated conservatively with analgesics and no weight bearing	Up to 24 mo	No	Symptomatic improvement in all but generally unsatisfactory results as regards reconstitution of the femoral head

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Ebong, 1986 <sup>94</sup>	R, Obs	AVN of the hip	NR	Hip x ray	Conservative management	75	100	Non-weight-bearing plaster of paris, 5 patients treated with rotation upper femoral osteotomy	NR	No	Perthes-like changes occurred in 40 hips, osteochondritis dissecans-like lesion occurred in 1 hip, and severe hip deformity in 45 hips. 4 of 5 hips with Perthes-like necrosis that were treated by rotation upper hip osteotomy had partial reconstitution of the femoral head, and all 5 patients were symptom-free. The other hips were treated conservatively with generally poor results
Hernigou, 2003 <sup>103</sup>	R, Obs	AVN of the hip	NR	Anteroposterior and lateral plain x rays or magnetic resonance imaging (MRI)	NR	64	100	Only surgical intervention	NA	No	Of the 75 hips without collapse of the femoral head at the initial evaluation, 65 demonstrated collapse within 5 yr after the diagnosis. At the most recent followup examination, 90 hips had had collapsed of the femoral head and 88 of the 92 hips had had surgery because of intractable pain
Hernigou, 2008 <sup>104</sup>	R, Obs	AVN of the hip	NR	MRI	Autologous bone marrow grafting, hip arthroplasty	38 (56 hips)		Decompression and autologous bone marrow grafting, total hip arthroplasty	NA	No	Patients who did not require total hip arthroplasty (n=51) had a mean HHS of 72 points preoperatively and 89 points postoperatively. Decompression and autologous bone marrow grafting decreased pain in all the patients postoperatively and delayed the progression of the disease to collapse during a period as long as 17 yr for the patients with the longest followup and with an average period of 14 yr for 87% of the hips (49 among 56 hips) of this series. Total hip arthroplasty was necessary in 5 hips that progressed to collapse. 15 hips demonstrated total resolution of osteonecrosis on MRI. All had stage I osteonecrosis of the femoral head at the time of treatment with autologous bone marrow grafting

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Mukisi-Mukaza, 2009 <sup>120</sup>	R, Obs	AVN of the hip	NR	Standard radiology, Technetium-99m diphosphonate bone scintigraphy, tomodensitometry (TDM) and MRI	Core depression of the necrotic hip	26	100	Followed drilling technique of Ficat and Grijalvo, on an orthopedic table, in the supine position, under image intensifier control assuring anterior-posterior and lateral views of the hip	NA	No operation, n=16	23 hips were conservatively treated by discharge (a pair of canes). After a followup period of 13.4±0.5 yr, no pain improvement was noted ( $p=.76$ ), and mean arterial pressure score was unchanged ( $p=.27$ ). Out of 23 hips managed by discharge, 9 stage IV hips (degenerative arthritis, 39.1%) underwent arthroplasty after an average delay of 2.6±2.4 yr. 42 hips were treated by core decompression. The duration of followup was 11.3±1.8 yr. Postoperatively, pain reduction and mean arterial pressure score improvement were significant in 39 out of 42 hips (93%, $p<.0001$ ). 29 out of these 42 hips had a favorable evolution. 10 hips (23.8%) progressed to total arthroplasty, after a period of 7.4±2.7 yr, longer than the 1 of the nonoperated group ( $p=.0007$ ). By comparing the 2 groups (operated and nonoperated), the benefit of core decompression appeared very significant ( $p<.0001$ ). In addition to indicating patients' osteonecrosis stages, the Koo and Kim Index estimated the severity and evolution of necrotic lesions in both groups. It indicated decline in the nonoperated group ( $p=.002$ ) and improvement for operated patient ( $p=.0002$ )
Neumayr, 2006 <sup>33</sup>	RCT	AVN of the hip	Steinberg Stage I, II, or III osteonecrosis of the femoral head	Clinical exam/ investigations	Hip core decompression followed by a physical therapy program	46	100	Total hip arthroplasty	Surgery and followup of 3 yr	Yes, physical therapy program alone	After a mean of 3 yr, the hip survival rate was 82% in the group treated with decompression and physical therapy and 86% in the group treated with physical therapy alone. According to a modification of the HHS, the mean clinical improvement was 18.1 points for the patients treated with hip core decompression and physical therapy compared with 15.7 points for those treated with physical therapy alone. With the numbers studied, the differences were not significant

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Sanjay, 1996 <sup>133</sup>	R, Obs	AVN of the hip	Not defined	Clinical exam/ investigations	Surgery	21 (26 hips)	100	Uncemented bipolar hip replacement	NA	No	After operation, the average HHS improved from 36 to 88. Bone culture was positive for bacterial growth in 4 hips (coagulase negative staphylococcus in 3). There was progressive wear of acetabular articular cartilage in 2 cases, but no clinical or radiological evidence of loosening of femoral stem. 17 complications occurred in 9 of 21 patients (43%), (5 in 1 patient). A longitudinal split of the femur was the commonest complications and occurred in 5 hips. Femoral medullary sclerosis was seen in 8 cases
Styles, 1996 <sup>141</sup>	R, Obs	AVN of the hip	NR	AP and frog-leg views on plain radiography and MRI	Surgery	10 (13 hips)	100	Core decompression (patients were admitted the day before the scheduled coring procedure and received intravenous (IV) hydration and red blood cell (RBC) transfusion. Core decompression was performed with a guide pin inserted into the femoral head from below the trochanteric ridge and directed toward the necrotic area)	Mean length of hospitalization was 7 d	No	None of the 10 patients has required further surgery. It was demonstrated that in early AVN, core decompression was beneficial for almost all patients, even with progression on x ray
Wu, 2005 <sup>160</sup>	R, Obs	AVN of the hip	NR	NR	Surgery	12	100	Placement of vascularized iliac graft	NA	No	Pain relief and hip function improved, no patient suffered from infection or any other complications, though no radiological evidence of improvement was noted
Al-Mousawi, 2002 <sup>166</sup>	P, Obs	AVN of the hip	NR	Clinical exam/ investigations on presentation with symptoms	Surgery	28	100	Total hip replacement	Mean operative duration: 2.2 h	No	In all patients HHS improved from a mean of 36 preoperatives to 86 postoperatives. However, at a mean followup of 9.5 (5–15) yr, 6 hips failed due to symptomatic loosening, and 1 failed due to late deep infection. Results support the decision to offer the procedure for patients with arthritic hips secondary to SCD but patients and surgeons should be aware of the complications possible

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Daltro, 2008 <sup>175</sup>	P, Obs	Femoral head necrosis	NR	X ray images at anteroposterior and anterolateral planes or by nuclear magnetic resonance images (NMRI)	Autologous bone marrow mononuclear cells implantation	8	100	Implanting autologous bone marrow mononuclear cells	Mean 2.5h	No	After 8 mo, 7 of the 8 patients reported improvement from symptoms. There were no complications during anesthetic and surgery procedures. There was a significant postoperative increase in the HHS (98.3±2.5 points) compared to preoperative HHS (78.5±6.2 points) ( $p<.001$ ). X-ray evaluation and cell parameters were found to be favorable
Hernigou, 1993 <sup>183</sup>	P, Obs	AVN of the hip	Not defined	Clinical exam/ investigations	Injection of acrylic cement	10 (16 hips)	100	Injecting low-viscosity cement	Acutely, 5 yr mean followup	No	There was early pain relief, and postoperative radiographs showed improvement in the shape of the femoral head. At a mean followup of 5 yr (3–7), 14 of 16 hips were still improved although some gave slight pain. Only 2 hips had required revision to total hip arthroplasty, at 1 yr and 2 yr, respectively
Ilyas, 2002 <sup>184</sup>	P, Obs	AVN of the hip	AVN due to intravascular sickling causes blood stasis, thrombosis, and ischemia resulting in infarcts of the femoral head, which leads to AVN and severe degenerative hip arthritis at a young age	NR	Surgery	18	100	Bilateral total hip arthroplasty	NA	No	The mean hemoglobin S (HbS) concentration in the blood was 76.16% (range, 69.7%–89.6%). The mean fetal hemoglobin (HbF) concentration was 21.2% (range, 6.6%–29.4%). The average hip score improved in the 3 categories of pain, function, and range of motion on both sides. Pain improved from a mean score of 1.6 to 5 on the right side and from 1.6 to 5.1 on the left side. Functional scores improved from 2.2 to 4.5 on both sides. Range of motion improved from a mean score of 2–4.6 on the right side and from 2.2 to 4.8 on the left side

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Moran, 1993 <sup>198</sup>	P, Obs	End-stage osteonecrosis of the femoral head secondary to sickle cell hemoglobinopathy	NR	Clinical exam/ investigations	Surgery	14 (22 hips)	100	Total hip arthroplasty	Acutely	No	There were 15 primary and 7 revision procedures; none were lost to followup evaluation. In the primary arthroplasty group, there were 2 deaths in patients whose implants were functioning well. The remaining 13 hips had a mean followup period of 4.8 yr. Failure occurred in 5 of these 13 hips (38%), 4 due to aseptic acetabular loosening and 1 due to sepsis. In the revision arthroplasty group, at a mean followup period of 5.3 yr, failure occurred in 3 hips (43%), 1 due to acetabular loosening, 1 due to femoral loosening, and 1 due to sepsis. Perioperative complication rates were high in both groups. Femoral intramedullary sclerosis and bone altered by marrow hyperplasia were associated with intraoperative technical difficulties as well as problems with achieving long-term component fixation
Alli, 2007 <sup>243</sup>	Case report/ case series	Skull bone infarction and deep vein thrombosis	The left parietal area was tender to percussion. There was no associated swelling of the scalp upon presentation	Computed tomography (CT) scan, Doppler ultrasound (US), radioisotope 2-phase bone scan	Enoxaparin	1	NA	Maximal doses of enoxaparin viz, 1 mg/kg/dose subcutaneously 12 h. In addition, aspirin was given orally at a daily dose of 150 mg. Enoxaparin administration was continued for 11 d, after which a switch to warfarin was made. Exchange transfusion: the HbS level dropped to 41 and 15%, after the 1st and 2nd exchange blood transfusions, respectively	14 d	No	Significant clinical improvement by way of analgesic requirements and facial swelling was apparent only after the 2nd transfusion, a gradual process which took approximately 14 d to resolve completely. Warfarin was discontinued after 5 mo and the patient is now well and asymptomatic

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Baykul, 2004 <sup>263</sup>	Case report/case series	AVN of the mandibular condyle	NR	A slowly growing restriction on the temporomandibular joint (TMJ). Radiological examination with orthopantomography revealed a flattened area on the right TMJ. The condylar head was concave and widened. CT demonstrated a wide and deformed condyle with flattening and sclerosis of the glenoid fossa on the right side. The TMJ space was obliterated on the anteromedial aspect of the joint	Surgery	1	100	Arthroplasty with an interpositional temporalis muscle flap	NA	No	The healing period was uneventful. Aggressive rehabilitation of the TMJ was started on postoperative d 3 with tongue blades. The patient was followed up for 7 mo and the interincisal opening was 45 mm. The function of the TMJ was normal, except for a deviation of the central line to the right side because of the short ramus
Disch, 2004 <sup>297</sup>	Case report/case series	Osteonecrosis	Patient presented with pain in both hips; MRI scan of the hips revealed multiple osteonecrotic areas and accompanying bone marrow edema of the femoral head and neck	Blood smear and blood sample analysis, radiographs, MRI	Iloprost, and isotonic sodium chloride solution	1	100	Iloprost, along with isotonic sodium chloride solution to prevent local vein irritations	NR	No	After the 3rd d of infusion, the patient reported an improvement of the hip pain, more so at rest than on movement. The day after the last infusion, the patient was able to return to work. 4 weeks later, the patient reported a further improvement of pain on movement. At followup 12 weeks after initiation of therapy, all clinical parameters remained stable. An MRI showed significant reduction of bone marrow edema in both hips
Dumarey, 2000 <sup>302</sup>	Case report/case series	Osteonecrosis of hips	NR	Clinical presentation, radiographs	Surgery	1	100	Hip arthroplasty	NR	No	Bilateral hip replacement and rehabilitation significantly improved functional outcomes
Hammersley, 1984 <sup>336</sup>	Case report/case series	Mandibular infarction	NR	X ray, Technetium-99m scan,	Intravenous fluids (IVF), analgesics, blood transfusion, exchange transfusion	1	NA	13 U of blood, 2 U of platelets, 4 U of fresh frozen plasma (FFP)	NR	No	Mandibular pain subsided completely in 8 d, but the accompanied paresthesia continued for 8 mo before it resolved completely

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Lau, 2007 <sup>385</sup>	Case report/ case series	Shoulder AVN	NR	X ray, MRI	Hemiarthroplasty, total shoulder arthroplasty, transfusion	8	100	2 patients received a preoperative transfusion to bring the hematocrit level to 30%. 2 patients received 2 U of packed red blood cells (PRBCs) intraoperatively. 1 patient received a transfusion postoperative d 1	NA	No	The mean ASES (American Shoulder and Elbow Surgeons) score improved from 15 to 46.9 at the latest followup. 7/8 patients had very poor preoperative function, with activities of daily living (ADL) scores below 10. All 7 had improvement in their ADL scores postoperatively (range, 19–47). 6/8 patients had improved range of motion, which correlated with the improvements in ADL scores. Forward elevation improved from a mean of 101–137°. Patients had a mean improvement of 20° in external rotation. 1 patient had an intraoperative rotator cuff tear. 2 had sickle cell crises in the immediate postoperative period. 1 patient developed stiffness that required arthroscopic capsular release 22 mo after her arthroplasty. Another patient with a hemiarthroplasty underwent revision to a total shoulder arthroplasty 5 yr after the index procedure. Only 2 patients reported improvement in pain as assessed with a visual analogue scale (VAS)
Mukisi-Mukaza, 2009 <sup>424</sup>	Case report/ case series	Osteonecrosis of the elbow	NR	The appearance of pain during SCA flareups. In this case, x ray, CT	Surgery	4	100	Surgery	NR	No	Treatment: Surgery—percutaneous core depression of the external epicondyle using a 3-mm trephine, which successfully halted the pain (2 patients). Surgery via the posterior approach removed the osteophytosis from the top of the olecranon, removed a foreign body from the posterior portion of the joint, and removed a number of foreign bodies in the anterior portion of the elbow by boring the olecranon fossa, which gave access to an anterior approach to the elbow. One of the patients had simple arthroscopic removal of foreign bodies, since the elbow had locked several times, without the x rays demonstrating osteophytosis or osteoarthritis

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Patel, 2006 <sup>440</sup>	Case report/case series	Osteonecrosis of the femoral head	NR	X ray, CT	Surgery	1	100	Valgus-flexion osteotomy of the proximal femur. For 10 weeks postoperatively, until the osteotomy site consolidated, the patient was to use crutches to ambulate, with toe-touch weight bearing on the left lower extremity. 4 weeks after that, partial weight-bearing was allowed. Then, full weight-bearing was allowed	Acutely	No	Patient was last seen at 42 mo followup. At that time, she was not using analgesics or a walking aid and walked without a limp. Her postoperative VAS pain score was minimal discomfort. With the patient standing on her left (operated) lower extremity, Trendelenburg results were negative. There was a 0.5-cm limb-length discrepancy, with the left lower extremity being shorter than the right. Her HHS was 92 points at last followup, and plain radiographs of the left hip showed healed proximal femoral osteotomy. Postoperative CT scan of the left hip showed the avascular segment healing satisfactorily and having sclerotic rim. The smooth contour of the femoral head was maintained with preservation of the joint space
Pruzansky, 1980 <sup>445</sup>	Case report/case series	Osteonecrosis	NR	X ray, bone biopsy	Antibiotics, open biopsy	1	100	Antibiotics, open biopsy of bone	NR	No	Symptoms resolved completely after the bone biopsy
Rand, 1987 <sup>449</sup>	Case report/case series	AVN of femoral head	Not defined	Clinical exam/investigations	Surgery, conservative management	5	100	2 cases: Total hip arthroplasty; 2 cases: Non-weight-bearing crutches; 1 case: Hemiarthroplasty	NR	No	2 patients (aged 13 and 17 yr) presented with Perthes- and osteochondritis desiccans-type lesions. These hips progressed to roller-bearing-type joints with good function and no pain following conservative management of weight restriction and rest. 3 patients (aged 14, 22 and 30 yr at original presentation) suffered whole-head necrosis. Initially, these 3 patients had 4 hip joints replaced, 2 cemented-stemmed types, 1 cemented double-cup and 1 un-cemented hemiarthroplasty. All 4 joints failed and were revised 21–61 mo after the original operation. 1 of the revision hips has now failed and is awaiting further surgery

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Resar, 1996 <sup>451</sup>	Case report/case series	Bone infarction of skull	NR	Clinical presentation, bone scan, CT, MRI	IV hydration and analgesia, antibiotics	1	100	IV hydration and analgesia, antibiotics	NR	No	Patient discharged with a large, soft triangular protrusion on the right parietal region of his scalp that continued to resolve over the following weeks. MRI 17 mo later showed bony defects in the frontal bones compatible with previous infarction with complete resolution of the epidural hematomas
Rijke, 1990 <sup>453</sup>	Case report/case series	Bilateral protrusio acetabuli	Bilateral AVN of the femoral heads that is protruding through eroded acetabular roof	Pelvic x ray	Multiple blood transfusions, prednisone	1	100	Prednisone 50 to 60 mg/d Later decreased by 5mg every 3 mo	NR	No	A pelvic roentgenogram obtained at admission showed severe osteoporosis of the pelvis and femurs without evidence of the previously note osteosclerosis. There was further progression of the bilateral AVN of the femoral heads this time with widening and erosion of the acetabular roofs and severe protrusio acetabuli
Shah, 1993 <sup>474</sup>	Case report/case series	Severe destruction of the knee joints, with severe results. Pain at rest	NR	Clinical presentation, knee x ray	Knee arthroplasties	5	100	Prophylactic antibiotics, Cafazoline 1 g IV perioperatively, and then every 6 h for another 48 h. 3 patients also received Gentamicin 80 mg IV every 8 h for 48 h	2–6 weeks	No	The mean preoperative range-of-motion was 37–73° of flexion. At the final followup, this had improved to 3–85°. All the knees were clinically stable. 5 patients had no pain at followup, 2 had occasional pain, and 1 patient was taking regular analgesics. The radiographs at the final followup showed no signs of loosening. Infection in Case 4 led to removal of the prosthesis and arthrodesis. There were no hematological complications. The results were 6 excellent, 1 good, 1 satisfactory, and 1 poor, based on the H.S.S. (Hospital for Special Surgery) Knee Score
Shash, 2003 <sup>480</sup>	Case report/case series	AVN of the hip	NR	X ray, MRI	NR	1	100	NR	NR	No	Diagnosis of bilateral AVN of the hip was established with x ray and MRI studies
Washington, 1985 <sup>525</sup>	Case report/case series	AVN of the femoral head	NR	Radiographs demonstrated Legg-Perthes type lesions in all 3 cases	Conservative management	3	100	The patients were treated with prolonged crutch walking and partial weight-bearing and range-of-motion exercises	NR	No	In all 3 cases, the lesion healed with satisfactory restoration of femoral head congruency; and all 3 became asymptomatic, regained good range of motion of the involved hips, and were subsequently able to resume previous ambulation activities

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Ziegler, 2006 <sup>539</sup>	Case report/ case series	Necrosis of the femoral head	NR	X rays, MRI, CT, dynamic contrast arthrography	Surgery	1	100	A triple pelvic osteotomy was performed under general anesthesia. The technique as described in Tachdjian textbook was applied. Postoperatively the patient was kept in a hip spica with the left hip in 30° of abduction and 10° of flexion and neutral rotation for 6 weeks	NA	No	4.5 yr postoperatively, the patient remains free of relapse. The radiographs show nearly symmetrical hips with spherical femoral heads, but a slightly larger diameter of the affected hip

**Table 15. Leg Ulcer Incidence and Outcomes**

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	Medication details/transfusion details	Duration of treatment	Secondary/control arm	N of patients	Control treatment	Reported results
Baum, 1987 <sup>8</sup>	RCT	Chronic leg ulcers of at least 3 mo duration, and a positive bacterial swab	Clinical, bacterial swab	Antimicrobial therapy	15	Aerosol preparation of neomycin, bacitracin and polymyxin B	8 weeks	Placebo	13	Sterile normal saline with 1:1000 red food coloring added in an aerosol dispenser	Reduction in ulcer size was significantly greater in treatment group than in the control group ( $p<.05$ ). Pain was generally reduced in both treatment and control groups. Pain scores were initially higher in the controls, marked pain (grades 2–4) occurring in 14/20 ulcers compared to 8/20 ulcers in the treatment group. After 8 weeks, marked pain persisted in 7 of the 14 control ulcers but in none of the 8 ulcers in the treated group
La Grenade, 1993 <sup>28</sup>	RCT	Sickle cell disease (SCD) leg ulcers of at least 6 mo duration and of at least 3 cm in the smallest dimension	Clinical	Solcoseryl (deproteinized extract of calf blood) duoderm	12 legs, 14 ulcers	Jelly applied to ulcer surface twice daily after cleaning with eusol and ointment applied to ulcer margin and covered with gauze dressing and supported by a bandage Duoderm: hydroactive dressing sheet, applied to surface of ulcer covered with gauze and bandage replaced weekly	3 mo	Control received conventional conservative therapy	21 ulcers	Control therapy: twice daily cleaning with a mild antiseptic (eusol), wet dressing and bandage.	Duoderm was not tolerated as >½ of patients randomized to its group defaulted from this treatment. Solcoseryl increased ulcer healing compared to controls, but the difference was insignificant. Solcoseryl, however, was well tolerated
McMahon, 2010 <sup>30</sup>	RCT	SCD leg ulcers refractory to standard treatment	Clinical	Arginine butyrate + standard local care	14	Arginine butyrate at 500 mg/kg 5 d/week + standard care (twice daily cleaning and wet-to-dry dressing changes) for 12 weeks	3 mo	Control, standard care only	12	Standard local care alone	Control arm subjects had 25 ulcers with a mean area of 25.7 cm <sup>2</sup> initially and 23.2 cm <sup>2</sup> after 12 weeks; 2/25 (8%) healed completely. Treatment arm subjects had 37 ulcers with a mean area of 50.6 cm <sup>2</sup> initially and 28.3 cm <sup>2</sup> at 12 weeks; 11/37 of these (30%) healed completely. After 3 mo, proportions of ulcers that healed were 6/25 (24%) and 29/37 (78%), in the control and treatment arms, respectively ( $p<.001$ )
Serjeant, 1997 <sup>44</sup>	RCT	SCD leg ulcers of at least 6 mo duration and at least 3 cm in diameter	Clinical	Propionyl-L-carnitine	7	Propionyl-L-carnitine 2 g bid, po	12 weeks	Placebo	8	Placebo containing lactose and microcrystalline cellulose	Ulcer areas showed no obvious difference between treatment and placebo groups at the beginning of the baseline or at the beginning and end of the treatment period. Ulcer area decreased in 5 of 7 patients in the propionyl-L-carnitine group (71%) and in 4 of 8 in the placebo group (50%), but the degree of change did not differ significantly between the groups

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	Medication details/transfusion details	Duration of treatment	Secondary/control arm	N of patients	Control treatment	Reported results
Wethers, 1994 <sup>52</sup>	RCT	Full-thickness lower leg or ankle ulcers that did not involve tendon or bone and had persisted for at least 1 mo	Clinical presentation	Standard care + arginyl-glycyl-aspartic acid (RGD) peptide matrix (synthetic extracellular matrix)	27	Standard care consisted of weekly ulcer cleaning and debriding as needed	10 weeks	Placebo	21	Standard care + saline placebo	Healing in patients with chronic ulcers (2 mo or greater in duration) was significantly accelerated ( $p=.0085$ ) in RGD peptide matrix recipients compared with the placebo group. In these chronic ulcer cases, the average percent ulcer closure in the RGD peptide matrix group ( $54.4\pm 8.9\%$ ) exceeded that in the placebo group ( $19.0\pm 24.3\%$ ), nearly threefold by study endpoint. Furthermore, RGD peptide matrix was equally effective in promoting healing of long persistent ulcers and ulcers of shorter duration. In contrast, standard therapy plus placebo was significantly less effective ( $p=.001$ ) in promoting healing for ulcers of progressively greater duration
Cackovic, 1998 <sup>79</sup>	Obs, R	NR	Clinical presentation	Medical/surgical	18	Hydroxyurea (HU), human erythropoietin, arginine butyrate, topical hydrocolloid dressing, surgical debridement	2–24 mo (dressing)	No	NA	NA	All treatment attempts failed and ulcers recurred. Subsequently, all patients were treated with a topical hydrocolloid. The hydrocolloid dressing was Duoderm CGF. 8 of the patients who were never operated on healed in 2–16 mo (mean 6.4) with only 1 recurrence at 4 mo. Of the 10 operative patients treated with a hydrocolloid-type dressing, 6 healed for periods up to 30 mo; 2 patients had a recurrence and resolution at 18 and 24 mo after restarting the dressing. 2 patients did not get worse and did not heal
Okany, 2004 <sup>200</sup>	Obs, P	Chronic leg ulcers	Clinical presentation	Natural honey dressing	11 ulcers	Pure unrefined natural honey	30 d	Eusol dressing	8 ulcers	Eusol(1.25% chlorinated lime and 1.225% Boric acid solution)	No significant differences were found in rates of healing of the ulcers in either treatment groups

Study label	Design	Definition of complication	Diagnosis	Treatment	N of patients	Medication details/transfusion details	Duration of treatment	Secondary/control arm	N of patients	Control treatment	Reported results
Serjeant, 1970 <sup>210</sup>	Obs, P	Active SCD leg ulcers	Clinical presentation	Oral zinc sulphate	15	220 mg zinc sulphate, oral	6 mo	Placebo	14	220 mg lactose taken orally 3 times a day	The average initial ulcer area was 855 mm <sup>2</sup> in the treatment group and 689 mm <sup>2</sup> in the placebo group. In the placebo group, 8 cases improved whereas in the treatment group 13 cases showed improvement. The average rate of healing among the 13 patients showing healing in the treatment group was 8.1 mm <sup>2</sup> /d (1.6–26.5 mm <sup>2</sup> /d). Among the 8 patients showing healing in the placebo group, that rate was 2.8 mm <sup>2</sup> /d (1–5 mm <sup>2</sup> /d). 9 ulcers healed completely: 6 in the treatment group and 3 in the placebo group. They were mostly of small initial size (mean area 420 mm <sup>2</sup> ) compared to the average initial ulcer size of 774 mm <sup>2</sup> . 2 patients in the treatment group developed new ulcers during the trial when both had elevated serum zinc levels. The effect of oral zinc sulphate in the healing of sickle cell was found to produce a healing rate that was 3 times faster than that observed in the placebo group
Cacciola, 1989 <sup>273</sup>	Case series	NR1	Clinical	A combination of subcutaneous calcium heparin and human antithrombin concentrate	10	Human antithrombin III concentrate intravenously at 1000 U/48 h for 2 weeks then 1000 U/72 h. Subcutaneous calcium heparin injections at 150 U/kg/d	6 weeks	No	NA	NA	Following injections, antithrombin cofactor and antithrombin antigen levels showed a mean increase of 37%, which approached the normal range. Leg ulcers began to heal and skin became smooth

**Table 16. Other Complications Incidence and Outcomes**

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Bellet, 1995 <sup>9</sup>	RCT	Acute pulmonary complications	NR	Bone scan, chest radiographs	2 groups received spirometry vs. no spirometry	29 (38 events)	100	Different analgesic agents were used to treat pain. The narcotics included morphine, hydromorphone, meperidine, methadone, fentanyl, oxycodone, and codeine (with acetaminophen). The dosage was adjusted according to the patient's comfort or tolerance. Nonnarcotic analgesic agents included ketorolac, naproxen, ibuprofen, and acetaminophen. The amount of narcotics given during each hospitalization was recorded in milligrams of morphine equivalents per kilogram of body weight and for ketorolac in milligrams of morphine equivalents per kilogram, assuming that 30 mg of intravenous (IV) ketorolac equals 12 mg of IV morphine	Acute, during hospitalization	Yes	Pulmonary complications developed during only 1 of 19 hospitalizations of patients assigned to receive spirometry, as compared with 8 of 19 hospitalizations in the nonspirometry group ( $p=.019$ ). Logistic-regression analysis confirmed that the risk of pulmonary complications was lower during spirometry hospitalizations than during nonspirometry hospitalizations, even when adjusted for the amount of narcotics used during each hospitalization ( $p=.02$ )
Bader-Meunier, 2009 <sup>71</sup>	R, Obs	Cerebral vasculopathy	NR	Transcranial Doppler (TCD), magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA)	Chronic exchange transfusions	24	100	Patients who presented with an acute neurological event received 1 exchange transfusion equal to 1/2 of their blood volume within 24 h following stroke. Remaining patients were put on a monthly transfusion program as soon as abnormal velocities were identified on TCD. Subsequently, all patients received exchange transfusions at 3–5-week intervals to maintain hemoglobin levels between 9 and 10 g/dL and sickle cell hemoglobin (HbS) <30%	Unclear, chronically	No	Followup MRAs showed improvement, stabilization or worsening of cerebrovascular lesions in 11, 6 and 7 patients, respectively. Complete normalization of MRA was observed in 6 patients within a mean time of 1.4 yr, but stenosis recurred at the same location in the 4 patients in whom transfusion therapy was discontinued. Baseline severe stenosis/ occlusion of large cerebral arteries and occurrence of moyamoya syndrome were significantly associated with an absence of improvement of the cerebral vasculopathy
Bernaudin, 1997 <sup>72</sup>	R, Obs	Multiple: stroke, acute chest syndrome (ACS), osteonecrosis and osteomyelitis	NR	NR	Bone marrow transplant (BMT) from human leukocyte antigen identical sibling	26	100	BMT	NR	No	Death rate 10%; otherwise, all complications improved or resolved
de Montalembert, 2004 <sup>99</sup>	R, Obs	Myocardial ischemia	Children with chest pain, heart failure, abnormal electrocardiogram (ECG), left ventricular dilatation, or hypokinetic left ventricle	ECG, single photon emission computer tomography (SPECT)	Hydroxyurea (HU)	22	100	HU treatment was begun in 8 children who had myocardial perfusion defects and other complications of sickle cell disease (SCD). HU was given at 20 mg/kg/d	6 mo	No	Myocardial perfusion was abnormal in 14 of 22 patients, and normal in 8 as demonstrated by SPECT. In the 14 patients with abnormal perfusion, 9 had reversible defects, and 5 had fixed defects. HU was given to 8 patients. SPECT was repeated 6 mo later in 3 of them. 2 patients had reversible defects that had improved, and 1 had a fixed defect, the size of which had decreased

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Hassel, 1994 <sup>102</sup>	R, Obs	Acute multiorgan failure	Acute failure of lungs, liver and kidneys	Chest x ray, oximetry, liver function tests (LFTs), serum creatinine	Transfusion	14 (17 events)	100	Simple transfusion (8 cases); transfusing 4–12 U of blood. Exchange transfusion (9 cases); transfusing 8–18 U	Acutely	No	All 17 cases were treated with aggressive red cell exchange (RCE) transfusion as soon as clinical deterioration was recognized. Dramatic clinical improvement was noted within 24 h of the initiation of transfusion, with clearing of encephalopathy, increases in urine output in the oliguric patients and decreases in oxygen requirements in all but 1 patient. This patient, a 61-yr-old woman with hemoglobin SC disease (HbSC) and chronic lung disease, had progressive respiratory failure despite exchange transfusion and died of pulmonary fat emboli. All other patients showed rapid reversal of organ dysfunction. The mean number of days to discharge in the exchange transfusion group was 7 (4–17) compared to 15 (6–27) in the simple transfusion group. Organ function returned to normal in all patients in the exchange transfusion group, compared to 5 patients in the simple transfusion group (2 had elevated creatinine on followup, and 1 had no followup data)
Hijazi, 2005 <sup>105</sup>	R, Obs	ACS and vaso-occlusive crisis	ACS was defined as acute pulmonary symptoms associated with chest pain, clinical signs of parenchymal involvement and pulmonary infiltrates on radiography	PFTs	NR	38	Not clear	NR	NR	17 age, sex, and anemia matched controls (with hemoglobin H disease (HbH))	Compared to controls (both healthy and those with HbH), patients with SCD had lower forced vital capacity, vital capacity, and forced expiratory flow at 1 second suggesting early restrictive and obstructive pulmonary function pattern in steady state

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Gill, 1995 <sup>180</sup>	P, Obs	Multiple complications	A painful event was defined as pain in the extremities, back, abdomen, chest, or head for which no other explanation (e.g., osteomyelitis or appendicitis) could be found. Meningitis was defined as abnormal cerebrospinal fluid (CSF) findings and culture of CSF. Acute anemic episode was defined as either an acute splenic sequestration defined as a decrease of the hemoglobin or hematocrit level of at least 20% from baseline accompanied by an increase in palpated spleen size of at least 2 cm from baseline or as another acute anemic event defined by an acute reduction of the hemoglobin or hematocrit level of at least 30% from baseline and not caused by non-sickle cell problems	NR	Transfusion	703	100	Not clear	Not clear	No	Conclusions: Rates per 100 person-yr of ACS, pain crises, bacteremia, splenic sequestration, severe anemia and stroke are provided. ACS, stroke, and anemia were higher in HbSS compared to HbSS $\alpha$ -thal; whereas painful crises were lower in HbSS. Mortality was overall low (20 patients, all with HbSS genotype)

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Steinberg, 2003 <sup>501</sup>	P, Obs	SCD-related complications and mortality	NR	Central review of medical records, and autopsy results	HU	75	25	HU	12+ mo	No	75 (25%) of the original 299 patients died, 28% from pulmonary disease. Common causes of death: pulmonary disease: 21 patients; during crisis: 9 patients; sepsis/infection: 5 patients; cardiovascular disease: 3 patients; cerebrovascular: 6 patients; hepatic disease: 4 patients. Patients with reticulocyte counts <250,000/mm <sup>3</sup> and Hg levels <9 g/dL had increased mortality ( $p=.002$ ). Cumulative mortality at 9 yr was 28% when hemoglobin F (HbF) levels were <0.5 g/dL after the initial RCT was complete, compared with 15% when HbF levels were 0.5 g/dL or higher ( $p=.03$ ). Individuals who had ACS during the trial had 32% mortality compared with 18% of individuals without ACS ( $p=.02$ ). Patients with $\geq 3$ painful episodes per year during the trial had 27% mortality compared with 17% of patients with less frequent episodes ( $p=.06$ ). Taking HU was associated with a 40% reduction in mortality ( $p=.04$ ) in this observational followup with self-selected treatment
Ahmed, 2003 <sup>229</sup>	Case report/case series	Acute pancreatitis during sickle cell painful vaso-occlusive crisis (VOC)	NR	Serum amylase, lipase, abdominal computed tomography (CT), and lab tests	Intravenous fluid (IVF), antibiotics, and bowel rest and/or blood transfusion	4	100	Intravenous fluids, antibiotics, bowel rest and received several units of hemoglobin S-free blood, hydromorphone, total parental nutrition	NR	No	Symptoms resolved, amylase and lipase level decreased
Ali, 1978 <sup>242</sup>	Case report/case series	Choreiform activity	NR	Clinical presentation shows facial twitching, flicking of the tongue, and jerking of all extremities	NR	1	100	NR	NR	No	Resolved after 4 mo of onset
Al-Rashid, 1979 <sup>247</sup>	Case report/case series	Massive sequestration crisis	NR	Clinical presentation	IVF, exchange transfusion	1	100	IVF, exchange transfusion	6 h	No	Patient died

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Ataga, 2000 <sup>254</sup>	Case report/case series	Bone marrow necrosis, acute multi-organ failure syndrome (AMOFS)	The morphological definition of bone marrow necrosis includes the destruction of hematopoietic tissue and stroma within the marrow cavity along with preservation of cortical bone	Clinical exam/investigations	Antibiotics, analgesics, oxygen, transfusions	2	100	Case 1: Treated with analgesics and oxygen. Case 2: Packed red blood cells (PRBCs), 6 U. Case 3: Platelets, fresh frozen plasma (FFP) and PRBCs	1–4 weeks	No	Both patients achieved complete hematologic recovery
Ballas, 1998 <sup>258</sup>	Case report/case series	Pulmonary fat embolism	NR	Clinical presentation, lab data	Exploratory laparotomy	1	100	Exploratory laparotomy	3 d	No	Patient died after an exploratory laparotomy for suspected acute abdomen that turned out to be acute abdominal sickle pain (the patient was not a known case of SCD antemortem)
Chehal, 2002 <sup>280</sup>	Case report/case series	AMOFS and thrombotic thrombocytopenic purpura	NR	Blood studies, bone marrow aspirate	Exchange transfusion, plasma exchange	1	100	1.5 plasma volume on a daily basis	12 d	No	Complete recovery patient discharged in folic acid and HU
Conrad, 1998 <sup>285</sup>	Case report/case series	Aplastic crisis	Severe anemia and reticulocytopenia	Complete blood count (CBC) + bone marrow biopsy	Transfusion of PRBCs	2	100	PRBCs, 2 U/d for 2 d	Case 1: 11 d Case 2: 14 d	No	Symptoms improved, bone marrow biopsy on discharge showed erythroid hyperplasia

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Deyman, 2003 <sup>296</sup>	Case report/case series	Acute myocardial infarction (AMI)	NR	ECG, cardiac enzymes	Prochlorperazine (Compazine), oxygen, normal saline fluid bolus, dopamine, milrinone, norepinephrine, lidocaine, Ceftriaxone, and exchange transfusion	1	100	<p>Prochlorperazine (Compazine) was given for nausea, and his oxygen requirement increased rapidly after arriving on the ward. After receiving a 1 L of normal saline fluid bolus over 1 h, he developed respiratory failure and was intubated as he rapidly developed cardiogenic shock and ventricular dysrhythmia. Aggressive inotropic support with dopamine, milrinone, and norepinephrine was required to maintain his blood pressure in the low normal range. Ventricular tachycardia was treated with lidocaine during the initial phase of myocardial ischemia.</p> <p>Exchange transfusion to improve microvascular circulation in light of myocardial ischemia and dysfunction. The resulting HbS after exchange transfusion was 30% with a total hemoglobin of 10.5 mg/dL</p>	NR	No	The resulting HbS after exchange transfusion was 30% with a total hemoglobin of 10.5 mg/dL. Before exchange transfusion, his ECG showed paradoxical septal motion, severe global akinesis of the myocardium, and an unmeasurable ejection fraction (EF) on transthoracic ECG. 3 h after exchange transfusion, his myocardial contractility was dramatically improved and his EF was estimated to be 46%. During the next 24 h, his cardiogenic shock improved and he was weaned off inotrope on hospital d 4. He was extubated on hospital d 5. His ECG changes resolved within the first 24 h, and his ECG pattern returned to his baseline abnormalities with absent initial upward deflections of the QRS complex (R waves) in unipolar electrocardiograms (V <sub>1</sub> and V <sub>2</sub> ). His simple transfusion segment changes had resolved. On hospital d 10 a stress perfusion scan revealed no fixed or reversible perfusion deficits and an EF of 40%. He was started on beta-blockers and angiotensin-converting enzyme inhibition. Incidentally, the patient disclosed after extubation that he had experienced chest pain on the day of admission during physical exercise
Engelhardt, 1989 <sup>309</sup>	Case report/case series	Ischemic intestinal necrosis	Not defined	Clinical exam/investigations	Exploratory laparotomy followed by segmental ileocolectomy with ileostomy and colonic mucus fistula	1	100	Vancomycin (1 gm intravenously) and gentamycin (80 mg/L of dialysate) with continuous peritoneal dialysis. Exploratory laparotomy followed by segmental ileocolectomy with ileostomy and colonic mucus fistula	72 hours	No	Patient recovered after surgery

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Filipek, 2000 <sup>315</sup>	Case report/ case series	Transient aortic thrombus	NR	Chest radiograph, electrocardiogram, chest CT	Heparin, aspirin	1	100	A week after hospitalization her chest and back pain persisted and she had hypertensive episodes. (Systolic pressures exceeding 180 mmHg). The patient's EKG then showed mild T wave inversion of the anterolateral leads, but no Q wave formation suggesting subendocardial ischemia versus transmural infarction. Subsequently, chest MRI was performed to further examine the aorta. The MRI also revealed intraluminal filling defect, with signal characteristics of acute thrombus. Patient was started on IV heparin and daily aspirin	NR	No	The patient was readmitted with chest pain 3 mo later and followup contrast-enhanced CT was performed. CT showed resolution of the thrombus in the aorta. The transient nature of the intraluminal filling defect in the aorta supported acute thrombus that had subsequently resolved. Aortic plaque would not spontaneously resolve in 3 mo
Horton, 1995 <sup>348</sup>	Case report/ case series	Fat embolism syndrome (FES)	FES classically involves the lungs, brain and skin and can often be fatal and may not be recognized before autopsy. It usually occurs after trauma with long bone fractures but may also be associated with nontraumatic conditions like connective tissue disorders, Insulin-dependent diabetes mellitus, cardiopulmonary bypass, pancreatitis, fatty liver, lipid infusion, anesthesia, SCD, etc.	Clinical exam/ investigations	Exchange transfusion, prednisone, phenytoin, haloperidol	1	100	Exchange transfusion, prednisone, phenytoin, haloperidol	8 weeks	No	2 mo after discharge from rehabilitation facility, all neurologic, psychiatric, and intellectual deficits were resolved and patient is stable on a monthly transfusion program
Karim, 2002 <sup>361</sup>	Case report/ case series	Fulminant ischemic colitis	NR	Abdominal CT, sigmoidoscopy	IV antibiotics, analgesics, surgery	1	100	IV ceftriaxone and azithromycin, hydromorphone, emergency total colectomy, and partial small bowel resection	NR	No	The patient continued to deteriorate, became hypotensive, and developed a severe coagulopathy and died
Kleinman, 1981 <sup>370</sup>	Case report/ case series	Acute respiratory distress	NR	NR	Erythrocytapheresis	1	100	RCE transfusion, otherwise not specified	Acutely	No	All patients treated with erythrocytapheresis for acute complication responded favorably with resolution of symptoms within 24–48 h. However, 1 patient who was apparently treated successfully returned 1 mo later with respiratory distress accompanied by clinical evidence of right ventricular failure. The patient died before any therapy could be initiated

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Kumar, 2007 <sup>378</sup>	Case report/case series	Portal hypertension	Patient presented with pain in abdomen, fever, joint pain, and hematemesis. Abdomen was soft and tender; spleen was palpable, nontender and firm	Abdominal imaging revealed splenomegaly, upper gastrointestinal (GI) endoscopy	Band ligation of esophageal varices	1	100	IVFs and pentazocine. On the 2nd d she was started on oral NSAIDs (nonsteroidal anti-inflammatory drugs) for her joint pains	NR	No	On the 3rd d she vomited about 1.5 L of blood. She was shifted to the intensive care unit (ICU) and was resuscitated. The patient underwent band ligation of varices and was well on propranolol and folic acid supplements
Loutfy, 1997 <sup>398</sup>	Case report/case series	AMI	NR	ECG, cardiac enzymes	Pain: Fluids, analgesia, and IV antibiotics. AMI: IV nitrogen, heparin, aspirin, rehydration. Transfusion	1	100	Patient was treated with RCE transfusion in the hospital and then received a 6-mo course of simple transfusion to maintain HbS concentration <30% (2 U PRBCs every 3–4 weeks)	6 mo	No	Serial ECGs revealed pathologic initial downward deflection of the QRS complex (Q waves) in leads I, automated volt left, V3–V6 normalization of simple transfusion segments and left ventricular hypertrophy. 2D ECG revealed a grade 2/4 left ventricle, normal right ventricle size and function. Recovery was uneventful and the patient was discharged 18 d later. Simple transfusion was stopped after 6 mo due to difficulty of finding antigen-matched units (5 alloantibodies present)
Markowitz, 1980 <sup>407</sup>	Case report/case series	Focal nodular hyperplasia of the liver	Back pain, fever; abdomen was distended and painful; liver edge was palpable 3 cm below the right costal margin; scan found a large defect. On admission hemoglobin was 8.5 g/dL	Physical examination, liver-spleen radionuclide scan, ultrasound (US), selective hepatic arteriography	Her large tumor mass in her liver was excised by blunt dissection	1	100	IVFs and meperidine	NR	No	The patient became profoundly hypotensive and required cardiac resuscitation during surgery. She remained comatose with signs of severe nervous system damage and died 19 d later
Nachmann, 2003 <sup>426</sup>	Case report/case series	Superficial thrombophlebitis of the penis	NR	US, Doppler	Naproxen sodium	1	100	550 mg naproxen sodium twice daily + warm compresses	6 weeks	No	Painless erections and no palpable cord along the dorsum of his penis after 6 weeks

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
O'Neil, 2001 <sup>434</sup>	Case report/case series	Severe anemia	NR	CBC	Transfusion, analgesics	2	100	Case 1: oxygen was provided via 100% nonrebreather, two 20 g IV lines were placed, and a fluid bolus of 40 cc/kg 0.9% saline. The patient was transfused with 5 cc/kg of uncross-matched blood in the ED and later 5 cc/kg of uncross-matched blood Case 2: oxygen was provided via face mask at 35%. A 22 g IV was established and blood work was obtained. Morphine 0.1 mg/kg and 0.9% normal saline solution 20 cc/kg were administered. Due to the fever, ceftriaxone 2 g IV was given. The patient's pain was managed with IV morphine as needed for the first 3 days, and then switched to oral morphine after that. IV fluids were continued for the first 2 days, and antipyretics were administered as needed	Case 1: 7d Case 2: 8 d	No	Resolution of severe anemia
Roohi, 2001 <sup>457</sup>	Case report/case series	Mono-neuropathy Multiplex	NR	Nerve conduction studies	None	1	100	NR	NA	No	Neurologic picture gradually improved without any specific treatment for the neuropathy
Sherman, 2004 <sup>483</sup>	Case report/case series	AMI	NR	Physical exam, ECG	Adenosine, aspirin, analgesics, transfusions	1	100	Adenosine 6 mg was administered intravenously and the rhythm converted to normal sinus. The patient was placed on continuous monitoring and given aspirin (4× 81 mg). He was treated with opiates for the persistent extremity pain. The patient required additional doses of morphine over the next 2 h to control the pain in the extremities. Laboratory results revealed hemoglobin 7.9 g/dL. The patient was transfused 2 U of PRBCs secondary to worsening anemia with a hemoglobin of 6.6 g/dL	NR	No	A transthoracic echocardiogram at 24 h postadmission demonstrated no regional wall motion abnormalities, moderate left ventricular hypertrophy, and normal left ventricular systolic function. He was discharged on hospital d 8 without any further sequelae
Van de Pette, 1982 <sup>513</sup>	Case report/case series	Life-threatening sickling crises (ACS, infarctive sickling crises)	NR	Clinical presentation	Exchange transfusion	5	100	Exchange transfusion decreasing HbS to <20%	Unclear	No	The exchange transfusion was successful in managing life-threatening sickling crises

Study label	Design	Specific complication	Definition of complication	Diagnosis	Treatment	N of patients	% of patients	Treatment/medication details	Duration of treatment	Secondary/control arm	Reported results
Wang, 2004 <sup>523</sup>	Case report/case series	ST elevation myocardial infarction	NR	ECG, serum cardiac enzymes	Aspirin and sublingual nitroglycerin were given, followed by heparin, metoprolol, and nitroglycerin paste and eventual blood transfusion	1	100	She underwent emergent red blood cell (RBC) exchange transfusion	NR	No	Her chest pain gradually resolved; her simple transfusion segment elevations improved significantly and her 1st deflections in the electrocardiogram following QRS complex (T waves) flattened and inverted, but she did not develop initial downward deflections of the QRS complex (Q waves). An ECG revealed concentric left ventricular hypertrophy with normal wall motion. Heparin, metoprolol, and nitroglycerin paste were added to her treatment regimen. She underwent emergent RBC exchange transfusion. Repeat hemoglobin electrophoresis after RBC exchange revealed a significant reduction of HbS to 14.6% and hemoglobin C (HbC) to 15.6%. Cardiac catheterization demonstrated normal coronary arteries. A subsequent persantine-thallium myocardial perfusion test showed no evidence of reversible ischemia
Wu, 1999 <sup>533</sup>	Case report/case series	Purpura	NR	Clinical presentation	Steroids	1	100	Low-potency topical steroid	NR	No	Patient recovered
Yeghen, 1995 <sup>536</sup>	Case report/case series	Right atrial thrombosis	NR	ECG	Streptokinase, heparin, warfarin	1	100	Streptokinase 500,000 U bolus then 90,000 U/d maintenance, heparin 30,000 U/d, warfarin for 6 mo	6 mo	No	Rapid clinical improvement and complete resolution of the thrombus was seen in electrocardiograph 24 h after administration of streptokinase

**Table 17. Randomized Controlled Trials Identified Through Supplemental Search (June 1, 2010–July 11, 2014)\*: Management of Sickle Cell Disease Complications**

Author, year	Location	Recruitment	Inclusion criteria	Intervention	Planned duration of treatment	Patient groups Intervention (N)	Age, mean (range) years	% Male	Genotype/haplotype, (%)	Methodological quality	Main findings (efficacy and side effects)
Gladwin, 2011 <sup>545</sup>	United States	NR	SCD ≥10 yr presenting with VOC	Nitric oxide for inhalation at a concentration of 800 ppm balanced with nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide) Placebo study: Gas was 100% grade 5 nitrogen gas	At least 8 h (max 72 h)	Nitric oxide (75) Placebo (75)	23	50	91% SS or SS β <sup>+</sup> -thal	Low risk of bias Patients and investigation blinded, allocation concealed, no loss to followup	No significant change in the time to resolution of crisis (73.0 h vs. 65.5 h, <i>p</i> =.87); no significant differences in multiple secondary outcome Side effects: No serious side effects
Morris, 2013 <sup>546</sup>	United States	NR	Children with an established diagnosis of SCD and VOC requiring parenteral opioids and admission	L-arginine hydrochloride (100 mg/kg/dose 3 times/d)	Up to a maximum dose of 10 g for 15 doses or until discharge	Arginine (26) Placebo (28)	14 (3–19)	48	SS (72%), SC (19%), Sβ <sup>+</sup> -thal (9%)	Moderate risk of bias Double-blinded (unclear who was blinded), unclear allocation concealment, 4 patients lost to followup	A significant reduction in total parenteral opioid use by 54% (1.9±2.0 mg/kg vs. 4.1±4.1 mg/kg, <i>p</i> =0.02) and lower pain scores at discharge (1.9±2.4 vs. 3.9±2.9, <i>p</i> =0.01) were observed in the treatment arm compared to placebo; no significant difference in hospital length of stay Side effects: None
Goldman, 2013 <sup>547</sup>	Canada	NR	Children with known SCD requiring admission for VOC	IV magnesium sulfate (MgSO <sub>4</sub> ) (100 mg/kg, maximum of 2 g/dose) 8 times per hour or IV placebo	8 times per hour until discharge (single admission)	MgSO <sub>4</sub> (51) Placebo (53)	12	26	SS (59%) SC (28%) Sβ <sup>+</sup> -thal (13%)	Low risk of bias Investigators, physicians, nurses, parents, and patients were blinded and allocation was concealed	No significant difference between groups for pain scores or analgesic requirements Side effects: No serious events, pain at the infusion site (14%)
Daak, 2013 <sup>548</sup>	Sudan	April 2009 to May 2010	In steady state (no fever or crisis in 4 weeks)	Daily 1 (2–4 years old; median weight: 13 kg), 2 (5–10; median weight: 25 kg), 3 (11–16; median weight: 37 kg), or 4 (17–24; median weight: 51 kg) omega-3 or placebo capsules	1 yr	Omega-3 fatty acid (70) Placebo (70)	8 (2–24)	40	SS	Low risk of bias Patients and investigators blinded, allocation concealed 15/140 lost to followup	Omega-3 fatty acid reduced the median rate of clinical vaso-occlusive events (0 compared with 1.0 per year, <i>p</i> <0.0001), severe anemia (3.2% compared with 16.4%; <i>p</i> <0.05), blood transfusion (4.5% compared with 16.4%; <i>p</i> <0.05) Side effects: Dyspepsia (2 in each arm)
Burnett, 2014 <sup>549</sup>	United States	June 2008 to November 2012	Confirmed SS or SC aged 14 to 45 yr, with at least 2 priapism episodes per week	Daily sildenafil 50 mg or placebo for 8 weeks followed by open-label sildenafil 50 mg to all participants	8 weeks	Sildenafil (6) Placebo (7)	22 23	100	SS and SC	Moderate risk of bias Double-blind (unclear who was blinded), unclear allocation concealment, 6 patients lost to followup	Priapism frequency reduction by 50% did not differ between sildenafil and placebo groups ( <i>p</i> =1.0). Side effects: No serious events; 33% had flushing

\* A supplemental search was conducted on July 11, 2014, to identify randomized controlled trials (RCTs) published after May 2010. The search was done in Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for RCTs of sickle cell disease (SCD). Two hundred seventeen citations were retrieved; of these, eight trials were included, with only five that were relevant to the Acute and Chronic complications chapters. Only trials of interventions that addressed the management of SCD or related complications were included.

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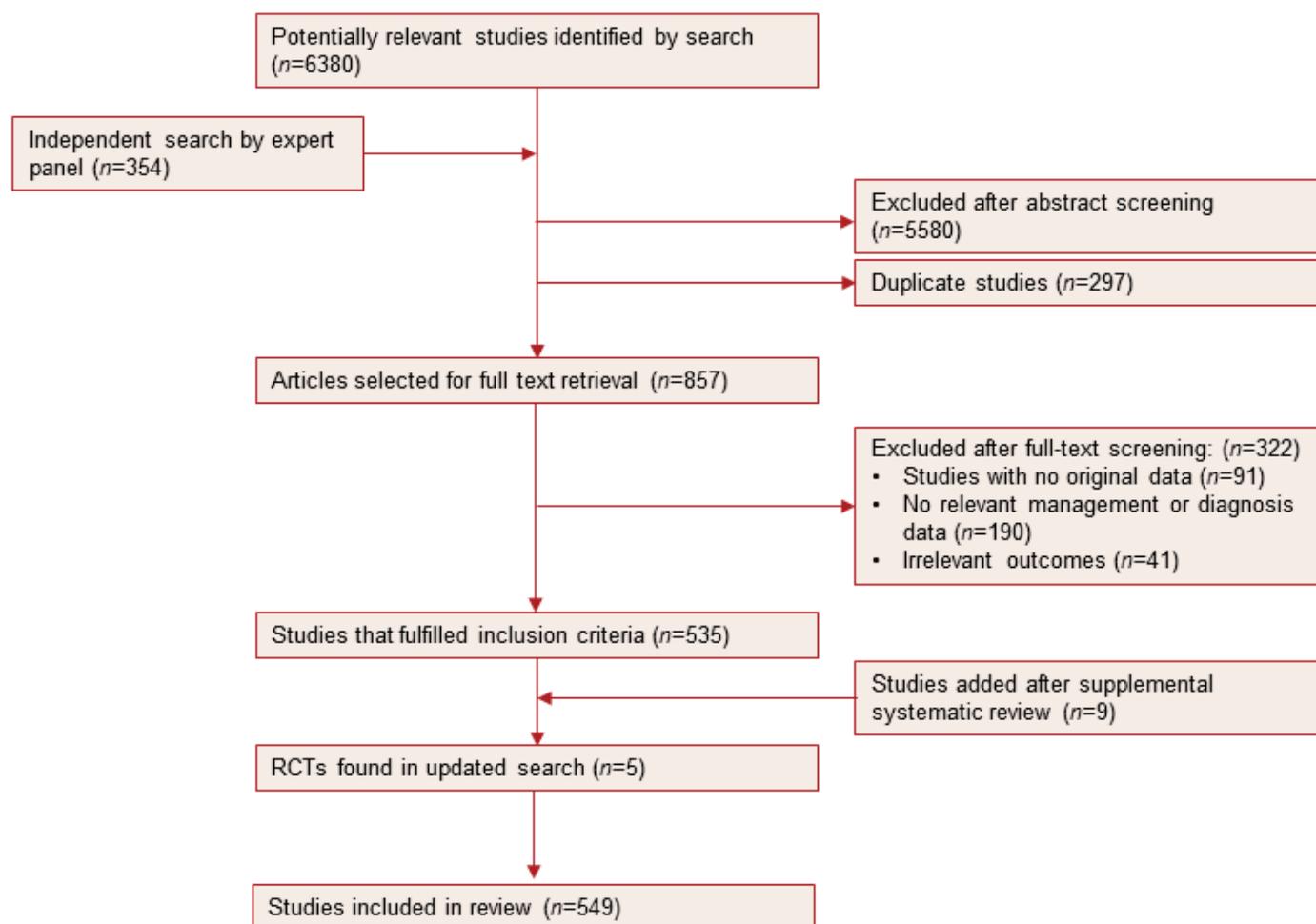
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## Appendix A: Study Selection Process



### Evidence Selection

Study selection started by screening abstracts for eligibility followed by screening of full-text articles. Both steps followed an a priori established protocol. Study selection and data extraction were performed using piloted online reference management software (Distiller SR™). Abstracts were reviewed in duplicates until adequate inter-reviewer agreement was observed (kappa statistic  $\geq 0.90$ ). Data extraction was done by one reviewer and confirmed by a second reviewer. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was used to evaluate the quality of the evidence.

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## Appendix B: Methods

### The Critical Question of the Systematic Review (PICOS)\*

**Patients:**

Patients with SCD and chronic or acute complications

**Intervention/Comparison:**

Alternative management and diagnosis strategies

**Outcomes:**

- Complication-specific outcomes including resolution of complication
- General SCD outcomes if relevant (death, stroke, pain crises, need for transfusion, hemoglobin and hemoglobin F levels)
- Outcomes of diagnostic studies: accuracy of diagnosis if reported

**Study design:**

Randomized or nonrandomized including case reports of rare complications

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\* PICOS = patients, intervention, comparison, outcomes, and study design.

## Appendix C: Data Sources and Search Strategies

A comprehensive search of several databases (from 1970 to July 2010, English language, any population) was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the Guideline methodologist. Controlled vocabulary supplemented with keywords was used to search for the topic: diagnosis and treatment of sickle cell disease complications. Additional references were identified by consulting with experts in the field.

### OID

Databases: EMBASE 1988 to 2010 Week 34, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to 2010, EBM Reviews—Cochrane Central Register of Controlled Trials 2nd Quarter 2010 Cochrane Database of Systematic Reviews

### Search Strategy

#	Searches	Results
1	exp Anemia, Sickle Cell/	28839
2	(sickle cell or "hemoglobin s" or drepanocytomia or "drepanocytic anemia" or drepanocytosis or "hemoglobin ss" or meniscocytosis or "sickle anemia" or "ss disease" or "hemoglobin sc").mp.	33041
3	1 or 2	33042
4	exp Pain/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	127359
5	exp pain/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	151550
6	exp Fever/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	6775
7	exp fever/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	8830
8	exp infection/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	612452
9	exp Infection/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	202441
10	exp Seizures/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	8997
11	exp seizure/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	15104
12	exp Stroke/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	20470
13	exp stroke/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	21274
14	exp transient ischemic attack/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	4135
15	exp Ischemic Attack, Transient/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	5693
16	exp Acute Chest Syndrome/di, dt, th [Diagnosis, Drug Therapy, Therapy]	150
17	exp acute chest syndrome/di, dm, dt, su, th [Diagnosis, Disease Management, Drug Therapy, Surgery, Therapy]	141
18	exp respiratory distress/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	13355
19	exp Respiratory Distress Syndrome, Adult/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	6502
20	exp Opioid-Related Disorders/di, dt, su, th [Diagnosis, Drug Therapy, Surgery, Therapy]	7225

#	Searches	Results
21	exp opiate addiction/di, dm, dt, su, th [Diagnosis, Disease Management, Drug Therapy, Surgery, Therapy]	3242
22	exp Femur Head Necrosis/di, dt, rt, su, th [Diagnosis, Drug Therapy, Radiotherapy, Surgery, Therapy]	4711
23	exp femur head necrosis/dm, dt, rt, su, th [Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	1266
24	exp depression/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	81861
25	exp Depression/di, dh, dt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Surgery, Therapy]	26506
26	exp Depressive Disorder/di, dh, dt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Surgery, Therapy]	49757
27	exp anxiety/di, dt, th [Diagnosis, Drug Therapy, Therapy]	13427
28	exp Anxiety/di, dh, dt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Surgery, Therapy]	11585
29	exp Anxiety Disorders/di, dh, dt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Surgery, Therapy]	34996
30	exp anxiety disorder/di, dm, dt, su, th [Diagnosis, Disease Management, Drug Therapy, Surgery, Therapy]	36941
31	exp addiction/di, dm, dt, su, th [Diagnosis, Disease Management, Drug Therapy, Surgery, Therapy]	29946
32	exp Substance-Related Disorders/di, dh, dt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Surgery, Therapy]	46879
33	exp Alcoholism/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	14891
34	exp alcoholism/di, dm, dt, su, th [Diagnosis, Disease Management, Drug Therapy, Surgery, Therapy]	10690
35	exp gallstone/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	4287
36	exp Gallstones/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	5810
37	exp Cholelithiasis/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	18186
38	exp cholelithiasis/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	14793
39	exp kidney disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	150532
40	exp Kidney Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	156360
41	exp Hypertension, Pulmonary/di, dt, rt, su, th [Diagnosis, Drug Therapy, Radiotherapy, Surgery, Therapy]	20573
42	exp pulmonary hypertension/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	11691
43	exp Behavior, Addictive/di, dt, su, th [Diagnosis, Drug Therapy, Surgery, Therapy]	30533
44	exp Cholecystectomy/	43701
45	exp spleen disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	9824
46	exp Splenic Diseases/di, dt, rt, su, th [Diagnosis, Drug Therapy, Radiotherapy, Surgery, Therapy]	16794
47	exp Central Nervous System Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	407861
48	exp central nervous system disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	432672
49	exp cholecystitis/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	5425
50	exp Cholecystitis/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	6715
51	exp Cholestasis, Intrahepatic/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	3916
52	exp intrahepatic cholestasis/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	1151
53	exp priapism/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	915

#	Searches	Results
54	exp Priapism/di, dt, rt, su, th [Diagnosis, Drug Therapy, Radiotherapy, Surgery, Therapy]	1909
55	exp Eye Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	184338
56	exp eye disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	176306
57	retina artery occlusion/di, dm, dt, su, th [Diagnosis, Disease Management, Drug Therapy, Surgery, Therapy]	622
58	exp Retinal Artery Occlusion/di, dt, rt, su, th [Diagnosis, Drug Therapy, Radiotherapy, Surgery, Therapy]	1836
59	exp Retinal Detachment/di, dt, rt, su, th [Diagnosis, Drug Therapy, Radiotherapy, Surgery, Therapy]	15214
60	exp retina detachment/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	5919
61	exp vitreous hemorrhage/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	1038
62	exp Vitreous Hemorrhage/di, dt, rt, su, th [Diagnosis, Drug Therapy, Radiotherapy, Surgery, Therapy]	1765
63	exp Heart Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	407282
64	exp heart disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	336702
65	exp liver function test/	37575
66	exp Pancreatitis/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	17000
67	exp pancreatitis/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	15616
68	exp gastrointestinal disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	7660
69	exp Gastrointestinal Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	326178
70	exp Liver Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	142750
71	exp liver disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	149718
72	exp biliary tract disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	46712
73	exp Biliary Tract Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	54715
74	exp Osteomyelitis/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	8536
75	exp osteomyelitis/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	10264
76	exp leg ulcer/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	3475
77	exp Leg Ulcer/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	9210
78	exp Delirium, Dementia, Amnestic, Cognitive Disorders/di, dh, dt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Surgery, Therapy]	57302
79	exp cognitive defect/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	12862
80	exp mental disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	313966
81	exp Mental Disorders/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	356233
82	exp Migraine Disorders/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	10284
83	exp migraine/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	13748
84	exp headache/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	10116
85	exp Headache/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	6364
86	exp Lung Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	271522

#	Searches	Results
87	exp lung disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	229750
88	exp urogenital tract disease/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	469583
89	exp Female Urogenital Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	414141
90	exp Male Urogenital Diseases/di, dt, su, th [Diagnosis, Drug Therapy, Surgery, Therapy]	824239
91	exp Urologic Diseases/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	250750
92	exp Hematuria/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	2310
93	exp hematuria/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	2335
94	exp proteinuria/di, dm, dt, rt, su, th [Diagnosis, Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	6662
95	exp Proteinuria/di, dh, dt, rt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	6202
96	exp Splenic Infarction/di, dt, su, th [Diagnosis, Drug Therapy, Surgery, Therapy]	704
97	exp spleen infarction/di, dt, su, th [Diagnosis, Drug Therapy, Surgery, Therapy]	468
98	exp iron overload/di, dm, dt, su, th [Diagnosis, Disease Management, Drug Therapy, Surgery, Therapy]	1819
99	exp Iron Overload/di, dh, dt, su, th [Diagnosis, Diet Therapy, Drug Therapy, Surgery, Therapy]	3370
100	(complication* or pain or fever or infection* or seizure* or stroke* or "transient ischemic attack*" or "acute chest syndrome" or "respiratory distress" or ((opiate or opioid or drug or substance) adj2 (addiction or dependency or disorder*)) or depression or "depressive disorder*" or anxiety or addiction or addictive or alcoholism or gallstone* or cholelithiasis or kidney or liver or renal or hepatic or spleen or splenic or eye or ocular or ophthalmologic or "nervous system" or cns or heart or cardiac or gastrointestinal or "biliary tract" or lung or urogenital or urologic or "pulmonary hypertension" or cholecystectomy or cholecystitis or cholestasis or priapism or (retina* adj2 (occlus* or detachment)) or "vitreous hemorrhage" or pancreatitis or osteomyelitis or "leg ulcer*" or delirium or dementia or amnes* or cognitive or cognition or mental or "neuro-psyc*" or neuropsych* or migraine* or headache* or hematuria or proteinuria or "iron overload" or "tubular necrosis" or "avascular necrosis" or avn or "pseudo-addict*" or pseudoaddict* or (opioid adj2 monitor*) or ((femur or femoral or hip) adj2 necrosis)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	11641977
101	(management* or treat* or therap* or surgery or radiotherap*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	9905663
102	100 and 101	4703219
103	or/4-99	5220817
104	3 and (102 or 103)	10796
105	limit 104 to english language [Limit not valid in CCTR,CDSR; records were retained]	9815
106	limit 105 to yr="1970 -Current"	9744
107	limit 106 to (editorial or letter or news) [Limit not valid in EMBASE,CDSR; records were retained]	616
108	106 not 107	9128
109	limit 108 to yr="2000 -Current"	5637
110	remove duplicates from 109	3793
111	108 not 109	3491
112	remove duplicates from 111	2494
113	110 or 112	6287

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## Scopus

1. TITLE-ABS-KEY("sickle cell" OR "hemoglobin s" OR drepanocytomia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease" OR "hemoglobin sc")
2. TITLE-ABS-KEY("complication\*" OR pain OR fever OR infection\* OR seizure\* OR stroke\* OR "transient ischemic attack\*" OR "acute chest syndrome" OR "respiratory distress" OR (opiate W/2 addiction) OR (opiate W/2 dependency) OR (opiate W/2 disorder\*) OR (opioid W/2 addiction) OR (opioid W/2 dependency) OR (opioid W/2 disorder\*) OR (drug W/2 addiction) OR (drug W/2 dependency) OR (drug W/2 disorder\*) OR (substance W/2 addiction) OR (substance W/2 dependency) OR (substance W/2 disorder\*) OR depression OR "depressive disorder\*" OR anxiety OR addiction OR addictive OR alcoholism OR gallstone\* OR cholelithiasis OR kidney OR liver OR renal OR hepatic OR spleen OR splenic OR eye OR ocular OR ophthalmologic OR "nervous system" OR cns OR heart OR cardiac OR gastrointestinal OR "biliary tract" OR lung OR urogenital OR urologic OR "pulmonary hypertension" OR cholecystectomy OR cholecystitis OR cholestasis OR priapism OR (retina\* W/2 occlus\*) OR (retina\* W/2 detachment) OR "vitreous hemorrhage" OR pancreatitis OR osteomyelitis OR "leg ulcer\*" OR delirium OR dementia OR amnes\* OR cognitive OR cognition OR mental OR "neuro-psyc\*" OR neuropsych\* OR migraine\* OR headache\* OR hematuria OR proteinuria OR "iron overload" OR "tubular necrosis" OR "avascular necrosis" OR avn OR "pseudo-addict\*" OR pseudoaddict\* OR (opioid W/2 monitor\*) OR (femur W/2 necrosis) OR (femoral W/2 necrosis) OR (hip W/2 necrosis))
3. TITLE-ABS-KEY("management\*" OR treat\* OR therap\* OR surgery OR radiotherap\*)
4. PUBYEAR AFT 1969 AND LANGUAGE(english)
5. PMID(0\*) OR PMID(1\*) OR PMID(2\*) OR PMID(3\*) OR PMID(4\*) OR PMID(5\*) OR PMID(6\*) OR PMID(7\*) OR PMID(8\*) OR PMID(9\*)
6. (1 and 2 and 3 and 4) and not 5

## Supplemental Search Strategy for Studies of Leg Ulcers in SCD

### OID

Database(s): EMBASE 1988 to 2011 Week 10, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Central Register of Controlled Trials 1st Quarter 2011, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to February 2011

### Search Strategy

#	Searches	Results
1	exp Leg Ulcer/	22460
2	(leg adj3 ulcer*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui, kw, tx, ct]	17497
3	1 or 2	25125
4	exp Anemia, Sickle Cell/	30155
5	(sickle cell or "hemoglobin s" or drepanocytomia or "drepanocytic anemia" or drepanocytosis or "hemoglobin ss" or meniscocytosis or "sickle anemia" or "ss disease" or "hemoglobin sc").mp.	34585
6	4 or 5	34586
7	3 and 6	564
8	remove duplicates from 7	403
9	limit 8 to english language [Limit not valid in CCTR,CDSR; records were retained]	381
10	limit 9 to yr="1970 -Current"	369
11	exp case study/	1514767
12	exp Cohort Studies/	1253849
13	exp longitudinal study/	835446
14	exp retrospective study/	588918
15	exp prospective study/	503717
16	exp observational study/	18754
17	exp comparative study/	2128559
18	exp clinical trial/	1439726
19	exp evaluation/	1034483
20	exp twins/	37655
21	exp validation study/	25431
22	exp experimental study/ or exp field study/ or exp in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/	6585950
23	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	6525308

#	Searches	Results
24	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui, kw, tx, ct]	141532
25	or/11-24	12323062
26	exp controlled study/	3491656
27	exp evidence based medicine/	493310
28	evidence-based.mp.	160871
29	((control\$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui, kw, tx, ct]	4462008
30	meta analysis/	80533
31	meta-analys\$.mp.	126160
32	exp "systematic review"/	39111
33	systematic review\$.mp.	87114
34	exp Guideline/ or exp Practice Guideline/	260237
35	guideline\$.ti.	81118
36	or/26-35	4944627
37	10 and (25 or 36)	187
38	from 10 keep 124-352	229
39	limit 38 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study or validation studies) [Limit not valid in EMBASE,CCTR,CDSR; records were retained]	32
40	37 or 39	187
41	limit 40 to (book or book series or editorial or erratum or letter or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legislation or news or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in EMBASE,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	29
42	from 41 keep 1-18	18
43	40 not 42	169
44	limit 43 to human [Limit not valid in CCTR,CDSR; records were retained]	161
45	limit 44 to humans [Limit not valid in CCTR,CDSR; records were retained]	161

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## Scopus

1. TITLE-ABS-KEY(leg w/3 ulcer\*)
2. TITLE-ABS-KEY("sickle cell" OR "hemoglobin s" OR drepanocytomia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease" OR "hemoglobin sc")
3. 1 and 2
4. TITLE-ABS-KEY( (evidence W/1 based) OR (meta W/1 analys\*) OR (systematic\* W/2 review\*) OR guideline OR (control\* W/2 stud\*) OR (control\* W/2 trial\*) OR (randomized W/2 stud\*) OR (randomized W/2 trial\*))
5. TITLE-ABS-KEY("comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey")
6. TITLE-ABS-KEY("retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis")
7. TITLE-ABS-KEY("incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis")
8. TITLE-ABS-KEY("observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies")
9. TITLE-ABS-KEY("clinical study" OR "clinical trial" or "evaluation study" OR "evaluation survey" OR "evaluation analysis" or "twin study" OR "twin survey" OR "twin analysis" or "validation study" OR "validation survey" OR "validation analysis" or "experimental study" OR "experimental analysis" or "field study" OR "field survey" OR "field analysis" or "in vivo study" OR "in vivo analysis" or "panel study" OR "panel survey" OR "panel analysis" or "pilot study" OR "pilot survey" OR "pilot analysis" or "prevention study" OR "prevention survey" OR "prevention analysis" or "replication study" OR "replication analysis" or "theoretical study" OR "theoretical analysis" or "trend study" OR "trend survey" OR "trend analysis")
10. 4 or 5 or 6 or 7 or 8 or 9
11. 3 and 10
12. PUBYEAR AFT 1969 AND LANGUAGE(english)
13. 11 and 12
14. PMID(0\*) OR PMID(1\*) OR PMID(2\*) OR PMID(3\*) OR PMID(4\*) OR PMID(5\*) OR PMID(6\*) OR PMID(7\*) OR PMID(8\*) OR PMID(9\*)
15. 13 and not 14
16. DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
17. 15 and not 16

## Appendix D: Excluded Studies

Author	Year	Title	Reason for Exclusion
Abdulrahman	2004	The kidney in sickle cell disease: Pathophysiology and clinical review	Not original research
Acsargn	2001	Hypnotic intervention for pain management in a child with sickle cell anemia	Not original research
Adams	1996	Caring for the pregnant woman with sickle cell crisis	Not original research
Adams	1998	Transfusion to prevent first stroke in children with sickle cell anemia	Not original research
Adams-Graves	2009	Title not available	No relevant management or diagnosis data
Adawy	2005	Day case management of painful sickle cell crisis in children using patient controlled analgesia	Not original research
Adekile	1988	Persistent gross splenomegaly in Nigerian patients with sickle cell anaemia: relationship to malaria	No relevant management or diagnosis data
Adewoye	2007	Effectiveness of a dedicated day hospital for management of acute sickle cell pain	Irrelevant outcomes
Agargun	2001	Hypnotic intervention for pain management in a child with sickle cell anemia	Irrelevant outcomes
Ahmed	2000	Erythrocyte sedimentation rate during steady state, painful crisis and infection in children with sickle cell disease	No relevant management or diagnosis data
Akenzua	1992	Alpha-hydroxybutyrate dehydrogenase and the diagnosis of painful crisis in sickle cell anaemia.	No relevant management or diagnosis data
Akinyanju	1979	Leg ulceration in sickle cell disease in Nigeria	No relevant management or diagnosis data
Akyurek Savas	2006	Chronic liver disease in a patient with sickle cell anemia	No relevant management or diagnosis data
Al-Amro	1997	Endogenous bacterial endophthalmitis in sickle cell anemia	No relevant management or diagnosis data
Alaud-Din	1998	Laparoscopic cholecystectomy and appendectomy with sickle cell disease	Irrelevant outcomes
Aldrich	1996	Pulmonary entrapment of sickle cells: the role of regional alveolar hypoxia	Irrelevant outcomes
Al-Fifi	2006	Vaso-occlusive crisis associated with prednisolone therapy in a sickler patient with bronchial asthma	No relevant management or diagnosis data
Alghzaly	2008	Microbial yield in febrile sickle cell disease patients with acute painful episode from a University Hospital in the Sultanate of Oman	Irrelevant outcomes
Al-Haggar	2006	Acute painful crises of sickle cell disease in Egyptian children: predictors of severity for a preventive strategy	No relevant management or diagnosis data
Alhashimi	2009	Blood transfusions for treating acute chest syndrome in people with sickle cell disease	Not original research
Alhashimi	2010	Blood transfusions for treating acute chest syndrome in people with sickle cell disease	Not original research
Al-Momen	1997	Clodronate in the management of acute sickle cell-related bone pain [abstract]	Not original research
Al-Saeed	1998	Splenic regrowth in Saudi children with sickle cell anaemia following hypertransfusion	No relevant management or diagnosis data
Al-Salem	1997	Sequential endoscopic/laparoscopic management of cholelithiasis and choledocholithiasis in children who have sickle cell disease	No relevant management or diagnosis data
Al-Salem	1997	Continuous intravenous infusion of morphine: A safe and effective method of post-operative analgesia in patients with sickle cell disease	No relevant management or diagnosis data
Al-Salem	1998	Experience of concomitant splenectomy and cholecystectomy in patients with sickle cell disease	Not original research

Author	Year	Title	Reason for Exclusion
Altintas	2003	Sickle cell anemia connected with chronic intrahepatic cholestasis: a case report	Irrelevant outcomes
Alvarez	2008	Short-term follow-up of patients with sickle cell disease and albuminuria	No relevant management or diagnosis data
Anie	2003	Pain, mood and opioid medication use in sickle cell disease	No relevant management or diagnosis data
Anonymous	2003	The child in chronic pain requires accurate assessment before starting treatment with an appropriate treatment	Not original research
Aoki	1995	Enalapril reduces the albuminuria of patients with sickle cell disease	No relevant management or diagnosis data
Asinobi	2003	Urinary tract infection in febrile children with sickle cell anaemia in Ibadan, Nigeria	No relevant management or diagnosis data
Assanasen	2003	Acute Myocardial Infarction in Sickle Cell Anemia	No relevant management or diagnosis data
Athanassiou-Metaxa	2002	Avascular necrosis of the femoral head among children and adolescents with sickle cell disease in Greece	Not original research
Avery	1996	Renal medullary carcinoma: clinical and therapeutic aspects of a newly described tumor	No relevant management or diagnosis data
Avriel	2009	Acute pulmonary disease in a young woman with sickle cell anemia and moyamoya disease	No relevant management or diagnosis data
Aygun	2009	Chronic transfusion practice for children with sickle cell anaemia and stroke	No relevant management or diagnosis data
Badmus	2003	Priapism in southwestern Nigeria	No relevant management or diagnosis data
Baig	2006	Renal medullary carcinoma	No relevant management or diagnosis data
Bailas	2000	Leukoreduction incidental to blood exchange transfusion in patients with sickle cell anemia (SS) and stroke contributes to decreased frequency of painful episodes	Not original research
Bakare	2007	Case Report: Psychosis in an adolescent with sickle cell disease	No relevant management or diagnosis data
Bakshi	1991	Febrile episodes in children with sickle cell disease treated on an ambulatory basis	No relevant management or diagnosis data
Balfour-Lynn	2009	BTS guidelines for home oxygen in children	Not original research
Ballas	2006	Hyperhemolysis during the evolution of uncomplicated acute painful episodes in patients with sickle cell anemia	Irrelevant outcomes
Ballas	1997	Misinterpretation of pain escalation in an adult patient with sickle cell anemia defers accurate diagnosis	No relevant management or diagnosis data
Banerjee	2001	Sickle cell hepatopathy	Not original research
Barreras	1971	Sodium citrate orally for painful sickle cell crises	No relevant management or diagnosis data
Barrett-Connor	1971	Acute pulmonary disease and sickle cell anemia	No relevant management or diagnosis data
Bassett	2010	Diagnostic and therapeutic options for the management of ischemic and nonischemic priapism	Irrelevant outcomes
Baum	1987	Topical antibiotics in chronic sickle cell leg ulcers	No relevant management or diagnosis data
Baumgartner	1989	The presentation and management of the acute abdomen in the patient with sickle-cell anemia	No relevant management or diagnosis data
Begliomini	2001	Priapism due to "S" and "C" hemoglobinopathy successfully treated with finasteride	Not original research
Benjamin	1991	Update: intravenous lysine acetylsalicylate for the treatment of acute pain in sickle cell disorders: potential alternative to narcotics [abstract]	Not original research
Bernini	1995	Dexamethasone therapy for children with acute chest syndrome (ACS) complicating sickle cell disease (SCD): a randomized, double-blind, placebo-controlled pilot study [Abstract]	Not original research

Author	Year	Title	Reason for Exclusion
Bertram	1985	Implantation of penile prostheses in patients impotent after priapism	No relevant management or diagnosis data
Beyer	1999	A chronology of pain and comfort in children with sickle cell disease	No relevant management or diagnosis data
Beyer	2000	Judging the effectiveness of analgesia for children and adolescents during vaso-occlusive events of sickle cell disease	Irrelevant outcomes
Birnbaum	2008	Sickle cell trait and priapism: a case report and review of the literature	No relevant management or diagnosis data
Black	1976	Aminocaproic acid in prolonged hematuria of patients with sickle cell anemia	No relevant management or diagnosis data
Bogue	2010	Risk factors, complications, and outcomes of gallstones in children: a single-center review	No relevant management or diagnosis data
Bowen	1991	Peak expiratory flow rate and the acute chest syndrome in homozygous sickle cell disease	No relevant management or diagnosis data
Boyd	2006	Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia	No relevant management or diagnosis data
Brazier	1986	Retinal detachment in patients with proliferative sickle cell retinopathy	No relevant management or diagnosis data
Brown Bodhise	2004	Non-pharmacologic management of sickle cell pain	No relevant management or diagnosis data
Brownstein	1999	A 3-year-old with fever and bone pain	No relevant management or diagnosis data
Cackovic	1998	Leg ulceration in the sickle cell patient	No relevant management or diagnosis data
Carey	1993	Managing sickle cell crisis in an unknown patient	Not original research
Carmel	2010	Low cobalamin levels associated with sickle cell disease: Contrasting origins and clinical meanings in two instructive patients	No relevant management or diagnosis data
Carney	1986	Iatrogenic choroidal neovascularization in sickle cell retinopathy	No relevant management or diagnosis data
Casella	2010	Design of the silent cerebral infarct transfusion (SIT) trial	No relevant management or diagnosis data
Casella	2000	Floccor's efficacy and safety in pediatric sickle cell patients experiencing acute vaso-occlusive crisis: A subgroup analysis	Not original research
Castro	1994	The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease	No relevant management or diagnosis data
Castro	2000	S $\alpha$ -thalassemia in a 91-year-old woman with mild sickle cell disease with two $\beta$ -thalassemia mutations on the same chromosome	No relevant management or diagnosis data
Chang	2005	Bilateral endogenous endophthalmitis in a patient with hemoglobin SC disease	No relevant management or diagnosis data
Channa Perera	2007	Sudden death due to sickle cell crisis during law enforcement restraint	No relevant management or diagnosis data
Chapman	2004	The utility of screening laboratory studies in pediatric patients with sickle cell pain episodes	No relevant management or diagnosis data
Chmel	1975	Hemoglobin S/C disease in a pregnant woman with crisis and fat embolization syndrome	No relevant management or diagnosis data
Close	1977	The management of ruptured intracranial aneurysm in sickle cell anemia. Case report	No relevant management or diagnosis data
Comber	1996	Evaluation of pulse oximetry in sickle cell anemia patients presenting to the emergency department in acute vasoocclusive crisis	No relevant management or diagnosis data
Condon	1974	Photocoagulation and diathermy in the treatment of proliferative sickle retinopathy	No relevant management or diagnosis data
Cummins	2003	A comparison of the outcome of cognitive behaviour therapy and hydroxyurea in sickle cell disease	Irrelevant outcomes
Dampier	2002	Characteristics of pain managed at home in children and adolescents with sickle cell disease by using diary self-reports	No relevant management or diagnosis data
D'Arcy	2004	Managing sickle-cell crisis	Not original research

Author	Year	Title	Reason for Exclusion
David	1993	The shoulder in sickle-cell disease	Not original research
Davis	2010	Retinal arteriolar occlusions during a sickle cell crisis	Not original research
De	2005	Sickle cell anaemia 2: management approaches of painful episodes	Not original research
de Araujo	1994	[Treatment of sickle cell anemia crisis with dipyron, hydrocortisone, and fluid therapy]	Not original research
De Oliveira	2008	Stroke in patients with sickle cell disease: Clinical and neurological aspects	No relevant management or diagnosis data
DeAngelis	1992	Case 1 presentation. Sickle cell sequestration crisis	Not original research
Denbow	1993	Pulmonary artery pressure and the acute chest syndrome in homozygous sickle cell disease	No relevant management or diagnosis data
Dhar	2003	Pernicious anemia with neuropsychiatric dysfunction in a patient with sickle cell anemia treated with folate supplementation	No relevant management or diagnosis data
Dimashkieh	2003	Renal medullary carcinoma: a report of 2 cases and review of the literature	No relevant management or diagnosis data
Dixon	2000	Zileuton: A potential new treatment approach for acute chest syndrome (ACS)	Not original research
Douvoyiannis	2010	Orbital compression syndrome presenting as orbital cellulitis in a child with sickle cell anemia	No relevant management or diagnosis data
Duckworth	2007	Physician-diagnosed asthma and acute chest syndrome: associations with NOS polymorphisms	No relevant management or diagnosis data
Durosini	1991	Chronic leg ulcers in sickle cell disease: experience in Ibadan, Nigeria	No relevant management or diagnosis data
Eaton	1995	Hospitalizations for painful episodes: association with school absenteeism and academic performance in children and adolescents with sickle cell anemia	Irrelevant outcomes
Ebong	1987	Septic arthritis in patients with sickle-cell disease	No relevant management or diagnosis data
Eke	2003	Effects of Pyrimethamine Versus Proguanil in Malarial Chemoprophylaxis in Children with Sickle Cell Disease: A Randomized, Placebo-Controlled, Open-Label Study	No relevant management or diagnosis data
el Younis	1996	Autoimmune hepatitis in a patient with sickle cell disease	No relevant management or diagnosis data
Ellison	2007	Socioeconomic status and length of hospital stay in children with vaso-occlusive crises of sickle cell disease	No relevant management or diagnosis data
Emodi	2001	Vertebral bone collapse in sickle cell disease: a report of two cases	No relevant management or diagnosis data
Ernst	2000	Blood pressure in acute vaso-occlusive crises of sickle cell disease	No relevant management or diagnosis data
Fertleman	1997	Evaluation of fast track admission policy for children with sickle cell crises: Questionnaire survey of parents' preferences	No relevant management or diagnosis data
Field	2008	Sibling history of asthma is a risk factor for pain in children with sickle cell anemia	No relevant management or diagnosis data
Firth,	2003	Transfusion-related acute lung injury or acute chest syndrome of sickle cell disease? - A case report	No relevant management or diagnosis data
Folkersson	1999	CPC-111 (Cypros Pharmaceutical Corp)	Not original research
Forbes	1996	Sickle cell pain crisis	Not original research
Fosdal	2007	Events of hospitalization among children with sickle cell disease	No relevant management or diagnosis data
France-Dawson	1994	Painful crises in sickle cell conditions	Not original research
Freilich	1977	Long-term follow-up of scleral buckling procedures with sickle cell disease and retinal detachment treated with the use of hyperbaric oxygen	No relevant management or diagnosis data

Author	Year	Title	Reason for Exclusion
Frost	1990	Treatment of sickle cell leg ulcers with pentoxifylline	No relevant management or diagnosis data
Fryer	2003	Sickle cell anemia with moyamoya disease: outcomes after EDAS procedure	No relevant management or diagnosis data
Galinos	1972	Photocoagulation therapy of sickle cell retinopathy	No relevant management or diagnosis data
Galinos	1979	Angioma-like lesion in hemoglobin sickle cell disease	Irrelevant outcomes
Gangahar	1981	Intrasplenic abscess: two case reports and review of the literature	No relevant management or diagnosis data
Garcia-Arias	2005	Pyogenic hepatic abscess after percutaneous liver biopsy in a patient with sickle cell disease	No relevant management or diagnosis data
Gelfand	1993	Simultaneous occurrence of rib infarction and pulmonary infiltrates in sickle cell disease patients with acute chest syndrome	No relevant management or diagnosis data
Gil	1994	Observation of pain behaviors during episodes of sickle cell disease pain	No relevant management or diagnosis data
Gil	2004	Daily mood and stress predict pain, health care use, and work activity in African American adults with sickle-cell disease	No relevant management or diagnosis data
Gilkeson	1997	Chest case of the day	No relevant management or diagnosis data
Gladwin	2000	Pathogenesis and treatment of acute chest syndrome of sickle-cell anaemia	Not original research
Gladwin	1999	The acute chest syndrome in sickle cell disease. Possible role of nitric oxide in its pathophysiology and treatment	Not original research
Gold, Jr.	1974	Letter: Hemodialysis and transfusions for uremic patients with sickle-cell disease	Not original research
Goldbaum	1978	Retinal depression sign indicating a small retinal infarct	No relevant management or diagnosis data
Goldbaum	1979	Cryotherapy of proliferative sickle retinopathy, II: triple freeze-thaw cycle	No relevant management or diagnosis data
Goldberg	1979	The diagnosis and treatment of secondary glaucoma after hyphema in sickle cell patients	No relevant management or diagnosis data
Goldberg	1971	Treatment of proliferative sickle retinopathy	No relevant management or diagnosis data
Goldberg	1973	Argon laser photocoagulation of proliferative sickle retinopathy	No relevant management or diagnosis data
Goldberg	1983	Treatment of neovascularization, vitreous hemorrhage, and retinal detachment in sickle cell retinopathy	Not original research
Gordon	2010	<i>Title not available</i>	Irrelevant outcomes
Goyal	2004	Is Chlamydia pneumoniae infection associated with stroke in children with sickle cell disease?	Irrelevant outcomes
Grace	2010	Resolution of cerebral artery stenosis in a child with sickle cell anemia treated with hydroxyurea	Not original research
Graido-Gonzalez	1998	Plasma endothelin-1, cytokine, and prostaglandin E2 levels in sickle cell disease and acute vaso-occlusive sickle crisis	No relevant management or diagnosis data
Griffiths	2005	Inhaled nitric oxide therapy in adults	Not original research
Gross	1993	Impact of anesthetic agents on patients with sickle cell disease	No relevant management or diagnosis data
Guvenc	2005	Renal vascular resistance in sickle cell painful crisis	No relevant management or diagnosis data
Guy	1973	In vitro and in vivo effect of hypotonic saline on the sickling phenomenon	No relevant management or diagnosis data
Hammer	2003	Perioperative care for patients with sickle cell who are undergoing total hip replacement as treatment for osteonecrosis	Not original research
Hammerman	1997	Endothelin-1 production during the acute chest syndrome in sickle cell disease	No relevant management or diagnosis data

Author	Year	Title	Reason for Exclusion
Hammerman	1999	Endothelial cell nitric oxide production in acute chest syndrome	No relevant management or diagnosis data
Haque	2002	Pulmonary hypertension in sickle cell hemoglobinopathy: A clinicopathologic study of 20 cases	No relevant management or diagnosis data
Harris	1976	Papillary necrosis in a child with homozygous sickle-cell anemia	No relevant management or diagnosis data
Hassan	1998	Hydroxyurea in the treatment of sickle cell associated priapism	Not original research
Hebra	1998	A new technique for laparoscopic splenectomy with massively enlarged spleens	No relevant management or diagnosis data
Hefton	1986	Grafting of skin ulcers with cultured autologous epidermal cells	No relevant management or diagnosis data
Hennemeyer	2000	Radiologic case study	No relevant management or diagnosis data
Hernigou	2010	Septic arthritis in adults with sickle cell disease often is associated with osteomyelitis or osteonecrosis	Irrelevant outcomes
Hickman	1997	Results and complications of total hip arthroplasties in patients with sickle-cell hemoglobinopathies. Role of cementless components	No relevant management or diagnosis data
Holcomb	1991	Laparoscopic cholecystectomy in the pediatric patient	Irrelevant outcomes
Homi	1997	Pulse oximetry in a cohort study of sickle cell disease	Irrelevant outcomes
Jaeckel	2010	The use of partial exchange blood transfusion and anaesthesia in the management of sickle cell disease in a perioperative setting: two case reports	Irrelevant outcomes
Jamison	2002	A special treatment program for patients with sickle cell crisis	Irrelevant outcomes
Jasper	2009	Use of tourniquet in a sickle cell patient for sequestrectomy and saucerisation: a case report	No relevant management or diagnosis data
Jennings	2008	Elevated urinary leukotriene E4 levels are associated with hospitalization for pain in children with sickle cell disease.	Irrelevant outcomes
Johal	2005	Bladder necrosis presenting with hematuria in a patient with sickle-cell disease	Irrelevant outcomes
Jones	2005	Windy weather and low humidity are associated with an increased number of hospital admissions for acute pain and sickle cell disease in an urban environment with a maritime temperate climate	Irrelevant outcomes
Jordan	2008	Assessment and treatment of stroke in children	Not original research
Kalala Okito	2004	Are spontaneous epidural haematoma in sickle cell disease a rare complication? A report of two new cases	No relevant management or diagnosis data
Kar	1999	Splenectomy in sickle cell disease	No relevant management or diagnosis data
Karaman	2005	Treatment of post-traumatic trabecular meshwork thrombosis and secondary glaucoma with intracameral tissue plasminogen activator in previously unrecognized sickle cell anemia	No relevant management or diagnosis data
Kattamis	2000	Serious adverse events and clinical course of young sickle cell patients treated with hydroxyurea	Not original research
Keeley	1982	Acute infarction of long bones in children with sickle cell anemia	No relevant management or diagnosis data
Kehinde	2008	Neurological complications of sickle cell anemia in Nigerian Africans--a case-control study	No relevant management or diagnosis data
Keidan	1987	Rheological effects of bed rest in sickle cell disease	No relevant management or diagnosis data
Khoury	1991	Bilateral lower limb salvage with free flaps in a patient with sickle cell ulcers	No relevant management or diagnosis data
King	2008	Blood transfusion therapy is feasible in a clinical trial setting in children with sickle cell disease and silent cerebral infarcts	No relevant management or diagnosis data

Author	Year	Title	Reason for Exclusion
Kingsley	1996	Anesthetic management of a patient with hemoglobin SS disease and mitral insufficiency for mitral valve repair	No relevant management or diagnosis data
Klings	2001	Increased F2 isoprostanes in the acute chest syndrome of sickle cell disease as a marker of oxidative stress	No relevant management or diagnosis data
Klings	2001	Role of free radicals in the pathogenesis of acute chest syndrome in sickle cell disease	Not original research
Knight	1998	Management of sickle cell disease. Acute chest syndrome is common in children before puberty	Not original research
Knight-Madden	2001	Invasive pneumococcal disease in homozygous sickle cell disease: Jamaican experience 1973-1997	No relevant management or diagnosis data
Kravis	1982	Fever in children with sickle cell hemoglobinopathies	No relevant management or diagnosis data
Kress	1999	Determination of hemoglobin saturation in patients with acute sickle chest syndrome: a comparison of arterial blood gases and pulse oximetry	No relevant management or diagnosis data
Krishnamoorthy	2006	Primary hyperparathyroidism mimicking vaso-occlusive crises in sickle cell disease	No relevant management or diagnosis data
Kumar	2008	Acute chest pain in a young woman with a chronic illness	No relevant management or diagnosis data
La Grenade	1993	A randomized controlled trial of solcoseryl and duoderm in chronic sickle-cell ulcers	No relevant management or diagnosis data
Lane	2001	Variable approaches to therapeutic options for children with Sickle Cell Disease (SCD): A practice survey of the American Society of Pediatric Hematology/Oncology (ASPH/O)	No relevant management or diagnosis data
Lantz	1995	Splenic-perisplenic infected hematoma detected on radiogallium- radiocolloid subtraction study	No relevant management or diagnosis data
Larocque	1974	Priapism: a review of 46 cases	Not original research
Lazio	2010	A comparison of analgesic management for emergency department patients with sickle cell disease and renal colic	Irrelevant outcomes
Leitão	2006	Renal medullary carcinoma: Case report and review of the literature	No relevant management or diagnosis data
Lemanek	2006	Effectiveness of auxiliary sickle cell disease management guidelines of children hospitalized with pain [abstract]	Not original research
Li	2003	Repeated testicular infarction in a patient with sickle cell disease: a possible mechanism for testicular failure	No relevant management or diagnosis data
Lionnet	2007	Tuberculosis in adult patients with sickle cell disease	No relevant management or diagnosis data
Lopez	1996	The complete blood count and reticulocyte count--are they necessary in the evaluation of acute vasoocclusive sickle-cell crisis?	No relevant management or diagnosis data
Lopez	1996	Nitric oxide metabolite levels in acute vaso-occlusive sickle-cell crisis	No relevant management or diagnosis data
Lopez	2000	Sequential nitric oxide measurements during the emergency department treatment of acute vasoocclusive sickle cell crisis	No relevant management or diagnosis data
Lott-Duarte	2008	Extensive spondylodiscitis with epidural abscess causing fever and lower limbs pain in a child with sickle cell disease	No relevant management or diagnosis data
Lykavieris	2006	Autoimmune liver disease in three children with sickle cell disease	No relevant management or diagnosis data
Mace	2009	Bilateral profound sudden sensorineural hearing loss presenting a diagnostic conundrum in a child with sickle cell anaemia	No relevant management or diagnosis data
Machado	2007	Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease.	Irrelevant outcomes
Madhavan	2001	Retinitis pigmentosa patients with sickle cell disease and dextrocardia and situs inversus syndrome	No relevant management or diagnosis data
Magargal	1989	Treatment of Eales' disease with scatter laser photocoagulation	No relevant management or diagnosis data
Mansi	2002	Myocardial infarction in sickle cell disease	Not original research

Author	Year	Title	Reason for Exclusion
Marangos	1998	Potential therapeutic applications of fructose-1,6-diphosphate	Not original research
Marti-Carvajal	2007	Antibiotics for treating acute chest syndrome in people with sickle cell disease	No relevant management or diagnosis data
Marti-Carvajal	2009	Antibiotics for treating community acquired pneumonia in people with sickle cell disease	No relevant management or diagnosis data
Marti-Carvajal	2009	Antibiotics for treating osteomyelitis in people with sickle cell disease	No relevant management or diagnosis data
Marti-Carvajal	2009	Interventions for treating painful sickle cell crisis during pregnancy	Not original research
Marti-Carvajal	2009	Treatment for avascular necrosis of bone in people with sickle cell disease	Not original research
Mason	2002	Surgical closure of macular hole in association with proliferative sickle cell retinopathy	Irrelevant outcomes
McCarthy	2006	Marrow emboli in acute chest syndrome: Artifact or etiology?	Irrelevant outcomes
McConachie	1998	Complications of sickle cell disease: intracranial aneurysms and their treatment	Irrelevant outcomes
McIntosh	1980	Fever in young children with sickle cell disease	No relevant management or diagnosis data
Mehta	1999	Hepatic sickling crisis mimicking recurrent cholangitis	Irrelevant outcomes
Meltzer	1996	Sickle cell pain crisis	Not original research
Meshikhes	1998	The safety of laparoscopic cholecystectomy in sickle cell disease: An update	Not original research
Mestre-Fusco	2008	Sickle cell anemia and functioning splenic tissue: Correlation of scintigraphic findings and CT	No relevant management or diagnosis data
Michaels	2003	Thrombosis and gangrene in a patient with sickle cell disease and dactylitis	No relevant management or diagnosis data
Miller	1995	Priapism in children with sickle cell disease	Not original research
Minniti	2009	<i>Title not available</i>	Not original research
Mitchell	2002	Meeting the challenge of managing vaso-occlusive crisis	No relevant management or diagnosis data
Mohanty	2002	Rare splenic manifestations of sickle cell disease	Irrelevant outcomes
Montague	2010	Sexual dysfunction: Immediate penile prosthesis for acute ischemic priapism	Not original research
Morris	1999	Clinician assessment for acute chest syndrome in febrile patients with sickle cell disease: is it accurate enough	No relevant management or diagnosis data
Morris	2000	Patterns of arginine and nitric oxide in patients with sickle cell disease with vaso-occlusive crisis and acute chest syndrome	Irrelevant outcomes
Morris	2006	New strategies for the treatment of pulmonary hypertension in sickle cell disease: The rationale for arginine therapy	Not original research
Nelson	2009	<i>Title not available</i>	Not original research
Neonato	2000	Acute clinical events in 299 homozygous sickle cell patients living in France. French Study Group on Sickle Cell Disease	No relevant management or diagnosis data
Ng	2003	Portal vein thrombosis following laparoscopic surgery in a patient with sickle cell disease	No relevant management or diagnosis data
Nguyen	2000	Leuprolide therapy in the treatment of sickle cell anemia—associated priapism in adolescents	Not original research
Nolan	2008	Association between wind speed and the occurrence of sickle cell acute painful episodes: results of a case-crossover study	Irrelevant outcomes

Author	Year	Title	Reason for Exclusion
Norris	2003	Positive blood cultures in sickle cell disease: time to positivity and clinical outcome	No relevant management or diagnosis data
Nourallah	1998	Diagnostic and therapeutic ERCP in children with sickle cell disease	No relevant management or diagnosis data
O'Brien	2009	Decision analysis of treatment strategies in children with severe sickle cell disease	No relevant management or diagnosis data
Odesina	2010	Evidence-based sickle cell pain management in the emergency department	No relevant management or diagnosis data
Oguz	1994	Vein of Galen and sinus thrombosis with bilateral thalamic infarcts in sickle cell anaemia: CT follow-up and angiographic demonstration	No relevant management or diagnosis data
Okany	2004	Efficacy of natural honey in the healing of leg ulcers in sickle cell anaemia	No relevant management or diagnosis data
Okuonghae	1993	Pattern of bacteraemia in febrile children with sickle cell anaemia	Irrelevant outcomes
Oluwasanmi	1980	Leg ulcers in haemoglobinopathies	No relevant management or diagnosis data
Onu	1991	Priapism not associated with sickle cell disease in a Nigerian. Case report	No relevant management or diagnosis data
Pandey	2010	Gonioaspiration for refractory glaucoma secondary to traumatic hyphema in patients with sickle cell trait	No relevant management or diagnosis data
Pate	1970	Thoracic surgery in the patient with sickle-cell hemoglobin	No relevant management or diagnosis data
Pavlakis	2009	Arterial ischemic stroke: common risk factors in newborns and children	Not original research
Pawar	2008	The effect of acute pain crisis on exhaled nitric oxide levels in children with sickle cell disease	No relevant management or diagnosis data
Paydas	1997	Bone marrow necrosis in antiphospholipid syndrome	No relevant management or diagnosis data
Perman	2004	A shift from demerol (Meperidine) to dilaudid (Hydromorphone) improves pain control and decreases admissions for patients in sickle cell crisis	Not original research
Pham	2009	<i>Title not available</i>	Irrelevant outcomes
Pichard	1987	[Effectiveness of treatment during osteoarticular pain crises in drepanocytosis; based on the example of pentoxifylline]	Not original research
Piomelli	1985	Chronic transfusions in patients with sickle cell disease. Indications and problems	Not original research
Platt	2008	Hydroxyurea for the treatment of sickle cell anemia	Not original research
Polizzotto	2008	Acute splenic sequestration complicating sickle cell disease	Not original research
Pollack	1991	Usefulness of empiric chest radiography and urinalysis testing in adults with acute sickle cell pain crisis.	Irrelevant outcomes
Pryle	1992	Toxicity of norpethidine in sickle cell crisis	Irrelevant outcomes
Pulido	1988	Pars plana vitrectomy in the management of complications of proliferative sickle retinopathy	No relevant management or diagnosis data
Quinn	2008	Daytime steady-state haemoglobin desaturation is a risk factor for overt stroke in children with sickle cell anaemia.	No relevant management or diagnosis data
Rahimy	1999	Outpatient management of fever in children with sickle cell disease (SCD) in an African setting	No relevant management or diagnosis data
Rajagopal	2010	Full-thickness macular hole in a patient with proliferative sickle cell retinopathy	Not original research
Ramu	2008	Uncommon neurological manifestations of hemolytic anemia: A report of two cases	No relevant management or diagnosis data
Rana	1997	Discontinuation of long-term transfusion therapy in patients with sickle cell disease and stroke	No relevant management or diagnosis data
Rao	1996	B19 parvovirus infection and transient aplastic crisis in a child with sickle cell anemia. Concomitant bone marrow/bone infarction and acute chest syndrome	No relevant management or diagnosis data

Author	Year	Title	Reason for Exclusion
Rea	1995	Haemoglobin SC disease presenting as a case of priapism to a GUM clinic	Irrelevant outcomes
Reindorf	1989	Rapid healing of sickle cell leg ulcers treated with collagen dressing	No relevant management or diagnosis data
Rengasamy	2002	Anesthesia considerations and management of pain in patients with sickle cell anemia	Not original research
Rifai	1997	Scintigraphy and ultrasonography in differentiating osteomyelitis from bone infarction in sickle cell disease	No relevant management or diagnosis data
Rinnert	1996	Management of nontraumatic subarachnoid hemorrhage in a patient with sickle-cell disease: a case report	No relevant management or diagnosis data
Robertson	1997	Unexpected hemoglobin electrophoresis results following red cell exchange in a sickle cell anemia patient with acute chest syndrome	No relevant management or diagnosis data
Rodman	1994	Meperidine-induced seizure in a sickle cell patient using a patient-controlled analgesia pump	No relevant management or diagnosis data
Rosenbloom	1994	Treatment of pain in sickle-cell crisis	Not original research
Roux	2010	Live birth after ovarian tissue autograft in a patient with sickle cell disease treated by allogeneic bone marrow transplantation	No relevant management or diagnosis data
Sadat-Ali	1994	The spine in sickle cell disease	No relevant management or diagnosis data
Sadiq	2004	Index of suspicion	No relevant management or diagnosis data
Saif	1997	Case in point. Salmon patch-hemorrhages (nonproliferative retinopathy associated with sickle-cell disease)	No relevant management or diagnosis data
Sangare	1990	Treatment results of ketoprofen (profenid) in the treatment of painful crises in sickle cell anemia	Not original research
Sathyamoorthy	2006	Renal medullary carcinoma in a patient with sickle-cell disease	No relevant management or diagnosis data
Sawyer	1978	New approaches in the therapy of the peripheral vascular ulcer	Not original research
Sawyer	1979	Wound healing effects of debrisan on varicose, postoperative, decubitus, and sickle-cell ulcers in man	No relevant management or diagnosis data
Sayag	2004	Peripheral retinal scatter photocoagulation for the treatment of proliferative sickle retinopathy: Is it always indispensable?	Not original research
Scothorn	2001	Non-stroke related hospitalization rates in children with sickle cell anemia receiving blood transfusion therapy for at least five years following stroke: A retrospective cohort study of 166 patients	Not original research
Seguier-Lipszyc	2001	Elective laparoscopic cholecystectomy: Treatment of choice for cholelithiasis in children with sickle cell disease?	Not original research
Serjeant	1990	Current concerns in haematology. 1. Is the painful crisis of sickle cell disease a "steal" syndrome?	Not original research
Serjeant	1977	Isoxsuprine hydrochloride in the therapy of sickle cell leg ulceration	No relevant management or diagnosis data
Serjeant	1970	Oral zinc sulphate in sickle-cell ulcers	No relevant management or diagnosis data
Shaw, Jr.	1979	Amaurosis fugax associated with SC hemoglobinopathy and lupus erythematosus	Irrelevant outcomes
Shende	1977	The use of partial exchange transfusion (ETX) in children with serious complications of sickle cell anemia (SS)	Not original research
Shetty	1998	Sickle cell anemia with systemic lupus erythematosus: response to hydroxyurea therapy	No relevant management or diagnosis data
Shiloh	2009	<i>Title not available</i>	Irrelevant outcomes
Shimomura	1979	Pain management of patients with sickle cell anemia	Not original research
Silbergleit	1999	Management of sickle cell pain crisis in the emergency department at teaching hospitals	No relevant management or diagnosis data

Author	Year	Title	Reason for Exclusion
Silva	2009	Brain magnetic resonance imaging abnormalities in adult patients with sickle cell disease: correlation with transcranial Doppler findings	No relevant management or diagnosis data
Simsek	2006	Renal amyloidosis in a child with sickle cell anemia	No relevant management or diagnosis data
Singhal	1995	Acceleration in linear growth after splenectomy for hypersplenism in homozygous sickle cell disease	No relevant management or diagnosis data
Sinha	1999	Symmetric avascular necrosis of the shoulders and hips in sickle cell disease	Irrelevant outcomes
Smith	1976	Nephrotic syndrome, sickle-cell disease and pregnancy	No relevant management or diagnosis data
Sommer	1971	Splenomegaly with hypersplenism in sickle cell anemia treated by radiation--case report	Not original research
Sprinz	2009	<i>Title not available</i>	Not original research
Stanca	2007	Exacerbation of sickle cell disease itself as a cause of abnormal liver chemistry tests	No relevant management or diagnosis data
Styles	1996	Phospholipase A2 levels in acute chest syndrome of sickle cell disease	No relevant management or diagnosis data
Sullivan	2001	Low exhaled nitric oxide and a polymorphism in the NOS 1 gene is associated with acute chest syndrome	No relevant management or diagnosis data
Tanabe	2010	Adult emergency department patients with sickle cell pain crisis: A learning collaborative model to improve analgesic management	No relevant management or diagnosis data
Tanabe	2010	Adult emergency department patients with sickle cell pain crisis: a learning collaborative model to improve analgesic management	Irrelevant outcomes
Tanner	2006	Myocardial infarction following sickle cell chest syndrome	Not original research
Tarer	2006	Sickle cell anemia in Guadeloupean children: pattern and prevalence of acute clinical events	No relevant management or diagnosis data
Teich	1986	The early diagnosis of splenic abscess	No relevant management or diagnosis data
Thomas	1986	Recurrent benign intracranial hypertension associated with hemoglobin SC disease in pregnancy	No relevant management or diagnosis data
Thomas	1997	Cognitive behavioural therapy for the management of pain in sickle cell disease [abstract]	Not original research
Thomas	1999	Cognitive-behaviour therapy for the management of sickle cell disease pain: An evaluation of a community-based intervention	Not original research
Thomas	2001	Cognitive-behavioural therapy for the management of sickle cell disease pain: identification and assessment of costs	No relevant management or diagnosis data
Todd	2006	Sickle cell disease related pain: crisis and conflict	No relevant management or diagnosis data
Tolaymat	1999	Parvovirus glomerulonephritis in a patient with sickle cell disease	No relevant management or diagnosis data
Trainor	1986	Venous ulcer in a sickle cell patient. Case report	No relevant management or diagnosis data
Trent	2004	Leg ulcers in sickle cell disease	Not original research
Uong	2006	Daytime pulse oximeter measurements do not predict incidence of pain and acute chest syndrome episodes in sickle cell anemia	No relevant management or diagnosis data
van der Valk	2009	A woman with a painful hip	No relevant management or diagnosis data
van Mieghem	2008	Myocardial infarction in a patient with sickle cell trait. Treatment dilemmas and imaging findings at follow-up	No relevant management or diagnosis data
Vicari	2004	Embolization of intracranial aneurysms and sickle cell disease	No relevant management or diagnosis data
Vichinsky	2004	Pulmonary hypertension in sickle cell disease	Not original research
Vichinsky	1994	A cautionary note regarding hydroxyurea in sickle cell disease	No relevant management or diagnosis data

Author	Year	Title	Reason for Exclusion
Vichinsky	1997	High rates of complications in sickle cell anemia (SCA) patients undergoing orthopedic surgery [abstract]	Irrelevant outcomes
Wade	1990	Subretinal hemorrhage management by pars plana vitrectomy and internal drainage	No relevant management or diagnosis data
Walker	1996	Biliary sludge in sickle cell disease	No relevant management or diagnosis data
Wallen	2007	A randomized pilot study exploring hypnosis as a pain and symptom management strategy in patients with sickle cell disease [abstract]	Not original research
Wang	2002	Pain at home in sickle cell disease: An underrecognized problem	Not original research
Wang	1991	High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease	No relevant management or diagnosis data
Ward	1974	Sickle cell leg ulceration--A non-operative outpatient method of management	No relevant management or diagnosis data
Ware	1995	Hydroxyurea: an alternative to transfusion therapy for stroke in sickle cell anemia	No relevant management or diagnosis data
Weinstein	2009	A new extended release formulation (OROSÂ®) of hydromorphone in the management of pain	Not original research
Weinzweig	1995	Lower limb salvage by microvascular free-tissue transfer in patients with homozygous sickle cell disease	No relevant management or diagnosis data
West	1994	The presentation, frequency, and outcome of bacteremia among children with sickle cell disease and fever	No relevant management or diagnosis data
West	2002	Predictors of bacteremia in febrile children with sickle cell disease	No relevant management or diagnosis data
Westring	1975	Long term administration of narcotics for chronic pain	Not original research
Wethers	1994	Accelerated healing of chronic sickle-cell leg ulcers treated with RGD peptide matrix. RGD Study Group	No relevant management or diagnosis data
Wierenga	2001	Significance of fever in Jamaican patients with homozygous sickle cell disease	No relevant management or diagnosis data
Wilhelm	1981	Erythropheresis in treating retinal detachments secondary to sickle-cell retinopathy	Not original research
Williams	1996	Outpatient therapy with ceftriaxone and oral cefixime for selected febrile children with sickle cell disease	No relevant management or diagnosis data
Wong	2007	Overt and incomplete (silent) cerebral infarction in sickle cell anemia: diagnosis and management	Not original research
Wook Huh	2004	Follow-up study of intravenous dexamethasone therapy for children with acute chest syndrome complicating sickle cell disease [abstract]	Not original research
Yale	2000	Acute chest syndrome in sickle cell disease	Not original research
Yallop	2007	The associations between air quality and the number of hospital admissions for acute pain and sickle-cell disease in an urban environment	No relevant management or diagnosis data
Yang	1990	Case report: Corporectomy for intractable sickle-associated priapism	Not original research
Yaranal	2005	Unusual presentation of sickle cell anaemia--paraplegia in a fifty year old man	Irrelevant outcomes
Yosef	1997	Comparison of tramadol efficiency versus oxycodone/acetaminophen in the management of pain associated with sickle cell anemia [abstract]	Not original research
Young	1992	Smoking is a factor in causing acute chest syndrome in sickle cell anemia	No relevant management or diagnosis data
Zar	2004	Etiology of sickle cell chest	Not original research
Zimmerman	2006	Childhood cerebrovascular disease sickle cell disease	No relevant management or diagnosis data

## Appendix E: Acronyms and Abbreviations

Numbered	
3TC	lamivudine
32P	radioactive phosphorous
51Cr-EDTA	chromium-51 labeled ethylenediaminetetraacetic acid; <i>see also</i> Cr-EDTA
6MWD	6-minute walk distance

A	
α	alpha, first letter of the Greek alphabet
α-thal	See α-thalassemia
α-thalassemia	alpha-thalassemia
AA	African American
AB	blood group AB
Ab	antibody
ABC	abacavir
ABG	arterial blood gas
A/C	albumin to creatinine ratio
ACE	angiotensin converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute chest syndrome
AE	adverse event
Æ	per each
AER	albumin excretion rate
AHR	airway hyperresponsiveness
AI	augmentation index
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ara-c	arabinosylcytosine (cytarabine)
ARV	antiretroviral
ASA	acetylsalicylic acid (aspirin)
ASPEN	Association of Sickle Cell Disease, Priapism, Exchange Transfusion and Neurological Events
ASSC	acute splenic sequestration crisis
AST	aspartate aminotransferase
atm	atmospheric

AUC	area under the curve
avL	automated volt left, EKG lead

B	
β	beta, second letter of the Greek alphabet\
β-thal	See β-thalassemia
β-thalassemia	beta thalassemia
β <sup>0</sup> -thal	beta zero-thalassemia
BABY HUG	Pediatric Hydroxyurea Phase III Clinical Trial
B cell	type of lymphocyte or immune mediator cell
beta	See β
b.i.d.	<i>bis in die</i> , twice a day
BM	Black male; bone marrow; bowel movement [see context]
BMI	Body Mass Index
BMT	bone marrow transplant
BP	blood pressure
B-TI	beta thalassemia intermedia
B-TM	beta thalassemia major

C	
C	Celsius
Ca	calcium
CAD	coronary artery disease
CAR	Central African Republic haplotype
CBD	cortical bone density
CBFv	cerebral blood flow velocity
CBT	cognitive behavioral therapy
CCNU	1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)
CCT	clinically controlled trial
CH	chronic hepatomegaly
CI	confidence interval
cm	centimeter
cm <sup>2</sup>	square centimeter
cm <sup>3</sup>	cubic centimeter
CML	chronic myelogenous leukemia

cMRI	conventional magnetic resonance imaging
CMV	cytomegalovirus
CNS	central nervous system
cP	centipoise
CrCl	creatinine clearance
Cr-EDTA	chromium 51-labeled ethylenediaminetetraacetic acid; see 51Cr-EDTA
Cross	cross-sectional study
CRP	C reactive protein
CSSCD	Cooperative Study of Sickle Cell Disease
CT	computed tomography
CTA	computed tomographic angiography; concurrent treatment with an antisickling agent
CTX	chronic transfusion therapy
CUI	cumulative incidence
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
CXR	chest x ray

## D

d	day
d4T	didehydrodeoxythymidine
DAT	direct antiglobulin test
DBP	diastolic blood pressure
ddl	didanosine, dideoxyinosine
DFO	deferoxamine
DH	day hospital
DHTR	delayed hemolytic transfusion reaction
DHTR/H	delayed hemolytic transfusion reaction/hyperhemolysis
dL	deciliter
DLCO	diffusing capacity of lung for carbon monoxide
DM	diabetes mellitus
DPI	dynamic pressure index
DTPA	diethylenetriamine pentaacetate
DW	dry weight
dyn	dyne
dx	diagnosis

## E

E	E antigen; HbE/β-thalassemia [see context]
E wave	electromagnetic wave
E/A	Doppler ratio of early (E) to late atrial (A) transmitral flow velocity
ECG	electrocardiogram
ECHO	echocardiogram, echocardiographic, echocardiography
ECMO	extracorporeal membrane oxygenation
ED or ER	emergency department or emergency room
EDD	end diastolic diameter
EF	ejection fraction
EFV	efavirenz
EPO	erythropoietin
ESD	end systolic diameter
ESSm	end-systolic wall stress
ET	essential thrombocytopenia; exchange transfusion [see context]

## F

F	female
F	Fahrenheit
f/u	follow up
FEF	forced expiratory flow
FEV1	forced expiratory volume at 1 second
fL	femtoliter
FS	fractional shortening
ft	feet
FVC	forced vital capacity

## G

g	gram
G	gauge
GFR	glomerular filtration rate; mL/min/1.73 m <sup>2</sup>
GI	gastrointestinal
GMP	granule membrane protein
Gp	group

**H**

h	hour
H1N1	respiratory virus, a variety of influenza A
H6CS	Harvard Six Cities Study
Hb	hemoglobin
HbA	hemoglobin A
HbAA	hemoglobin AA
HbAS	hemoglobin AS
HbF	hemoglobin F; fetal hemoglobin
HbH	hemoglobin H
HbI	hemoglobin I
HBM	health belief model
HbS	hemoglobin S; sickle cell hemoglobin
HbS $\alpha^+$ -thal	hemoglobin S alpha plus-thalassemia
HbS $\beta$ -thal	hemoglobin S beta-thalassemia
HbS $\beta^0$ -thal	sickle hemoglobin beta zero-thalassemia
HbS $\beta^+$ -thal	sickle hemoglobin beta positive-thalassemia
HbSC	hemoglobin SC disease; sickle hemoglobin C disease
HbSD	hemoglobin SD disease
HbSD <sup>LA</sup>	hemoglobin SD disease, Los Angeles; also known as D-Punjab
HbS/O-Arab	hemoglobin SO-Arab
HbSS	homozygous sickle cell disease
Hct	hematocrit
HES	Health Examination Survey
Hg	mercury
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPRT	hypoxanthine phosphoribosyl transferase
HR	heart rate
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
HTN	hypertension
HTR	hemolytic transfusion reaction
HU	hydroxyurea
HUG KIDS	Phase I-II trial of the safety of HU in children by the Pediatric Hydroxyurea Group
HUSOFT	The Hydroxyurea Safety and Organ Toxicity trial
hx	history

**I**

IAT	indirect antiglobulin test
IDV	indinavir
IFN	interferon
i.m.	intramuscular
INO or INO	inhaled nitric oxide
INR	international normalized ratio
IQR	interquartile range
IR	index of rigidity
IU	International unit
i.v. or IV	intravenous
IVIG	intravenous immunoglobulin
IVS	interventricular septal thickness

**K**

K	Kell
kg	kilogram
kJ	Kilojoule
kPa	kilo-Pascal

**L**

L	liter
LA	left atrium, left atrial
LACA	left anterior cerebral artery
LDH	lactate dehydrogenase
LFT	liver function test
LIC	liver iron content; liver iron concentration [see context]
LMCA	left main coronary artery
LOS	length of stay
Lp(a)	lipoprotein (a)
LPCA	left posterior cerebral artery
LQTS	long QT syndrome
LV	left ventricle; left ventricular
LVDD	left ventricular diastolic dimension
LVEDD	left ventricle end-diastolic dimension
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic dimension

LVH	left ventricular hypertrophy
LVPWD	left ventricular posterior wall dimension
LVPWT	left ventricular posterior wall thickness
<b>M</b>	
μ	Greek letter mu; micro-
m	milli-; moles per liter [see context]
m	meter
m <sup>2</sup>	square meter
MAP	mean arterial pressure
MCA	middle cerebral artery
MCT	methacholine challenge test
MCV	mean corpuscular volume; mean cell volume
MedAd	median study medication
MF	myelofibrosis
mg	milligram
MI	myocardial infarction
min	minute
mL	milliliter
mm	millimeter
mm <sup>3</sup>	cubic millimeter
mmHg	millimeters of mercury
mmol	millimolar
mo	month
mol	mole
mPAP	mean pulmonary artery pressure
MPD	myeloproliferative disorder; maximal permissible dose [see context]
MPI	myocardial performance index
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
ms	millisecond
MSH	Study of Hydroxyurea for Sickle Cell Anemia
MTD	maximum tolerated dose

<b>N</b>	
n	nano
<i>n</i>	sample size

<i>N</i>	population size
NA or N/A	not applicable
NC	not clear
ng	nanogram
ng/mL	nanograms per milliliter
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
nmol	nanomole
NO or NO <sub>x</sub>	nitric oxide
NR	not reported
NR/NC	not reported/not clear
NS	not significant; normal saline [see context]
ns	nanosecond

<b>O</b>	
Obs	observational
OCP	oral contraceptive pill
Od or o.d.	<i>omni die</i> , every day
Op	Operation; opioid [see context]
OR	odds ratio

<b>P</b>	
<i>p</i>	probability
P, Obs	prospective observational
PAH	pulmonary arterial hypertension
PaO <sub>2</sub>	symbol for partial pressure of oxygen in arterial blood
PASP	pulmonary artery systolic pressure
PCA	patient-controlled analgesia
pcMV	pressure-controlled mechanical ventilation
Pcr	plasma creatinine
PCV	packed cell volume
PCWP	pulmonary capillary wedge pressure
PEF	peak expiratory flow
PFT	pulmonary function test
pg	picogram
PH, PHT, PHTN	pulmonary hypertension
PICU	pediatric intensive care unit

PLC	propionyl-L-carnitine
plt	platelets
PMN	polymorphonuclear leukocytes
pmol	picomole
pO <sub>2</sub> or PO <sub>2</sub>	partial oxygen pressure
POD	postoperative day
postop	postoperative
ppm	parts per million
PRBC	packed red blood cells
preop	preoperative
Prn	as needed
PSR	proliferative sickle retinopathy
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
PVR	pulmonary vascular resistance
PWV	pulse wave velocity

## Q

Q	quality
Q wave	the initial downward deflection of the QRS complex
QID or q.i.d.	<i>quater in die</i> ; 4 times a day
QOD	every other day
QTc	corrected QT interval

## R

R wave	the initial upward deflection of the QRS complex
R, Obs	retrospective, observational
R-P, Obs	retrospective-prospective observational
RACA	right anterior cerebral artery
RAD	reactive airway disease
RBC	red blood cell
rCBF	regional cerebral blood flow
RCT	randomized controlled trial
RE	right extremity; right eye [see context]
retic	reticulocytes
Rev.	reviewer
RGD	arginyl-glycyl-aspartic acid (peptide)

RHC	right heart catheterization
RMCA	right middle cerebral artery
RPCA	right posterior cerebral artery
RR	relative risk
rTPA	recombinant tissue plasminogen activator
RV	right ventricle; right ventricular
RVEDD	right ventricular end-diastolic dimension
RVEF	right ventricular ejection fraction
RVESD	right ventricular end-systolic dimension
RVP	right ventricle pressure

## S

s	seconds
S/O	hemoglobin SO Arab
S/O-Arab	hemoglobin SO-Arab
SA	substance abuse
SBP	systolic blood pressure
SCA	sickle cell anemia
SCD	sickle cell disease
SD	standard deviation
SEM	standard error of the mean
SF	serum ferritin
SLE	systemic lupus erythematosus
SPT	service perception test
STOP	Stroke Prevention Trial in Sickle Cell Anemia
sx	symptom

## T

T wave	the first deflection in the electrocardiogram following the QRS complex
TACO	transfusion-associated circulatory overload
TAMMV	time-averaged mean of the maximum velocity
TCD	transcranial Doppler
TENS	transcutaneous electrical nerve stimulation
thal	thalassemia
TIA	transient ischemic attack
t.i.d.	<i>ter in die</i> ; three times a day
TLC	total lung capacity

TNF- $\alpha$	tumor necrosis factor alpha
TRF2	telomeric repeat-binding factor 2
TRV, TRJV	tricuspid regurgitant velocity, tricuspid regurgitant jet velocity
TScr	tubular secretion of creatinine
tx	therapy

## U

U	unit
UAE	urinary albumin excretion
$\mu\text{g}$	microgram
$\mu\text{l}$	microliter
ULN	upper limit of normal
$\mu\text{m}$	micrometer
$\mu\text{mol}$	micromole
UNTH Enugu	University of Nigeria Teaching Hospital at Enugu
US	ultrasound; ultrasonography
UTI	urinary tract infection

## V

V/Q	ventilation-perfusion scan
V <sub>1</sub> , V <sub>2</sub> , V <sub>3</sub> , V <sub>3</sub> -V <sub>6</sub>	unipolar electrocardiogram lead (1-6)

VAS	visual analogue scale
VC	Vital capacity
VCFc	velocity of circumferential fiber shortening
VOC	vaso-occlusive crisis
Vrft	velocity of regurgitant flow of tricuspid
vs.	versus

## W

walk-PHaSST	Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy
WBC	white blood cell; white blood cell count
wt	weight

## Y

yr	year
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## Z

ZDV	zidovudine
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