
Hydroxyurea for Sickle Cell Disease: A Systematic Review of Benefits, Harms, and Barriers of Utilization, 2012

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Disclaimer

This document contains evidence tables that have been prepared in good faith on the basis of published data. Data published prior to June 2007 were extracted from a systematic review by Segal et al.* (available at <http://www.ahrq.gov/research/findings/evidence-based-reports/hydscd-evidence-report.pdf>) and modified when needed. The National Heart, Lung, and Blood Institute (NHLBI) does not guarantee or warrant the accuracy, reliability, completeness, or currency of the information in this publication.

* Segal JB, Strouse JJ, Beach MC, Haywood C, Witkop C, Park HS, et al. Hydroxyurea for the treatment of sickle cell disease. Evidence Report/Technology Assessment No. 165. (Prepared by Johns Hopkins University Evidence-based Practice Center under contract No. 290-02-0018). AHRQ Publication No. 08-E007. Rockville, MD. Agency for Healthcare Research and Quality, February 2008.

Contents

Included Studies	3
Table 1. Description of Randomized Controlled Trials Investigating the Efficacy of Hydroxyurea Treatment for Sickle Cell Disease.....	3
Table 2. Quality of Randomized Controlled Trials of Hydroxyurea in Sickle Cell Disease	5
Table 3. Description of Patient Populations in Randomized Controlled Trials Concerning the Efficacy of Hydroxyurea in Sickle Cell Disease	5
Table 4. Efficacy Results of Randomized Controlled Trials in Sickle Cell Disease.....	6
Table 5. Toxicity Results in Randomized Controlled Trials of Hydroxyurea Treatment in Sickle Cell Disease	8
Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease.....	9
Table 7. Quality of Observational Studies on Hydroxyurea Use in Sickle Cell Disease**	18
Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease.....	21
Table 9. Efficacy and Effectiveness Results of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease.....	25
Table 10. Toxicities of Hydroxyurea in Observational Studies in Sickle Cell Disease	34
Table 11. Toxicities of Hydroxyurea Reported in Multiarm Observational Studies in Sickle Cell Disease Published After 2007	36
Table 12. Toxicity Results From Case Reports in Hydroxyurea Treatment of Sickle Cell Disease Only*	37
Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease.....	38
Table 14. Patient Characteristics in Studies Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease.....	42
Table 15. Adequacy of Reporting in Biomarker Studies in Sickle Cell Disease	43
Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease.....	44
Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease*	48
Table 18. Hydroxyurea Toxicity Results From Case Reports in Diseases Other Than Sickle Cell Disease*	53
Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease.....	55
Table 20. Summary of Barriers and Facilitators	60
Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers	61
Table 22. Description of Interventions To Improve Patient Care in Sickle Cell Disease.....	65
Table 23. Results of Interventions To Improve Patient Care in Sickle Cell Disease.....	67
Table 24. Outcome Data Stratified by Dosage in Adults	69
Table 25. Outcome Data Stratified by Dosage in Children.....	71
Table 26. Randomized Controlled Trials Identified Through Supplemental Search (June 1, 2010–July 11, 2014)	74
References	75
Appendix A. Study Selection Process	89
Appendix B. Methods	90
Appendix C. Data Sources and Search Strategies	91
Appendix D. Excluded Studies	104
Appendix E: Acronyms and Abbreviations	111

Included Studies

Table 1. Description of Randomized Controlled Trials Investigating the Efficacy of Hydroxyurea Treatment for Sickle Cell Disease*

Author, year	Location	Design	Recruitment start date – end date	Inclusion and exclusion criteria †	Intervention: Starting dose—titration dose	Planned duration of treatment	Quality score ‡
Adults-MSH: Ballas, 2006 ¹	North America	Randomized controlled trial (RCT)	Jan. 1992–Apr. 1993	Inclusion: Age >18 yr; sickle cell anemia (SCA); HbS α^+ -thal, pain >3/yr. Exclusion: HbS β^+ -thal; HbS β^0 -thal; HbSC; transfusion dependent; pregnancy; Opioid use (Op); substance abuse (SA); concurrent treatment with an antisickling agent (CTA); stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding.	Hydroxyurea (HU): 15 mg/kg/d—Increased 5 mg/kg every 12 weeks if absolute neutrophil count (ANC) \geq 2,000, retic and platelets \geq 80,000/ μ L, and Hb \geq 4.5 g/dL Placebo: Escalation per Data Coordinating Center (random)	2 yr	4
Adults-MSH: Ballas, 2009 ²	North America	RCT	Jan. 1992–Apr. 1993	Inclusion: Age >18 yr; SCA; HbS α^+ -thal, pain >3/yr. Exclusion: HbS β^+ -thal; HbS β^0 -thal; HbSC; transfusion dependent; pregnancy; Op; SA; CTA; stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding.	HU: 15 mg/kg/d—Increased 5 mg/kg every 12 weeks if ANC \geq 2,000, retic and platelets \geq 80,000/ μ L, and Hb \geq 4.5 g/dL Placebo: Escalation per Data Coordinating Center (random)	2 yr	4
Adults-MSH: Charache, 1995 ³	North America	RCT	Jan. 1992–Apr. 1993	Inclusion: Age >18 yr; SCA; HbS α^+ -thal, pain >3/yr. Exclusion: HbS β^+ -thal; HbS β^0 -thal; HbSC; transfusion dependent; pregnancy; Op; SA; CTA; stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding.	HU: Initial dose of 15 mg/kg/d, increased by 5 mg/kg/d every 12 weeks, unless marrow depression (ANC < 2,000 per cubic millimeter, a retic or platelet < 80,000 per cubic millimeter, or a Hb < 4.5 g/dl) was present. If present, treatment was stopped until blood counts recovered, then resumed at a dose that was 2.5 mg per kilogram lower than the dose associated with marrow depression, starting a new 12-week cycle. Placebo: Adjusted by the data coordinating center in a similar manner in order to maintain blinding.	2 yr	5
Adults-MSH: Charache, 1996 ⁴	North America	RCT	Jan. 1992–Apr. 1993	Inclusion: Age >18 yr; SCA; HbS α^+ -thal, pain >3/yr. Exclusion: HbS β^+ -thal; HbS β^0 -thal; HbSC; transfusion dependent; pregnancy; Op; SA; CTA; stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding.	NA	2 yr	4

* One ongoing trial at the time of the literature review was not included in this table, i.e., Thompson BW, et al. The pediatric hydroxyurea phase III clinical trial (BABY HUG): challenges of study design. *Pediatr Blood Cancer*. 2010;54(2):250-5. The same trial was later published as Wang WC, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377(9778):1663-72.

† When there is no excusion in the table, exclusion criteria were not reported in the articles.

‡ Quality score according to Jadad scale (5 is the max on this scale)

Author, year	Location	Design	Recruitment start date – end date	Inclusion and exclusion criteria †	Intervention: Starting dose—titration dose	Planned duration of treatment	Quality score †
Adults-MSH: Hackney, 1997 ⁵	North America	RCT	Jan. 1992–Apr. 1993	Inclusion: Age >18 yr; SCA; HbSα ⁺ -thal, pain >3/yr. Exclusion: HbSβ ⁺ -thal; HbSβ ⁰ -thal; HbSC; transfusion dependent; pregnancy; Op; SA; CTA; stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding.	NA	18 mo	3
Adults-MSH: Moore, 2000 ⁶	North America	RCT	Jan. 1992–Apr. 1993	Inclusion: Age >18 yr; SCA; HbSα ⁺ -thal, pain >3/yr Exclusion: HbSβ ⁺ -thal; HbSβ ⁰ -thal; HbSC; transfusion dependent; pregnancy; Op; SA; CTA; stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding	NA	2 yr	4 (Quality deficiency: No description of withdrawals or dropouts)
Adults-MSH: Steinberg, 1997 ⁷	North America	RCT	Jan. 1992–Apr. 1993	Inclusion: Age >18 yr; SCA; HbSα ⁺ -thal, pain >3/yr. Exclusion: HbSβ ⁺ -thal; HbSβ ⁰ -thal; HbSC; transfusion dependent; pregnancy; Op; SA; CTA; stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding.	NA	2 yr	4
Adults-MSH: Steinberg, 2003 ⁸	North America	Cohort (followup of MSH)	1996–May 2001	Inclusion: Age >18 yr; SCA; HbSα ⁺ -thal, pain >3/yr. Exclusion: HbSβ ⁺ -thal; HbSβ ⁰ -thal; HbSC; transfusion dependent; pregnancy; Op; SA; CTA; stroke in last 6 yr; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding.	NA	NA	Observational study
Adults-MSH: Steinberg, 2010 ⁹	North America	Cohort (followup of MSH)	Jan 1992–August 1999	Original MSH patient participants	Although patients were followed prospectively using a predetermined protocol, ethical tenets required that treatment no longer be randomized. Therefore, hydroxyurea was used according to patient and physician discretion	2 yr for RCT (followup of 17.6 yr)	Observational study
Pediatric-Belgian Trial: Ferster, 1996 ¹⁰	Europe	Cross-over	June 1992–Dec. 1993	Inclusion: SCA, HbSα ⁺ -thal; 3/yr pain episodes, stroke; acute chest syndrome (ACS); splenic sequestration. Exclusion: HbSβ ⁺ -thal; HbSβ ⁰ -thal	HU: 20 mg/kg/d—Increased by 5 mg/kg/d after 2 mo, if no response increased to 25 mg/kg. Placebo: Not described	HU: 6 mo Placebo: 6 mo	3

Table 2. Quality of Randomized Controlled Trials of Hydroxyurea in Sickle Cell Disease

RCT	Blinding: Patients	Blinding: Outcome assessors	Blinding: Data collectors	Blinding: Data analysts	Blinding: Caregivers	Allocation concealment	Loss to followup described	Discontinued trial
MSH , Charache, 1995 ³	Yes	Yes	Yes	NR	Yes	Yes	No	Yes
Belgian trial: Ferster, 1996 ¹⁰	Yes	No	No	No	No	Yes	Yes	No

Table 3. Description of Patient Populations in Randomized Controlled Trials Concerning the Efficacy of Hydroxyurea in Sickle Cell Disease

Author, year	Patient groups Intervention (N)	Recruitment start date – end date	Mean Age	% Male	Race, n	Genotype/haplotype, n (%)	Last observation
MSH: Ballas, 2006 ¹	HU (141) Placebo (136)	Jan. 1992–Apr. 1993	Mean age NR Age Distribution: 18–29 (51%) 30– 39 (39%) 40–49 (9%) >=50 (1%)	49	NR	HbSS (100)	24 mo
MSH: Ballas, 2009 ²	HU (16) Non-HU (33) Unknown HU exposure (45)	Jan. 1992–Apr. 1993	27 (females), 29.8 (males)	45	NR	HbSS (100)	17 yr
MSH: Charache, 1995 ³	HU (152) Placebo (147)	Jan. 1992–Apr. 1993	HU: 30 Placebo: 31	HU: 49 Placebo: 48	HU: Black non-Hispanic, 149; Black Hispanic, 1; Other, 2 Placebo: Black non-Hispanic, 142; White Hispanic, 2; Other, 3	HU: HbSS, 151; HbSβ ⁰ -thal, 1 Benin/Benin, (36); Benin/CAR, (21); Benin/Senegal, (3); Senegal/CAR, (3); Other (23) Placebo: HbSS, 145; HbSβ ⁰ -thal, 2, Benin/Benin, (43); Benin/CAR, (20); Benin/Senegal, (3); Senegal/CAR, (3); Other (17)	28 mo
MSH: Charache, 1996 ⁴	HU (152) Placebo (147)	Jan. 1992–Apr. 1993	HU: 30 Placebo: 31	HU: 49 Placebo: 48	HU: Black non-Hispanic, 149; Black Hispanic, 1; Other, 2 Placebo: Black non-Hispanic, 142; White Hispanic, 2; Other, 3	HU: HbSS, 151; HbSβ ⁰ -thal, 1 Benin/Benin, (36); Benin/CAR, (21); Benin/Senegal, (3); Senegal/CAR, (3); Other (23) Placebo: HbSS, 145; HbSβ ⁰ -thal, 2, Benin/Benin, (43); Benin/CAR, (20); Benin/Senegal, (3); Senegal/CAR, (3); Other (17)	HU: mean 28±6 mo Placebo: mean 28±7 mo
MSH: Hackney, 1997 ⁵	HU (10) Placebo (14)	Jan. 1992–Apr. 1993	HU: 30.5 Placebo: 29.8	HU: 60 Placebo: 57	NA	HbSS (100)	18 mo
MSH: Moore, 2000 ⁶	HU (152) Placebo (147)	Jan. 1992–Apr. 1993	HU: 30 Placebo: 31	HU: 49 Placebo: 48	HU: Black 149 Other: 3 Placebo: Black 144 Other: 3	NR	NR
MSH: Steinberg, 1997 ⁷	HU (152) Placebo (147)	Jan. 1992–Apr. 1993	HU: 30 Placebo: 31	48	NR	HbSS 296 (98.7) HbSβ ⁰ -thal 3 (1) HbSβ ⁺ -thal 1 (0.3)	Mean 28 mo (range=21–38)

Author, year	Patient groups Intervention (N)	Recruitment start date – end date	Mean Age	% Male	Race, n	Genotype/haplotype, n (%)	Last observation
MSH: Steinberg, 2003 ⁸	HU (152) Placebo (147)	Jan. 1992–Apr. 1993	NR	NR	NR	NR	HU: 7.7 yr Placebo: 7.4 yr
MSH: Steinberg, 2010 ⁹	Never on HU (44) HU <5 yr (140) HU 5–10 yr (55) HU 10–15 yr (40) HU >15 yr (20)	Jan. 1992–Apr. 1993	NR	Never on HU: 47.7 HU <5 yr: 43.6 HU 5–10 yr: 60 HU 10–15 yr: 50 HU >15 yr: 55	NR	NR	17.5 yr
Belgian trial: Ferster, 1996 ¹⁰	HU (25)	June 1993–Dec. 1993	Median, 9; range, 2–22	48	Black non-Hispanic, 25	HbSS, 25	12 mo

Table 4. Efficacy Results of Randomized Controlled Trials in Sickle Cell Disease

Author, year	Intervention (N)	Mean durations of drug and followup	Deaths, n (%)	HbF, % ± SD	F cells, % ± SD	Hemoglobin, g/dL	MCV, fL ± SD	Reticulocyte count, k/μL	Weight change, kg (%)	Change in peak power, watts ± SEM	Pain crises and admissions	Transfusion
MSH: Ballas, 2006 ¹	HU (141) Placebo (136)	HU: 24 mo Placebo: 24 mo	1 (0.36)	HU: Mean increase of 0.4 g/dL from baseline PL: Mean loss of 0.1 g/dL from baseline	NR	NR	NR	NR	NR	NR	NR	NR
MSH: Charache, 1995 ³	HU (152) Placebo (147)	HU: 24 mo Placebo: 28 mo	8 (2.7)	HU: 8.6±6.8 Placebo: 4.7±2.2	NR	HU: 9.1±1.5 Placebo: 8.5±1.3	NR	HU: 231±100 Placebo: 300±99	HU: (3) Placebo: (6)	NR	HU: ACS, 25 [#] Placebo: ACS, 51 ^{††}	HU: 48 ^{**} Placebo: 73 ^{†††}
MSH: Charache, 1996 ⁴	HU (152) Placebo (147)	HU: 24 mo Placebo: 28±6 mo	HU: 2 Placebo: 5 or 6	NA	NA	NA	NA	NA	NA	NA	NA	HU: 55 Placebo: 79
MSH: Hackney, 1997 ⁵	HU (10) Placebo (14)	HU: 24 mo Placebo: 18 mo	NA	NA	NA	NA	NA	NA	HU: 3.2±0.8 [†] Placebo: 1.8±0.8 [‡]	HU: 104.9±31 Placebo: 57.7±20	NA	NA
MSH: Moore, 2000 ⁶	HU (152) Placebo (147)	HU: 24 mo Placebo: NR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MSH: Steinberg, 1997 ⁷	HU (152) Placebo (147)	HU: 24 mo Placebo: 28 mo (range, 21–38)	NA	HU: 3.6±5.4 [§] Placebo: -0.4±2 [§]	HU: 15.2±17.3 [§] Placebo: 2.3±7.1 [§]	NA	HU: 9.7±11.2 [§] Placebo: -0.4±4.8 [§]	HU: 97±107 [§] Placebo: 21±72 [§]	NA	NA	NA	NA

Author, year	Intervention (N)	Mean durations of drug and followup	Deaths, n (%)	HbF, % ± SD	F cells, % ± SD	Hemoglobin, g/dL	MCV, fL ± SD	Reticulocyte count, k/μL	Weight change, kg (%)	Change in peak power, watts ± SEM	Pain crises and admissions	Transfusion
MSH: Steinberg, 2003 [§]	HU (152) Placebo (147)	HU: 7.7 yr Placebo: 7.4 yr	HU: 36 (23.7) Placebo: 39 (26.5)	NA	NA	NA	NA	NA	NA	NA	HU: stroke, 8* Placebo: stroke, 6*	NA
MSH: Steinberg, 2010 [§]	Never on HU (44) HU <5 yr (140) HU 5–10 yr (55) HU 10–15 yr (40) HU >15 yr (20)	Never on HU: 17.5 yr HU <5 yr: 17.5 yr HU 5–10 yr: 17.5 yr HU 10–15 yr: 17.5 yr HU >15 yr: 17.5 yr	Never on HU: 16 (36) HU <5 yr: 78 (56) HU 5–10 yr: 26 (47) HU 10–15 yr: 9 (23) HU >15 yr: 0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Other controlled trial: Ferster, 1996 ¹⁰	HU (22) Placebo (22)	HU: 6 mo Placebo: 22 mo	NA	HU: 10.8 ^{§§}	NA	HU: 0.4 [§]	HU: 10.41 ^{§§}	HU: -46 ^{§§}	NA	NA	HU: 1.1 ^{††} Placebo: 2.8 ^{##}	NA

* Stroke

† Mean ± SEM, $p < .005$

‡ (Mean ± SEM)

§ Change from baseline, mean±SD where applicable.

|| Patients, $P = .002$, red blood cell (RBC) units transfused, 423 $P = .002$

†† Patients, RBC units transfused, 670.

$p < .001$, Median time to first crisis, 3 mo, $p < .01$, pain crises per yr, 2.5 (Odds Ratio (OR) 0.6–7).

** $p < .001$, RBC units transfused, 336.

†† Median time to first crisis, 1.5 mo. Pain crises per yr, 4.5 (IQR 2–10.2)

RBC units transfused, 586

§§ $p < .001$

|| $p = NS$

††† $p = .016$, days hospitalized, 3.6, $p = .0027$, hospitalizations/yr

days hospitalized, 11.7, hospitalizations/yr

Table 5. Toxicity Results in Randomized Controlled Trials of Hydroxyurea Treatment in Sickle Cell Disease

Author, year	Intervention (N)	Mean drug duration	Death, n (%)	Thrombocytopenia	Neutropenia, %	Absolute neutrophil count, $\mu\text{L}\pm\text{SD}$	% Gastrointestinal (GI) disturbance	% rash or nail changes	Lower extremity ulcers	Other toxicities
MSH: Ballas, 2009 ²	HU (16) Non-HU (33) Unknown HU exposure (45)	NR	NA	NA	NA	NA	NA	NA	NA	Study conducted to assess HU exposure effects on abortion for female patients and female partners of male patients. Authors concluded that exposure of the fetus to HU does not cause teratogenic changes in pregnancies that terminate in live birth (full term or premature)
MSH: Charache, 1995 ³	HU (152) Placebo (147)	HU: 24 mo Placebo: 28 mo	HU: (2) Placebo: (5)	HU: 4 Placebo: 5	NR	HU: 4,900 \pm 2,000 Placebo: 6,400 \pm 2,000	NR	NR	HU: 15 Placebo: 17	HU: Hb >12.8 g/dL, 11 platelets >800,000/ μL , 4 Placebo: Hb >12.8 g/dL, 1 total; bilirubin >10 mg/dL, 4
MSH: Charache, 1996 ⁴	HU (152) Placebo (147)	HU: 24 mo Placebo: 28 \pm 6 mo	HU: (2) Placebo: (6)	NR	66	NA	HU: 59 Placebo: 58	HU: 25 Placebo: 25	HU: 15 Placebo: 17	HU: hair loss, 18; fever, 91; aplastic crisis, 1; aseptic necrosis, 9; lymphadenopathy, 45; bleeding tendency, 7 Placebo: hair loss, 28; fever, 96; aplastic crisis, 5; aseptic necrosis, 9; lymphadenopathy, 56; bleeding tendency, 3
MSH: Steinberg, 1997 ⁷	HU (152) Placebo (147)	HU: 24 mo Placebo: 28 mo (range, 21–38)	NR	NR	NR	HU: 1,900* \pm 2,400 Placebo: 400 \pm 2,200	NR	NR	NR	NR
MSH: Steinberg, 2003 ⁸	HU (152) Placebo (147)	HU: 7.7 yr Placebo: 7	HU: 36 (23.7) Placebo: 39 (26.5)	NR	NR	NR	NR	NR	NR	HU: malignancy, 1; sepsis/infection, 18; hepatic failure, 3; renal failure, 14 Placebo: malignancy, 1; sepsis/infection, 20; hepatic failure, 10; renal failure, 14

Author, year	Intervention (N)	Mean drug duration	Death, n (%)	Thrombocytopenia	Neutropenia, %	Absolute neutrophil count, $\mu\text{L}\pm\text{SD}$	% Gastrointestinal (GI) disturbance	% rash or nail changes	Lower extremity ulcers	Other toxicities
MSH: Steinberg, 2010 ⁹	Never on HU (44) HU <5 yr (140) HU 5–10 yr (55) HU 10–15 yr (40) HU >15 yr (20)	Never on HU: None HU <5 yr: HU 5–10 yr: HU 10–15 yr: HU >15 yr:	Never on HU: 16 (36) HU <5 yr: 78 (56) HU 5–10 yr: 26 (47) HU 10–15 yr: 9 (23) HU >15 yr: 0 (0)	NR	NR	NR	NR	NR	NR	Never on HU: stroke: 0; renal disease: 9; hepatic disease: 5; malignancy: 0; infection: 3 HU <5 yr: stroke: 12; renal disease: 27; hepatic dis-ease: 9; malignancy: 1; infection: 27 HU 5–10 yr: stroke: 3; renal disease: 10; hepatic disease: 3; malignancy: 2; infection: 15 HU 10–15 yr: stroke: 0; renal disease: 5; hepatic disease: 1; malignancy: 0; infection: 10 HU >15 yr: stroke: 3; renal disease: 1; hepatic dis-ease: 0; malignancy: 0; Infection: 0
Belgian Study: Ferster, 1996 ¹⁰	HU or placebo (25)	6 mo 22 mo	0	6 mo: 2 22 mo: 0	NR	NR	NR	NR	NR	6 mo: No clinically significant toxicity

* Change from baseline, mean \pm SD.

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
Al-Jam'a, 2002 ¹¹	Middle East	Adults, children/prospective	Efficacy	To assess the efficiency and safety of HU in patients with SCD from the Eastern Province, Kingdom of Saudi Arabia	Inclusion: Age: >5 yr, SCA, HbS β^+ -thal, HbS β^0 -thal, HbS α^+ -thal, pain \geq 4 admissions for vaso-occlusive crisis (VOC) in past year. Exclusion: Transfusion, pregnancy, renal failure, abnormal renal tests, liver failure, abnormal hepatic function tests, HIV+, progesterones other than in oral contraceptive pills (OCPs), theophyllines, androgens, estrogens	500 mg/d, 500 mg QID if wt <50 kg: 500 mg each month until maximum tolerated dose (MTD) or 35 mg/kg reached	18.5 [12–49]	89
Ataga, 2006 ¹²	North America	Adults/prospective	Effectiveness	To evaluate the trends of development of pulmonary hypertension (PHTN), the association of PHTN with clinical and laboratory measures and the effect of PHTN on mortality in SCD patients	Inclusion: SCA, HbS β^+ -thal, HbS β^0 -thal, HbS α^+ -thal, HbSC. Exclusion: ACS in last 4 weeks, current crisis, or acute illness	NR	NR	40

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
Bakanay, 2005 ¹³	North America	Children and adults, retrospective	Effectiveness	To report on the demographic, clinical, and laboratory characteristics of a group of patients who died of complications while on HU therapy compared with HU-treated surviving patients	Patients with SCD who were followed up at the Sickle Cell Center (Medical College of Georgia, Augusta) and were treated with HU for 1 to 180 months	15 mg/kg/d: 5 mg/kg as tolerated	36 [5–78]	50
Berthaut, 2008 ¹⁴	Europe	Adult males/retrospective	Toxicity	To investigate the toxicity of HU on sperm parameters and fertility	Inclusion: SCD males	20–30 mg/kg/d	NR	33
Chaine, 2001 ¹⁵	Europe	Adults/retrospective	Toxicity	To evaluate the risk of cutaneous adverse reactions in SCD patients treated with HU	Inclusion: Adult, SCA, HbSβ ⁺ -thal, HbSβ ⁰ -thal, HbSα ⁺ -thal, HbSC, on HU ^{††}	14–28 mg/kg/d	12 (MTD plus time to escalate)	52
Charache, 1992 ¹⁶	North America	Adults/prospective	Efficacy	To assess pharmacokinetics, toxicity, and increase in HbF production in response to daily doses of HU in patients with SCA	Inclusion: Age: >18 yr, SCA, HbSα ⁺ -thal, pain admissions >1 in last year (including emergency department (ED) visits) Exclusion: HbSβ ⁺ -thal, HbSβ ⁰ -thal, transfusion, pregnancy, renal failure, abnormal renal function tests, liver failure, abnormal hepatic function tests, HIV+, AST>100 U/L, albumin <3 g/dL, theophylline containing drugs, androgens, estrogens, or progesterones (other than birth control)	10–20 mg/kg/d depending on area under the curve (AUC) at 6 h: Increase 5 mg/kg/d every 8 weeks	9 [0–25]	89
Cummins, 2003 ¹⁷	Europe	Adults/prospective	Efficacy	To compare patients with SCD treated with cognitive behavioral therapy with patients treated with HU in terms of quality of life, pain experience, health service utilization, and pain coping strategies	Inclusion: Age=adult, SCA, HbSβ ⁺ -thal, HbSβ ⁰ -thal, HbSα ⁺ -thal, HbSC	Weight-based	23 [12–39]	37
Dahoui, 2010 ¹⁸	Middle East	Children, adults/cross-sectional	Prevalence of comorbidity	To assess the prevalence of PHTN in patients with SCD	Inclusion: HbSS, HbSβ ⁰ -thal, and HbSβ ⁺ -thal	HU initiated at 10–15 mg/kg/d then increased until reaching adequate clinical response	44.4 [36-56]	44
de Montalembert, 1997 ¹⁹	Europe	Children/prospective	Efficacy	To observe the safety and efficacy of HU in previously severely ill children with SCD	Inclusion: Age=4–20 yr, SCA, HbSβ ⁺ -thal, HbSβ ⁰ -thal, HbSα ⁺ -thal, HbSC, pain ≥3 hospitalizations in last yr Exclusion: HIV+, renal insufficiency CrCL <120 mL/min/1.73 m ² , iron deficiency or current iron supplementation, history of frequent and severe infections, monthly followup would be difficult, hypersplenism, hepatic insufficiency (ALT>5xULN, or chronic hepatic disease)	20 mg/kg/d 4 d/week: In-crease 5 mg/kg/d every 4 weeks to a maximum dose of 40 mg/kg/d	32 [12–59]	85

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
de Montalembert, 1999 ²⁰	Europe	Children/prospective	Toxicity	To evaluate the tolerance of HU in children affected with SCD	Inclusion: Age=2–20 yr when starting HU	NR	22 [0.5–93]	18
de Montalembert, 2006 ²¹	Europe	Children/prospective	Toxicity	To assess the tolerability of HU treatment in 225 children with SCD	Inclusion: Pain ≥3 admissions, stroke and unable or refused transfusion, ACS, recurrent severe chronic anemia Hb <6–7, high transcranial Doppler (TCD) velocity, cardiac ischemia	20 mg/kg/d 4 d/week, then 4–7 d/week from 1997 to 2003: Up to 40 mg/kg/d, increased to 40 mg/kg/d if no response after 6 mo	46 [0–152]	71
el-Hazmi, 1992 ²²	Middle East	Adults/prospective	Efficacy	To assess the effective-ness of HU in managing severe forms of SCD	NR	20 mg/kg/d: No titration	3	57
Ferguson, 2002 ²³	North America	Adults/retrospective ^{††}	Effectiveness	To assess the efficacy of HU in settings outside a clinical trial with longer followup	Inclusion: Age=adults, SCA, treated at 2 hospitals Exclusion: HbSβ ⁺ -thal, HbSβ ⁰ -thal, HbSα ⁺ -thal, HbSC, transfusion, pregnancy, SA, stroke in past 6 yr	Every 8 weeks. Dosing based on MSH model	21.6 [3–60] ^{§§}	57
Ferster, 2001 ²⁴	Europe	Children/prospective	Effectiveness	To evaluate the long-term efficacy and toxicity of HU in the Belgian registry of HU-treated SCD patients	Inclusion: Age=children and young adults; pain ≥2 admissions/yr; or stroke, or transient ischemia attack (TIA), or ACS, or priapism, ischemic bone	20 mg/kg; 5 mg/kg at the will of the doctor [¶]	42	63
Flanagan, 2010 ²⁵	North America	Children/prospective	Effectiveness	To investigate the effect of HU on production of micronuclei (MN) in RBCs	Inclusion: Children with SCD	25 mg/kg/d, escalating to MTD	24	39
Gordeuk, 2009 ²⁶	United States	Children, young adults/cross-sectional	Effectiveness	The role of HU and HbF in protecting from PHTN	Inclusion: Age=3–22 yr, HbSS, HbSC, HbSβ-thal	NR	24	38
Gulbis, 2005 ²⁷	Europe	Children/prospective	Effectiveness	To assess the efficacy and safety of HU	Inclusion: Age=children and young adults; pain ≥2 admissions/yr; or stroke, or TIA, or ACS, or priapism, or ischemic bone	20 mg/kg; 5 mg/kg at will of doctor	47 [#]	54
Hanft, 2000 ²⁸	North America	Adults, children/retrospective	Toxicity	To investigate the mutagenic and carcinogenic potential of long-term HU use in patients with SCD or myeloproliferative disorders (MPDs)	Inclusion: SCA, MPD, abnormal TCD, cardiac ischemia	NR	Up to 180	31
Hankins, 2005 ²⁹	North America	Children/prospective	Efficacy	To study the long-term efficacy and toxicity of HU on infants, and to define the role of HU in preventing organ dysfunction	Inclusion: Enrolled in HUSOFT [§]	20 mg/kg; 5 mg/kg every 6 mo to maximum 30 mg/kg	58.8 [25–72]	67

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
Hankins, 2007 ³⁰	North America	Children/prospective	Effectiveness	To investigate the effects of HU on spleen and brain through retrospective data review of children with SCD treated with HU	Inclusion: Children, SCA, HbS β^0 -thal	15–20 mg/kg/d: Every 8 weeks to 3,035 mg/kg ^{†††}	29 [2–103]	43
Hankins, 2008 ³¹	North America	Children/retrospective	Effectiveness	To evaluate the effect of HU in the preservation of spleen and brain function in children with SCD	Inclusion: Children with HbSS or HbS β -thal, on HU, and performed either LS scan or brain magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA)	15–20 mg/kg/d, increased to a MTD that did not exceed 30–35 mg/kg/d, dose escalation occurred at 8-week intervals over a 6-mo period	36	63
Harrod, 2007 ³²	North America	Children/prospective	Toxicity	To quantitate Howell-Jolly Bodies in a large cohort of children with SCD and analyze according to sickle genotype, age, splenectomy status, and HU exposure	Inclusion: <20 yr of age Exclusion: HbS β^+ -thal, HbS β^0 -thal	NR	NR	39
Helton, 2009 ³³	United States	Children/cross-sectional	Efficacy	To evaluate cerebral blood flow in grey and white matter of children with SCD	Inclusion: Children, HbSS Exclusion: Children requiring sedation to undergo MRI	NR	NA	64
Italia, 2009 ³⁴	South Asia	Children, adults/prospective	Efficacy	To examine the efficacy of HU on adults and children with SCD and adult HbS β -thal	Inclusion: Frequent VOCs (>5/yr), central nervous system (CNS) affected at least once in the past, ACS >twice in the past, avascular necrosis of femoral head along with any of the above	10–15 mg/kg/d	24	75
Khayat, 2006 ³⁵	Central or South America or Mexico	Adults, children/retrospective	Toxicity	To determine the frequency of chromosome aberrations and the mitotic index as a criteria for evaluation of the genotoxicity and cytotoxicity of HU in SCD patients	NR	25 mg/kg/d	12	27
Kinney, 1999 ³⁶	North America	Children/prospective	Toxicity	To determine the safety and efficacy of HU in pediatric patients with SCA. This is the phase I/II HUG KIDS study. The goal was to establish MTD	Inclusion: 5–15 yr, SCA, pain \geq 3/yr or ACS episodes in last year, 6 documented heights and weights for at 2 yr preceding enrollment Exclusion: Transfusion, pregnancy, renal failure, liver failure, sepsis, ALT>2, HIV+, theophylline containing drugs, estrogen, Ca-blockers	15 mg/kg/d: Up 5 mg/kg for 8 weeks up to 30 mg/kg	Up to 24	86

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
Kratovil, 2006 ³⁷	North America	Children/prospective	Efficacy	To determine if HU therapy affected TCD velocities and whether changes in velocities could be associated with changes in hematologic parameters	Inclusion: SCA, pain >5/yr, stroke and not transfused, 2nd alloantibodies, or poor chelation, severe ACS, TCD exam before and during HU Exclusion: Transfusion, none in 6 mo, substance abuse, drugs	15 mg/kg/d: 5 mg/kg/d every 8 weeks to maximum of 30–2 mg/kg/d or 2,000 mg/d or MTD	[6–48]	73
Lefevre, 2008 ³⁸	Europe	Children/retrospective	Effectiveness	To evaluate the effect of HU in prevention of stroke in children with SCD	Inclusion: Children with SCD with TCD preformed within last 25 yr	NR, not MTD	NR	33
Little, 2006 ³⁹	United States	Adults/retrospective	Safety and efficacy	To evaluate toxicity and safety of concomitant use of HU and erythropoietin	Inclusion: HbSS, HbSC, adults	HU: 7.9–24.5 mg/kg/d Erythropoietin (EPO): >963 (>327 to 2,718) U/kg/week in group A (high-risk, HU intolerant) patients, and >589 (>107 to 734) U/kg/week In group B (high-risk, relative renal insufficiency) patients	Median = 16 [11+ to 34+]	75
Loukopoulos, 1998 ⁴⁰	Europe	Adults/retrospective	Efficacy	To report on the effectiveness of HU in patients with thalassemia—a report of a physician's experiences	Inclusion: Age=adults, HbSβ ⁺ -thal, HbSβ ⁰ -thal	20 mg/kg/d: No titration	NR	23
Loukopoulos, 2000 ⁴¹	Europe	Adults/prospective	Efficacy	To report on a clinical trial of HU in 55 Greek-origin patients with sickle cell/β-thalassemia and patients with HbSS who had been treated with HU for several years	Inclusion: Age: ≥17 yr, SCA, HbSβ ⁺ -thal, HbSβ ⁰ -thal, pain ≥3/yr, severe disease (e.g., stroke, hyperbiliuremia) Exclusion: Pregnancy or intention to conceive	15 mg/kg/d for 4 d/week, then 25 mg/kg/d: Titrate up to 25 mg/kg/d stable for 6 mo and taper to 1.0 g daily	[6–48]	63
Lukusa, 2009 ⁴²	Europe	Adults/cross-sectional	Toxicity	Study the effects of HU and bone marrow transplant on semen variables and hormone profiles	NR	20 mg/kg/d	HU: median: 126 [96–180] HSCT: median: 186 [96–252]	50
Maier-Redelsperger, 1998 ⁴³	Europe	Children/prospective	Efficacy	To study the cellular and molecular responses to long-term HU treatment in 29 severely affected young patients with SCD	Inclusion: Pain Exclusion: Pregnancy, renal failure, renal function within normal limits, liver failure, ALT>1.5 ULN, HIV+, history of severe infections, iron deficiency	20 mg/kg/d 4 d/week: Increase 5 mg/kg/d monthly to maximum 40 mg/kg/d [↓]	22 [12–36]	77

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
Marsenic, 2008 ⁴⁴	North America	Children/prospective	Effectiveness	To investigate the extent and type of proteinuria that occurs in children with a spectrum of HbSS disease. Also to characterize glomerular permselectivity and investigate for tubular proteinuria in children with SCD. The enhanced characterization will allow better understanding of the renoprotective role of therapies such as ACEi, HU and blood transfusions	Inclusion: Stable patients with SCD	NR	NR	44
McKie, 2007 ⁴⁵	North America	Children/prospective	Effectiveness	To define the age of on-set of microalbuminuria and proteinuria in children with SCD and evaluate their association with age, sex, and Hb levels. Also to explore the safety and utility of HU and angiotensin-converting enzyme inhibitor (ACEI) in prevention and treatment of sickle cell nephropathy	Inclusion: Age: >2 and <21 yr, SCA	15–30 mg/kg/d: Based on clinical responses, mean corpuscular volume (MCV), HbF	21.8	50
Odievre, 2008 ⁴⁶	Europe	Children/cross-sectional	Effectiveness	To investigate the effect of HU on RBC adhesion molecules	Inclusion: Children, HbSS	20–25 mg/kg/d	NA (single visit)	39
Olivieri, 1998 ⁴⁷	North America	Children/prospective	Toxicity	To monitor compliance with treatment of HU and evaluate the impact of HU on splenic function in children with SCD	Inclusion: SCA, pain ≥ 3 in the previous yr, ACS, any episode in the previous yr Exclusion: Neutropenia, transfusion, pregnancy, substance abuse, or severe psychological disease interfering with accurate reporting of pain, renal failure, liver failure, ALT > x2ULN, untreated folate or iron deficiency, thrombocytopenic conditions	12.9 \pm 2.7 mg/kg/d, reduced to 10 mg/kg/d later: Dose increased by 5 mg/kg q 8–2 weeks until ANC < 2,000/ mL, retic < 80,000/mL, platelets < 100 k/ μ L, or Hb > 2 g/dL below steady state	18	88
Pashankar, 2008 ⁴⁸	United States	Children/prospective	Efficacy	To prospectively follow up on SCD patients who have PHTN and identify risk factors	Inclusion: Children, PHTN (TVR > 2.5 m/s), age > 6 yr Exclusion: Pulmonary valve stenosis, other structural obstruction to pulmonary flow	20 mg/kg/d	Median: 23 [19–31]	81
Puffer, 2007 ⁴⁹	North America	Children/cross-sectional	Effectiveness	To examine the potential cognitive benefits of HU in children with SCD and no history of overt stroke	Inclusion: 6–21 yr of age and SCD Exclusion: History of overt stroke or developmental disorders (e.g., mental retardation, cerebral palsy, etc.)	NR	NA	44

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
Rigano, 2001 ⁵⁰	Europe	Adults/prospective	Efficacy	To evaluate the efficacy of HU in a group of 22 Sicilian patients with HbS/β-thal by studying the incidence of crises, frequency of hospitalization, complications, and mortality	Inclusion: Sicilians, ≥3 sickle crises (any type) in previous yr Exclusion: HIV+, bone marrow hypoplasia	15 mg/kg/d: Increased after 3 mo if no response	>24	70
Santos, 2002 ⁵¹	Central, South America	Children/prospective	Effectiveness	To evaluate the effects of long-term therapy with HU on recovery of splenic function	Inclusion: Ages 3–22 yr, SCA, HbSβ ⁰ -thal, ≥2 episodes of priapism or ACS, ≥6 painful crisis	15 mg/kg/d: Every 8 weeks increase by 5 mg/kg/d to maximum of 30 mg/kg/d or toxicity	12	47
Schultz, 2003 ⁵²	North America	Adults/retrospective	Toxicity	To report on cases of malignancy in patients with SCD	NC	NR	22	14
Scott, 1996 ⁵³	North America	Children/prospective	Efficacy	To assess the safety and efficacy of HU for the treatment of severe SCD in children	Inclusion: Ages 10–17 yr, SCA, HbSβ ⁰ -thal, HbSα ⁺ -thal, pain admissions ≥3/yr, ACS, or priapism, contraceptive measures to prevent pregnancy Exclusion: Abnormal renal or hepatic function, noncompliance	10–20 mg/kg/d: 5 mg/kg/d every 12 weeks	43.6 [24–63]	93
Singh, 2010 ⁵⁴	India	NR/prospective	Effectiveness	To determine the efficacy of HU to treat SCD	Inclusion: HbSS	20 mg/kg/d, increased by 5 mg/kg/d when deemed appropriate	1 yr	33
Svarch, 2006 ⁵⁵	Central or South America or Mexico	Children/retrospective	Efficacy	To demonstrate that good results can be achieved and toxicity avoided by maintaining dose of HU at 15 mg/kg/d in patients with SCD	Inclusion: Ages 4–18 yr, SCA, pain ≥3 in past year, or sepsis ≥1 in past 2 yr Exclusion: ACS	15 mg/kg/d: No titration	Median=24	35
Thornburg, 2009 ⁵⁶	United States	Children/prospective	Safety and efficacy	To assess the safety and efficacy of HU in young children with SCD and to prospectively assess kidney and brain function	Inclusion: Ages 1.5–5 yr, HbSS or HbSβ ⁰ -thal	20 mg/kg/d, escalating to MTD	25	75
Thornburg, 2010 ⁵⁷	United States	Children/prospective	Adherence	Association between adherence and HbF %, barriers and facilitators to adherence	Inclusion: Children, SCD, receiving HU for at least 5 mo	The mean dose at the time of the study was 24.4 mg/kg/dose (range, 16.6–31.6 mg/kg/dose)	55.2 [4.8–135.6]	75
Vicari, 2005 ⁵⁸	Central or South America or Mexico	Adults/prospective	Effectiveness	To see if genetic determinants influence response and toxicity with HU	Inclusion: Ages >18 yr, SCA, pain ≥3/yr, ACS Exclusion: HIV+, bone marrow depression	NR, dosing similar to MSH model	30.45 [12–60]	25

Author	Location	Patient type/design	Study goal	Objective	Inclusion and exclusion criteria	HU starting dose: titration schedule	Mean observation duration in months, (SD) [range]	Quality score***
Voskaridou, 1995 ⁵⁹	Europe	Adults/prospective	Efficacy	To report on the response of Caucasian patients with SCD with complications of the disease (pain crises) to high "subtoxic" doses of HU	Inclusion: HbSβ ⁺ -thal, HbSβ ⁰ -thal, pain frequent	15 mg/kg/d, rounded up to the next 500 mg 4 d/week: Increase by 5 mg/kg increments, rounded up to the next 500 mg q 4 weeks, maximal total dose of 2.5 g/d**	[5–8.7]	54
Voskaridou, 2010 ⁶⁰	Europe	Adults/prospective	Safety and efficacy	To evaluate efficacy and safety of HU therapy on patients with SCD	Inclusion: Age: >16, 3+ painful attacks needing hospital/ER visits in the preceding year, presence of jaundice at presentation or complication of SCD Exclusion: <2 painful crises in preceding yr, presence of end-stage renal failure, pregnancy, no patient agreement on regular visits for testing and mental inability to sign forms	20 mg/kg/d single oral dose, d/c when neutrophil count <1.5 × 10 ⁹ /L and platelet count <100 × 10 ⁹ /L then restarted at 15 mg/kg/d increasing to 20 within 1 mo. If lack of response to initial dose, increased to 35 mg/kg/d and patients were dropped if no response was elicited after 6 mo	HU: 96 [1.2–204] Non-HU: 60 [1.2–216]	63
Wang, 2001 ⁶¹	North America	Children/prospective	Efficacy	To conduct a collaborative pilot trial of HU in infants with SCA to assess (1) feasibility of administration, (2) toxicity, (3) hematologic effects, and (4) effect on spleen function†	Inclusion: infants (not specified by age), SCA, HbSβ ⁰ -thal Exclusion: Splenomegaly, pregnancy, renal failure, CrCL<120 mL/min/1.73 m ² , liver failure, ALT>5n, HIV+, iron deficiency, HbA >10% from transfusion, significant nonsickle-related medical problem	20 mg/kg: No titration	24	67
Ware, 2002 ⁶²	North America	Children/prospective	Efficacy*	To identify predictors of Hb response in school-aged children with SCA receiving HU at MTD	Inclusion: Age=children, pain ≥3 in past year or ≥3 pain and ACS episodes within 1 yr of enrollment, ACS ≥3 in past 2 yr Exclusion: renal failure, "dysfunction," liver failure	15 mg/kg/d: Increase every 8 weeks to MTD or 30 mg/kg	11.7	86
Ware, 2004 ⁶³	North America	Children/prospective	Effectiveness	To describe the clinical outcome and long-term followup for a cohort of pediatric patients with SCD receiving HU for prevention of secondary stroke	Inclusion: Age=pediatric, SCA, transfusion, stroke Exclusion: HbSβ ⁺ -thal, HbSα ⁺ -thal, HbSα ⁺ -thal, HbSC	15–20 mg/kg/d, escalating to MTD	29 [12–49]	88
Zimmerman, 2004 ⁶⁴	North America	Children/prospective	Effectiveness	To investigate the long-term efficacy of HU (in improving hematologic parameters) in children with SCD receiving the MTD [†]	Inclusion: On HU for at least 6 mo, SCD	15 or 20 mg/kg: Up to 30 mg/kg if tolerated	45 (24) [6–10]	88
Zimmerman, 2007 ⁶⁵	North America	Children/prospective	Efficacy	To describe a prospective, single-institution phase II trial of HU for children with SCD and increased TCD flow velocities	Inclusion: Age all pediatric, SCA HbS/O-Arab Exclusion: HbSβ ⁺ -thal, HbSβ ⁰ -thal, HbSα ⁺ -thal, HbSC	"As in routine practice": To MTD. Dose not specified	10 (5) Median=8	73

* Used data from the phase I/II HUG KIDS study but analyses only included children who reached MTD; 5.6% of pills were returned.

† Included patients who were in HUG KIDS (n=15), in HUSOFT (n=7), and 33 patients in a secondary prevention of stroke study.

‡ Investigators matched 3 patients from CSSCD to enrolled patients by diagnosis, gender, age.

§ This was the extension study of HUSOFT. Of the 21 who completed the 2 yr in HUSOFT, 17 (of the 21) completed 4 yr, and 11 (of the 21) completed 6 yr from start.

|| Mean dosage 34.2 mg/kg administered 4 d/week.

¶ At the end of year 1 of the study, 55% were on 20–25 mg/kg, 41% were under 20 mg/kg, 4% were on 25–30 mg/kg, and 1 was on more than 30 mg/kg.

109 patients for a total of 426 patient-yr. The initial 109 children were followed for up to 8 yr (14 children with this duration).

** The maintenance phase (after first 24 weeks) was 100 mg/d for 4d/week and then patients were put into 1 of 3 arms that differed slightly in administration.

†† Recruited all adult patients who came to their institution for skin exam who had SCD and were on HU.

‡‡ Patients were stratified by duration of therapy (or completeness of therapy). 14 patients had previously participated in MSH study.

§§ Mean observation duration was 9.7 mo in the group on HU for <24 mo.

||| The cross-sectional design was based on questionnaires (in 2002 for HU patients, 2000 for cognitive behavioral therapy (CBT) patients) and review of records: There is a strong likelihood of selection bias.

¶¶ The median MTD was 30 mg/kg/d (range 15–35 mg/kg/d).

*** Study quality was assessed by either summing the ratings of 2 independent reviewers (in that case, quality will be reported in 2 rows) or by 1 reviewer, after high agreement of kappa >0.90 have been established between 2 independent reviewers (in that case, quality will be reported in 1 row). Blank cells indicate “not applicable” response by 1 reviewer. Median age reported instead of mean. Q = quality; Rev. = reviewer.

Quality of included studies was calculated by adding up the scores the study received per question if applicable. Then the result is divided by the maximum score a similar study could obtain and the percentage is used to reflect the quality of the included study. A study received 2 points for a “yes” answer, 1 point for a “to some extent/unclear” answer and no points for a “no” answer. If a question was inapplicable to current study, the answer was left blank and the question was excluded from quality measurement.

The questions used were:

1. Did the study describe the setting or population from which the study sample was drawn?
2. Were the inclusion or exclusion criteria described? (just saying “sickle cell disease” is insufficient)
3. Does the study describe the key characteristics of study participants at enrollment/baseline?
4. Was the intervention described? (intervention may be a drug or an intervention to overcome a barrier)
5. Was there a description of adherence to the drug or the completeness of the intervention?
6. Do the authors report an adjusted or stratified estimate of the treatment effect if this study compared two or more groups?
7. Do the authors report at least one objective outcome from the intervention?
8. Did the study report the number of participants lost to followup?

Table 7. Quality of Observational Studies on Hydroxyurea Use in Sickle Cell Disease*

Author, year	Study description	Inclusion or exclusion criteria described	Key characteristics of participants described	Intervention described	Adherence to the drug described	Adjusted or stratified estimate of the treatment effect provided	Reported >1 objective outcomes	Reported number of participants lost to followup	Quality score
Al-Jam'a, 2002 ¹¹	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	89
Ataga, 2006 ¹²	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 1 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	Rev. 1: 2 Rev. 2: 0	Rev. 2: 0	40
Bakanay, 2005 ¹³	Rev. 1: 2 Rev. 2: 1	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	50
Berthaut, 2008 ¹⁴	Rev.: 1	Rev.: 1	Rev.: 1	Rev.: 1	NR	NR	Rev.: 2	NR	33
Chaine, 2001 ¹⁵	Rev. 1: 2 Rev. 2: 0	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	NR	52
Charache, 1992 ¹⁶	Rev. 1: 0 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	89
Cummins, 2003 ¹⁷	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 0	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 2: 0	37
Dahoui, 2010 ¹⁸	Rev.: 2	Rev.: 0	Rev.: 1	Rev.: 2	Rev.: 0	Rev.: 0	Rev.: 2	Rev.: 0	44
de Montalembert, 1997 ¹⁹	Rev. 1: 0 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 1	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2	85
de Montalembert, 2006 ²¹	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 2	Rev.: 1	NR	Rev.: 2	Rev.: 1	71
el-Hazmi, 1992 ²²	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0	Rev. 1: 2 Rev. 2: 2	Rev. 2: 0	57
Ferguson, 2002 ²³	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 1	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 2: 0	57
Ferster, 2001 ²⁴	Rev. 1: 2 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 2	63
Flanagan, 2010 ²⁵	Rev.: 1	Rev.: 1	Rev.: 2	Rev.: 1	NR	NR	Rev.: 2	NR	39
Gordeuk, 2009 ²⁶	Rev.: 1	Rev.: 0	Rev.: 1	Rev.: 0	Rev.: 0	Rev.: 2	Rev.: 2	Rev.: 0	38
Gulbis, 2005 ²⁷	Rev. 1: 1 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 1	Rev. 2: 0	Rev. 1: 2 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	54
Hanft, 2000 ²⁸	Rev. 1: 1 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 2: 0	31
Hankins, 2005 ²⁹	Rev. 1: 1 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	67
Hankins, 2007 ³⁰	Rev. 1: 0 Rev. 2: 2	Rev. 1: 1 Rev. 2: 0	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	43
Hankins, 2008 ³¹	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 1	NR	Rev.: 2	Rev.: 2	NR	63
Harrod, 2007 ³²	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	NR	39
Helton, 2009 ³³	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	Rev.: NA	64
Italia, 2009 ³⁴	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 0	Rev.: 2	Rev.: 0	75

Author, year	Study description	Inclusion or exclusion criteria described	Key characteristics of participants described	Intervention described	Adherence to the drug described	Adjusted or stratified estimate of the treatment effect provided	Reported >1 objective outcomes	Reported number of participants lost to followup	Quality score
Khayat, 2006 ³⁵	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	NR	Rev. 1: 2 Rev. 2: 2	Rev. 2: 0	27
Kinney, 1999 ³⁶	Rev. 1: 1 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	86
Kratovil, 2006 ³⁷	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 2: 1	73
Lefevre, 2008 ³⁸	Rev.: 1	Rev.: 1	Rev.: 1	Rev.: 1	NR	NR	Rev.: 2	NR	33
Little, 2006 ³⁹	Rev.: 2	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	75
Loukopoulos, 1998 ⁴⁰	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 1	Rev. 1: 0 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0	Rev. 1: 1 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	23
Loukopoulos, 2000 ⁴¹	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	63
Lukusa, 2009 ⁴²	Rev.: 2	Rev.: 0	Rev.: 1	Rev.: 2	Rev.: 0	Rev.: 0	Rev.: 2	Rev.: 1	50
Maier-Redelsperger, 1998 ⁴³	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	77
Marsenic, 2008 ⁴⁴	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 2	NR	NR	Rev.: 1	NR	44
McKie, 2007 ⁴⁵	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 0	50
Odievre, 2008 ⁴⁶	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 1	NR	NR	Rev.: 2	NR	39
Olivieri, 1998 ⁴⁷	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	NR	Rev. 1: 2 Rev. 2: 2	NR	88
Pashankar, 2008 ⁴⁸	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	81
Puffer, 2007 ⁴⁹	Rev.: 2	Rev.: 2	Rev.: 2	NR	Rev.: 0	Rev.: 0	Rev.: 2	NR	44
Rigano, 2001 ⁵⁰	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 0 Rev. 2: 2	Rev. 1: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	70
Santos, 2002 ⁵¹	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1 Rev. 2: 2	NR	47
Scott, 1996 ⁵³	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	93
Singh, 2010 ⁵⁴	Rev.: 1	Rev.: 1	Rev.: 0	Rev.: 1	NR	NR	Rev.: 2	Rev.: 1	33
Svarch, 2006 ⁵⁵	Rev. 1: 0 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	NR	Rev. 1: 2 Rev. 2: 1	Rev. 2: 0	35
Thornburg, 2009 ⁵⁶	Rev.: 2	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	75
Thornburg, 2010 ⁵⁷	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 0	75
Vicari, 2005 ⁵⁸	Rev. 1: 0 Rev. 2: 0	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 1	Rev. 1: 0 Rev. 2: 0	Rev. 1: 0 Rev. 2: 0	NR	Rev. 1: 1 Rev. 2:	Rev. 1: 0 Rev. 2: 0	25
Voskaridou, 1995 ⁵⁹	Rev. 1: 0 Rev. 2: 1	Rev. 1: 1 Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 1	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	54

Author, year	Study description	Inclusion or exclusion criteria described	Key characteristics of participants described	Intervention described	Adherence to the drug described	Adjusted or stratified estimate of the treatment effect provided	Reported >1 objective outcomes	Reported number of participants lost to followup	Quality score
Voskaridou, 2010 ⁶⁰	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 0	63
Wang, 2001 ⁶¹	Rev. 1: 1 Rev. 2: 1	Rev. 1: 1 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 0	Rev. 2: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	67
Ware, 2002 ⁶²	Rev. 1: 1 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 1 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	NR	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	86
Ware, 2004 ⁶³	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 1	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	NR	Rev. 1: 2 Rev. 2: 2	NR	88
Zimmerman, 2004 ⁶⁴	Rev. 1: 2 Rev. 2: 1 Rev. 3: 2	Rev. 1: 1 Rev. 2: 2 Rev. 3: 1	Rev. 1: 2 Rev. 2: 2 Rev. 3: 1	Rev. 1: 2 Rev. 2: 2 Rev. 3: 1	Rev. 1: 1 Rev. 2: 2 Rev. 3: 2	NR	Rev. 2: 2 Rev. 3: 2	Rev. 2: 2 Rev. 3: 1	86
Zimmerman, 2007 ⁶⁵	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 2	Rev. 1: 2 Rev. 2: 1	Rev. 1: 0 Rev. 2: 1	Rev. 1: 0	Rev. 1: 2 Rev. 2: 2	Rev. 1: 0 Rev. 2: 2	73

* Study quality was assessed by either summing the ratings of 2 independent reviewers (in that case, quality will be reported in 2 rows) or by 1 reviewer, after high agreement of kappa >0.90 have been established between 2 independent reviewers (in that case, quality will be reported in 1 row). Blank cells indicate “not applicable” response by 1 reviewer. Median age reported instead of mean. Rev. = reviewer.

Quality of included studies was calculated by adding up the scores the study received per question if applicable. Then the result is divided by the maximum score a similar study could obtain and the percentage is used to reflect the quality of the included study. A study received 2 points for a “yes” answer, 1 point for a “to some extent/unclear” answer and no points for a “no” answer. If a question was inapplicable to current study, the answer was left blank and the question was excluded from quality measurement.

The questions used were:

1. Did the study describe the setting or population from which the study sample was drawn?
2. Were the inclusion or exclusion criteria described? (just saying “sickle cell disease” is insufficient)
3. Does the study describe the key characteristics of study participants at enrollment/baseline?
4. Was the intervention described? (intervention may be a drug or an intervention to overcome a barrier)
5. Was there a description of adherence to the drug or the completeness of the intervention?
6. Do the authors report an adjusted or stratified estimate of the treatment effect if this study compared two or more groups?
7. Do the authors report at least one objective outcome from the intervention?
8. Did the study report the number of participants lost to followup?

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease

Author, year	Number of patients	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Acharya, 2009 ⁶⁶	HU 4 HSCT 6	NR	NR	Median: 32 [18–34]	100	NR	NR
Al-Jam'a, 2002 ¹¹	27	NR	NR	21.3 [10–36]	67	NR	Yearly pain crises 6.5 (2.8); days in hospital 34 (26)
Ataga, 2006 ¹²	HU with PHTN 9 HU without PHTN 32	HbSS 74; HbSC 12; HbSβ ⁰ -thal 5; HbSβ ⁺ -thal 9 (PHTN and no PHTN groups combined)	NR	HU with PHTN: 42.3 (11) HU without PHTN: 38.4 (12)	HU with PHTN: 42 HU without PHTN: 38	NR	HU with PHTN: History of ACS, 88%; crises in past year, 3.0 (3.6); history of stroke, 15% HU without PHTN: History of ACS, 82%; crises in past year: 3.8 (4.3); history of stroke, 8%
Bakanay, 2005 ¹³	226	NR	NR	NR	51	NR	NR
Berthaut, 2008 ¹⁴	Before HU 34 During HU 5 After HU 8	HbSS n=41, HbSC n=1, HbSβ ⁰ -thal n=2	NR	25.8 [16–48]	100%	NR	NC
Chaine, 2001 ¹⁵	17	HbSS 94; HbSβ ⁰ -thal 6	Benin 12.5; Senegal 2; CAR 3	27.1 [19–51]	53	Black (100)	2 with leg ulcers
Charache, 1992 ¹⁶	49	HbSS 100	Benin 61; Senegal, 9.3; CAR 25	27.6	55	Black (100)	NR
Cummins, 2003 ¹⁷	HU 15 CBT21	HbSS, 72 HbSC, 17 Unknown, 11	NR	HU: 33 CBT: 30.9	HU: 67 CBT: 33	NR	NR
Dahoui, 2010 ¹⁸	Normal tricuspid regurgitant velocity (TRV) 58 PHTN 27	TRV: • HbSS: 70.7 • HbSβ ⁰ : 5.2 • HbSβ ⁺ : 24.1 PHTN: • HbSS: 77.8 • HbSβ ⁰ : 3.7 • HbSβ ⁺ : 18.5	NR	12.9 (7) [2–30]	TRV: 53.5 PHTN: 55.6	Middle Eastern	94.4% with PHTN 5.6% on HU but without elevated TRV at beginning of study developed abnormal TRV on followup Mean = 44.4 months [36–56]
de Montalembert, 1997 ¹⁹	35	HbSS 94; HbSβ ⁰ -thal 3; HbSβ ⁺ -thal 3	NR	11* [3–20]	74	NR	Hospital days 29 [0–117]
de Montalembert, 1999 ²⁰	101	HbSS 98; HbSβ ⁺ -thal 1; HbSβ ⁰ -thal 1	NR	9.8 [2–20]	55	NR	1 HIV+
de Montalembert, 2006 ²¹	225	HbSS 94; HbSC 1.3; HbSβ-thal 3.5; Hb-Punjab 0.8	NR	9.2 [1.42–19]	61	NR	NR

Author, year	Number of patients	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
el-Hazmi, 1992 ²²	21	HbSS 71; HbSβ ⁰ -thal 28	NR	[17–32]	NR	NR	NR
Ferguson, 2002 ²³	HU ≥24 mo :30 HU <24 mo :30	HU ≥24 mo: HbSS 100 HU <24 mo: NR	NR	HU ≥24 mo: [20–58] HU <24 mo: [19–54]	HU ≥24 mo: 43 HU <24 mo: 30	NR	HU ≥24 mo: Transfusions 5/yr; hospitalizations 3.3/yr HU <24 mo: Transfusions 5.8/yr; hospitalizations 5.7/yr
Ferster, 2001 ²⁴	93	HbSS 99; Hb-Punjab 1	NR	7* [0.7–45]	52	Black (94)	67 had ≥2 pain crises; 9 had stroke; 19 had prior ACS
Flanagan, 2010 ²⁵	HU 37	NR	NR	NR	NR	NR	NR
Gordeuk, 2009 ²⁶	HU 150	HbSS, HbSβ, HbSD ^{LA} : 76	NR	13 [12–14]	55	NR	NR
Gulbis, 2005 ²⁷	109	HbSS 93; HbSC 3; HbSβ ⁰ -thal 3	NR	6 [0.75–19]	NR	NR	99 had ≥2 pain crises, 21 had prior ACS, 7 had prior stroke, 1 with prior TIA
Hanft, 2000 ²⁸	Adults with MPD and HU exposure 12 Adults with SCD and short HU exposure 15 Children with SCD and no HU 21 Children with SCD and low HU exposure 17	NR	NR	Adults with MPD and HU exposure: 62 Adults with SCD and short HU exposure: 29 Children with SCD and no HU: 11 Children with SCD and low HU exposure: 11	NR	NR	NR
Hankins, 2005 ²⁹	21	HbSS 95; HbSβ ⁰ -thal 5	NR	3.4* [2.6–4.4]	43	Black (100)	NR
Hankins, 2007 ³⁰	52	HbSS 99; HbSβ ⁰ -thal 1	NR	9.9* [3–17.6]	65	Black (98)	NR
Hankins, 2008 ³¹	HU 52	HbSS, 98 HbSβ ⁰ -thal, 2	NR	Spleen function (median=10) Brain function (median=11)	65%	52 Black (98%), 1 White Hispanic (2%)	NR
Harrod, 2007 ³²	HU, no splenectomy 46 No HU, no splenectomy 58 HU with splenectomy 11 No HU with splenectomy 10	HU, no splenectomy: HbSS 100 No HU, no splenectomy: NR HU with splenectomy: NR No HU with splenectomy: NR	NR	HU, no splenectomy: 12.1 No HU, no Splenectomy: 4.6 HU with splenectomy: 10.7 No HU with splenectomy: 8.7	NR	NR	NR
Helton, 2009 ³³	HU 21	HbSS, 100	NR	12 [5–17]	71	African American	Patients had a median of 1 (0–15) painful event within 2 yr before MRI examination and a median of 2 (0–4) lifetime ACS episodes

Author, year	Number of patients	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Italia, 2009 ³⁴	Adult HbSS 29 Children HbSS 25 Adult HbSβ-thal 23	Adult HbSS: 38 Children HbSS: 32 Adult HbSβ-thal: 30	Adult and children HbSS: 104/108 sickle chromosomes of groups 1, 2 were linked to the Arab-Indian haplotype: (+++++). 3/108 were linked to an atypical haplotype (----+----) and 1 to another atypical haplotype (+----+----). Adult HbSβ-thal: All sickle chromosomes were linked to the Arab-Indian haplotype except 1 linked with: (+-----)	Adult HbSS: [18–35] Children HbSS: [5–17] Adult HbSβ-thal: [18–35]	62	South-Asian	Adult HbSS: VOCs >5/yr: 100% Hospitalizations 1–2/yr: 52% Hospitalizations 3–4/yr: 17%. Hx of ACS: 10% Blood transfusions 1–2/yr: 62% Blood transfusions 3–5/yr: 10% Blood transfusions >5/yr: 3% Children HbSS: VOCs >5/yr: 100% Hospitalizations 1–2/yr: 32% Hospitalizations 3–4/yr: 56% History of ACS: 8% Blood transfusions 1–2/yr: 64% Blood transfusions 3–5/yr: 16% Adult HbSβ-thal: VOCs >5/yr: 100% Hospitalizations 1–2/yr: 43% Hospitalizations 3–4/yr: 30% History of ACS: 0% Blood transfusions 1–2/yr: 35% Blood transfusions 3–5/yr: 35%
Khayat, 2006 ³⁵	8	NR	NR	[7–20]	NR	NR	NR
Kinney, 1999 ³⁶	84	HbSS 100	NR	9.8; 9.1* [5–15]	NR	Black (100)	NR
Kratovil, 2006 ³⁷	HU 24 No HU 24	HU: HbSS 100 No HU: NR	NR	HU: 9.9 [1.7–16] No HU: 9.4 [2.1–16]	HU: 58 No HU: 67	NR	HU: Average of maximum TCD velocity 125 (32.3) cm/s ² No HU: Average of maximum TCD velocity, 128.9 cm/s ² range 79–220
Lefevre, 2008 ³⁸	HU 80 No HU 39	NR	NR	NR	NR	NR	HU: 2 strokes
Little, 2006 ³⁹	HU + EPO 13	HbSS: 92 HbSC: 8	NR	Median: 51 [24–60]	54	NR	NR
Loukopoulos, 1998 ⁴⁰	44	HbSβ ⁺ -thal: 34; HbSβ ⁰ -thal: 65	NR	NR	NR	NR	NR
Loukopoulos, 2000 ⁴¹	69	HbSS 20; HbSβ ⁰ -thal 79	All HbS were Benin	[17–50]	58	White (100)	NR
Lukusa, 2009 ⁴²	HU 4 HSCT6	NR	NR	Median: 32 [18–34]	100	NR	NR
Maier-Redelsperger, 1998 ⁴³	29	NR	Benin 9; Senegal 3; CAR 8	10.9 [4–19]	72	NR	NR

Author, year	Number of patients	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Marsenic, 2008 ⁴⁴	On HU 10 Non-HU 22	On HU: HbSS: 100	NR	On HU: 11.6 Non-HU: 8.7	On HU: 40% Non-HU: 50%	NR	NR
McKie, 2007 ⁴⁵	HU no microalbuminuria 19 HU and microalbuminuria 9 ACE-Inhibitor for microalbuminuria 9 Usual care 154	HU no microalbuminuria: HbSS, 100 HU and microalbuminuria: NR ACE-Inhibitor for microalbuminuria: NR Usual care: NR	NR	NR	NR	NR	NR
Odievre, 2008 ⁴⁶	On HU and had vaso-occlusive events 26 Non-HU and had vaso-occlusive events 20 Never had vaso-occlusive events 28 Non-SCD (controls) 27	On HU and had vaso-occlusive events: HbSS, 100 Non-HU and had vaso-occlusive events: HbSS, 100 Never had vaso-occlusive events: HbSS, 100 Non-SCD: HbAS n=21 HbAA n=6	NR	On HU and had vaso-occlusive events: Median=10; [4.0–19.0] Non-HU and had vaso-occlusive events: Median=9.5; [6.0–17.0] Never had vaso-occlusive events: Median=10.5; [5.0–20.0] Non-SCD: HbAS: median=41 [7.0–66.0] HbAA: median=17 [10.0–36.0]	NA	Black (100)	NR
Olivieri, 1998 ⁴⁷	17	NR	NR	12.4 [5–18]	NR	NR	Transfusions, 1.8; (0.5)/yr Chest syndrome, 1.3; (0.5)/yr Hospitalized days, 29.1; (4.8)/yr
Pashankar, 2008 ⁴⁸	HU 11 Non-HU 8	HBSS,100	NR	HU: 13.1 Non-HU: 13.3	47.4	NR	NR
Puffer, 2007 ⁴⁹	HU 15 No HU 50	HU: HbSS n=14, HbSβ ⁺ -thal n=1 No HU: HbSS n=37, HbSC n=8, HbSβ ⁺ -thal n=4, HbSβ ⁰ -thal n=1	NR	HU: 14.88 (5.04) No HU: 11.55 (3.03)	NR	NR	NR
Rigano, 2001 ⁵⁰	22	HbSβ ⁰ -thal, 73; HbSβ ⁺ -thal, 27	Benin 100%	[29–53]	68	White (100)	Pain crises 7/yr (mean)
Santos, 2002 ⁵¹	HU 21	HbSS n=14; HbSβ ⁰ -thal n=7	NR	Mean, 11.7 [3–22]	14	NR	NR
Schultz, 2003 ⁵²	Patients with cancer 49 Patients on HU who developed cancer 3	Patients with cancer: HbSS, 63; HbSC, 22; HbSβ ⁺ -thal, 14 Patients on HU who developed cancer: NR	NR	Patients with cancer: 34* [1.2–62]	NR	NR	NR

Author, year	Number of patients	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Scott, 1996 ⁵³	15	HbSS, 73; HbSβ ⁰ -thal, 13; HbSα ⁺ -thal, 13	NR	14 [10–17]	40	NR	NR
Singh, 2010 ⁵⁴	HU 24	NR	NR	NR	NR	NR	NR
Svarch, 2006 ⁵⁵	51	HbSS, 100	NR	[4–18]	NR	NR	Pain crises 3 [0–4] Transfusions 3.9 [0–8] Chest syndrome [0–3] Hospitalizations admissions 4 [0–6]
Thornburg, 2009 ⁵⁶	HU 14	HbSS: 100	NR	2.9 [1.75–4.4]	100	NR	12/14 subjects had significant acute clinical events, including dactylitis, painful vaso-occlusive event, bacteremia, ACS, and acute anemia. 2 underwent splenectomy for acute splenic sequestration before enrollment; 2 with subacute splenic sequestration did not undergo splenectomy; 1 developed acute splenic sequestration immediately prior to enrollment; 2 experienced only fever before enrollment
Thornburg, 2010 ⁵⁷	HU 75	HbSS: 100	NR	11.2 [3.5–17.8]	53	African/African American (74) American Indian (1)	NR
Vicari, 2005 ⁵⁸	22	HbSS: 100	Homo Bantu, 41; homo Benin, 18; hetero Bantu-Benin, 31	25.6 [18–46]	32	NR	NR
Voskaridou, 1995 ⁵⁹	14	HbSβ ⁺ -thal, 42; HbSβ ⁰ -thal, 58	NR	28.6 [19–48]	64	NR	NR
Voskaridou, 2010 ⁶⁰	HU 131 No HU 199	HbSS, 10.3; HbSβ ⁰ -thal, 40; HbSβ ⁺ -thal, 50	NR	42 [20–76]	41.2	NR	Pain crises: 7.34 (6.5) Hospitalizations: 2.11 (2.96) Transfusions required: 1.53 (5.92)
Wang, 2001 ⁶¹	28	HbSS, 96; HbSβ ⁰ -thal, 4	NR	1.3* [0.5–2.3]	57	NR	NR
Ware, 2002 ⁶²	68	NR	NR	9.5	NR	NR	NR
Ware, 2004 ⁶³	35	HbSS, 94; HbSβ ⁰ -thal, 3; HbS/O-Arab, 3	NR	11.9 [3–19.9]	66	NR	Stroke incidence, 5.7/100 patient-yr
Zimmerman, 2004 ⁶⁴	122	HbSS 86; HbSC 5.7; HbSβ ⁰ -thal 5.7; S/O-Arab 1.6	NR	11.1* [0.5–19.7]	58	NR	NR
Zimmerman, 2007 ⁶⁵	Increased TCD velocities 37	NR	NR	6.8; 5.6*	NR	NR	Median RMCA, 162 cm/s ² ; Median LMCA, 166 cm/s ²

* Mean, (SD) [range] unless otherwise noted

Table 9. Efficacy and Effectiveness Results of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease

Author	Patients/design	Study arm (N)	HbF%	%F cells	Hemoglobin (g/dL)	MCV (fL)	White blood cell (WBC) count (/μL)	Pain crises	Hospital admissions	Comments
Al-Jam'a, 2002 ¹¹	Adults-children/prospective	Post-HU 27 Pre-HU	Post-HU: 25.7 (7.3) Median= 25 [#] Pre-HU: 12.6 (5.4)	NR	Post-HU: 10.7 (1.4) Median=10.8 [#] Pre-HU: 9.71 (1.2)	NR	Post-HU: 6,260 (2,580) Median 5,600 [#] Pre-HU: 8,990 (3,480)	Pre-HU: 6.5/yr (2.8)	Post-HU: 0.93 (2.2) Median=0 [†] ; Hospital days 5.1 (13.5) median 0 [#] Pre-HU: Hospital days 33.9 (26.1)	NR
Ataga, 2006 ¹²	Adults/prospective	HU with PHTN 9 HU without PHTN 32	NR	NR	NR	NR	NR	NR	NR	In patients with PHTN, 9/26 (35%) were on HU. In patients without PHTN, 32/50 (65%) were on HU
Bakanay, 2005 ¹³	Children/retrospective	HU 226	NR	NR	NR	NR	NR	NR	NR	Very little description of study population and treatment; also raised concern about confounding by indication
Berthaut, 2008 ¹⁴	Adult males/retrospective	Before HU 34 During HU 5 After HU 8	NR	NR	NR	NR	NR	NR	NR	Before HU: Volume of ejaculate 3.08± 1.67 mL; spermatozoa concentration 38.55±43.12 ×10 ⁶ /mL; total sperm count 114.17±124.12 ×10 ⁶ ; initial forward motility 28.66±18.38% of motile; spermatozoa morphology 21.92±14.63% of normal; vitality 59.75±21.61% of living During HU: Volume of ejaculate 2.68± 1.28 mL; spermatozoa concentration 2.66±3.75 ×10 ⁶ /mL; total sperm count 7.02±10.18 ×10 ⁶ ; initial forward motility 30.00±5.77% of motile; spermatozoa morphology 34.50±21.92% of normal; vitality 52.00±14.23% of living After HU: Volume of ejaculate 2.99± 2.85 mL; spermatozoa concentration 18.46±26.86 ×10 ⁶ /mL; total sperm count 61.12±107.37 ×10 ⁶ ; initial forward motility 29.46±20.13% of motile; spermatozoa morphology 19.16±16.3% of normal; vitality 44.40±20.12% of living
Charache, 1992 ¹⁶	Adults/prospective	Post-HU (at MTD) 32 completed Pre-HU 49	Post-HU (at MTD): 15 (6) [†] Pre-HU: 4 (2)	Post-HU (at MTD): 73 (17) [†] Pre-HU: 28 (14)	Post-HU (at MTD): 9.7 (1.8) [†] Pre-HU: 8.4 (1.4)	Post-HU (at MTD): 117 (15) [†] Pre-HU: 94 (8)	Post-HU (at MTD): 8,400 (1,400) [†] Pre-HU: 13,400 (3,200)	Post-HU (at MTD): 1.3 (2)/6 mo [0-9] Pre-HU: 4 [0-20]/6 mo	NR	Post-HU (at MTD): Mean 4.3 kg weight gain [†]
Cummins, 2003 ¹⁷	Adults/prospective with comparison group	HU 15 CBT 21	NR	NR	NR	NR	NR	HU: 1.4/yr (2.1) [#] CBT: 4.3/yr (4.3)	HU: 1.1/yr (2.4) CBT: 0.9/yr (1.2)	Significant improvement in general health perception (Standard Form 36) over CBT group

Author	Patients/design	Study arm (N)	HbF%	%F cells	Hemoglobin (g/dL)	MCV (fL)	White blood cell (WBC) count (/μL)	Pain crises	Hospital admissions	Comments
Dahoui, 2010 ¹⁸	Children/adults cross-sectional	Normal TRV 58 PHTN 27	NR	NR	NR	NR	NR	NR	NR	Patients on HU had a higher prevalence of PHTN and HU was not able to stop PHTN from developing in 5 patients
de Montalembert, 1997 ¹⁹	Children/prospective	Post-HU 35 Pre-HU	Post-HU: 13.7 [3.2–27.0] [†] Pre-HU: 4 [0.85–13.9]	NR	Post-HU: 9 (1.4) <i>p</i> =.03 Pre-HU: 8.4 (1.2)	NR	NR	NR	NR	All but 2 patients had decreased frequency or termination of crises. No clear difference in weight or height velocity
el-Hazmi, 1992 ²²	Adults/prospective	Post-HU 21 Pre-HU NR	Post-HU: 19.8 (4) [†] Pre-HU: 11.8 (3.5)	NR	Post-HU: NR [†]	Post-HU: NR [†]	Post-HU: 6,629 (2,603) [†] Pre-HU: 140,667 (6,716)	NR	NR	P-value relative to baseline
Ferster, 2001 ²⁴	Children/prospective	Post-HU 93 Pre-HU NR	Post-HU: 16.7 (10.6) Pre-HU: 7.3	NR	Post-HU: 8.8 (1.2) Pre-HU: 8.2	Post-HU: 94 (11) Pre-HU: 91 [70,118]	NR	NR	Post-HU: 1.06/patient-yr Pre-HU: 2.76 (2.3)/patient-yr	Acute chest was 3.5/100 patient-yr, with no strokes during study
Flanagan, 2010 ²⁵	Children/prospective	HU 105	Baseline Median =5.9 MTD Median =19.1	NR	Baseline Median=8.1 MTD Median =9.1	Pre-HU: 86.2 Post-HU: 104.2 at MTD	Baseline Median=12.4 MTD Median =8.5	NR	NR	RBC count (baseline median=2.7 MTD median=2.5) Platelet count (baseline median=495 MTD median=364) Absolute neutrophil count (baseline median=5,989 MTD median=3,510) Absolute reticulocyte count (baseline median=246 MTD median=126)
Gordeuk, 2009 ²⁶	Children/young adults cross-sectional	HU 150 Non-HU 247	HU: 13 [11–15], only in 76 subjects Non-HU: 9 [7–10], only in 121 subjects	NR	HU: 9.7 [9.4–9.9], in 147 subjects Non-HU: 9.1 [8.9–9.3], in 235 subjects	HU: 92 [90–93], 146 subjects Non-HU: 81 [79–82], 230 subjects	HU: 8.8X10 ⁹ /L [8.2–9.5], 143 subjects Non-HU: 10.7 x10 ⁹ /L [10.2–11.2], 230 subjects	NR	NR	Study done to assess possible role of HU and HbF in PHTN. Patients on HU had higher Hb, HbF but no difference in TRV. Higher level of HbF was independently associated with higher TRV
Gulbis, 2005 ²⁷	Children/prospective	Post-HU 70 Pre-HU 109	Post-HU: 1.4 g/dL (HbF) Pre-HU: 0.3 g/dL (HbF)	NR	Post-HU: 8.7 [6.8–13] at 3 yr Pre-HU: 8.2 [6.7–10]	Post-HU: 91[70,118] Pre-HU: 83[68,113]	Pre-HU ANC: 5.2 x 10 ⁹ /L (2.8–9.3) 6 years post-HU ANC : 4.6 x10 ⁹ /L (2.0–15)	Post-HU: 2.2/patient-yr that required hospitalization	Post-HU: 1.38/patient-yr Pre-HU: 3.2 (2.7)/patient-yr	There were 426 total patient-yr of followup. Hematological outcomes at 3 yr (n=70) were 1 stroke and 5 transient ischemic attacks (1.3/100 patient-yr)

Author	Patients/design	Study arm (N)	HbF%	%F cells	Hemoglobin (g/dL)	MCV (fL)	White blood cell (WBC) count (/μL)	Pain crises	Hospital admissions	Comments
Hankins, 2005 ²⁹	Children/prospective	Post-HU 21 Pre-HU NR	Post-HU: 23.7 (7.4) [†] Pre-HU: 21.8 (7.8)	Post-HU: 82.6 (7.9) [†] Pre-HU: 80.6 (14.1)	Post-HU: 9.1 (1.4) [†] Pre-HU: 8.5 (1.2)	Post-HU: 95.1 (10.4) [†] Pre-HU: 81.7 (8.0)	Post-HU: 10,100 (5,000) [†] Pre-HU: 12,600 (4,400)	Post-HU: 33.8/100 patient-yr compared to 32.4/100 patient-yr in CSSCD [§]	NR	Post-HU: Outcomes are for 17 children after 4 yr of therapy
Hankins, 2007 ³⁰	Children/prospective	HU 25 Chronic red cell transfusion 6 Stem cell transplantation 4	NR	NR	NR	NR	NR	NR	NR	6 patients had recovery of splenic function; 24/25 had stable brain MRIs
Hankins, 2008 ³¹	Children/retrospective	Spleen function recovered or was preserved 8 Spleen function had no effect from HU 35	Spleen function recovered or pre-served: before HU =9.3, during HU =22.3. Spleen function had no effect from HU: before HU=4.0, during HU =18.2	NR	Spleen function recovered or preserved: before HU =9.1, during HU =11.1. Spleen function had no effect from HU: before HU =8.6, during HU =9.2	Spleen function recovered or pre-served: before HU =86 during HU=104. Spleen function had no effect from HU: before HU =86, during HU=107	Spleen function recovered or preserved: before HU =13.5, during HU=8.7. Spleen function had no effect from HU: before HU =15.9, during HU=8.1	NR	NR	Patients whose brain function showed improvement on MRI (n=24) Patients whose brain function worsened on MRI (n=1) (patient had a new punctate hemorrhagic area in the right deep frontal white matter) Patients whose brain function was stable on MRA (n=24) Patients whose brain function showed improvement on MRA (n=1)
Harrod, 2007 ³²	Children/cross-sectional	HU, no splenectomy 46 No HU, no splenectomy 58 HU with splenectomy 11 No HU with splenectomy 10	NR	NR	NR	NR	NR	NR	NR	HU, no splenectomy: Mature reticulocytes with Howell-Jolly bodies: 3,533±2,665 No HU, no splenectomy: 1,263±1,193 HU with splenectomy: 4,984±2,037 No HU with splenectomy: 2,101±945
Helton, 2009 ³³	Children/cross-sectional	HU 21	NR	NR	NR	NR	NR	NR	NR	Authors concluded that HU may normalize gray matter cerebral blood flow in children with SCD, but altered perfusion in white matter may persist

Author	Patients/design	Study arm (N)	HbF%	%F cells	Hemoglobin (g/dL)	MCV (fL)	White blood cell (WBC) count (/μL)	Pain crises	Hospital admissions	Comments
Italia, 2009 ³⁴	Children/adults prospective	Adult HbSS 29 Children HbSS 2) Adults HbSβ-thal 23	Adult HbSS: 23.1 (5.2) Children HbSS: 24.4 (6.3) Adults HbSβ-thal: 26.9 (10)	Adult HbSS: 82.7 (8.7) Children HbSS: 84.4 (10.8) Adults HbSβ-thal: 70.3 (18.2)	Adult HbSS: 10.7 (1.5) Children HbSS: 9.4 (1.9) Adults HbSβ-thal: 9.8 (1.7)	Adult HbSS: 95.4 (11.8) Children HbSS: 94.5 (10.6) Adults HbSβ-thal: 77.2 (12)	Adult HbSS: 8 (2) Children HbSS: 9.1 (3.4) Adults HbSβ-thal: 8.2 (3.3)	Adult HbSS: 0–1/yr: 83% 2–3/yr: 17% Children HbSS: 0–1/yr: 64% 2–3/yr: 36% Adults HbSβ-thal: 0–1/yr: 87% 2–3/yr: 13%	Adult HbSS: None: 97% 1–2/yr: 3% Children HbSS: None: 96% 1–2/yr: 4% Adults HbSβ-thal: None: 100%	NR
Kinney, 1999 ³⁶	Children/prospective	Post-HU 84 Pre-HU NR	Post-HU: 17.8 (7.2) [†] Pre-HU: 7.3	Post-HU: 66.5 (19.6) [†] Pre-HU: 34.6 (17.8)	Post-HU: 9 (1.4) [†] Pre-HU: 7.8	Post-HU: 101.3 (10.2) [†] Pre-HU: 85.9 (6.6)	Post-HU: 9,200 (3,200) [†] Pre-HU: 13,600	NR	NR	Hematological effects were attained by 6 mo (even before MTD). There was little difference between 6 and 12 mo data. Continued weight gain and linear growth
Kratovil, 2006 ³⁷	Children/prospective with a comparison group	HU 24 No HU NR	HU: 11.79 [3.8–25.4] ^{††} relative to untreated	NR	HU: 8.2 [5.2–10.6] ^{††} relative to untreated	NR	NR	NR	NR	HU: Mean of maximum TCD=111.2 cm/s. No HU: Mean of maximum TCD=124 cm/s
Lefevre, 2008 ³⁸	Children retrospective	HU 80 Non-HU 39	NR	NR	NR	NR	NR	NR	NR	HU: 2 presented stroke; 4 patients with a previous history of stroke but only 1 presented a new episode; recurrence rate of stroke was 2.9 for 100 patient-yr; incidence of first stroke 0.36 for 100 patient-yr. Non-HU: Velocity increases with age to a maximum between ages 6–9 yr
Little, 2006 ³⁹	Adults/retrospective	A: High-risk SCD with HU intolerance 5 B: High-risk SCD with relative renal insufficiency 5 C: Misc 3	13.5 [3.1–21], up from 5 [1.6–14]	47.5 [24–75], up from 22 [13–66]	8.5 [6.7–11.5], rose up from 6.4 [4.7–8.6]	NA	NA	NA	NA	NA
Loukopoulos, 1998 ⁴⁰	Adults/retrospective	Post-HU 44 Pre-HU NR	Post-HU: 23.1 (9.2) Pre-HU: 6.7(4.7)	NR	Post-HU: 9.3 Pre-HU: 8.9	Post-HU: 98.1 (15) Pre-HU: 75.7 (11)	NR	NR	NR	NR

Author	Patients/design	Study arm (N)	HbF%	%F cells	Hemoglobin (g/dL)	MCV (fL)	White blood cell (WBC) count (/μL)	Pain crises	Hospital admissions	Comments
Loukopoulos, 2000 ⁴¹	Adults/prospective	HbSS 14 HbSS 14 HbSβ ⁰ -thal 35 HbSβ ⁺ -thal 20	HbSS: M: 28 (6.5), F: 26.6 (6.7) HbSβ ⁰ -thal: M: 34.2 (12.8), F: 27.9 (14.3) HbSβ ⁺ -thal: M: 25 (6.3), F: 25.2 (6.4)	NR	HbSS: M: 10.7 (0.8), F: 9.4 (1.5) HbSβ ⁰ -thal: M: 9.8 (1.7), F: 8.8 (0.8) HbSβ ⁺ -thal: M: 9.2 (1.7), F: 9.1 (1.1)	HbSS: M: 121.5 (17.3), F: 125.4 (8.3) HbSβ ⁰ -thal: M: 100.4 (12.3) F: 100 (9.4) HbSβ ⁺ -thal: M: 90.9 (11.1) F: 88.7 (12.4)	NR	NR	NR	Mean clinical severity score of 81.7 over 12,018 patient-weeks was down from base-line score of 1,182 (arbitrary scale) Outcomes measured at maximum HbF concentrations. HbF% difference was very significant (<i>P</i> <.001) in all but female patients with HbSS. Hb difference was very significant (<i>P</i> <.001) only in male patients with HbSβ ⁰ -thal
Maier-Redelsperger, 1998 ⁴³	Children/prospective	Post-HU 29 Pre-HU NR	Post-HU: 13 (9.4) Pre-HU: 4 [0.85–13.9]	Post-HU: 54.2 (22.1) Pre-HU: 24.4	Post-HU: 9.1 (0.9) Pre-HU: 8.4 (1.2)	Post-HU: 101.8 (15.9) Pre-HU: 84.5	NR	NR	NR	NR
Marsenic, 2008 ⁴⁴	Children/cross-sectional	On HU 10 Non-HU 22	NR	NR	On HU: 9.13 Non-HU: 8.5	NR	NR	NR	NR	On HU: 60% had no proteinuria Non-HU: 42% had no proteinuria
McKie, 2007 ⁴⁵	Children/prospective	HU with no microalbuminuria 19 HU + microalbuminuria 9 HU + microalbuminurea at baseline 9 Baseline pre-HU 154	HU + microalbuminuria: 19.8 (21.5) <i>n</i> =7 HU + microalbuminurea at baseline: 8.6 (1.0)	NR	HU + microalbuminuria: 8.6 (1.0) HU + microalbuminurea at baseline: 8.0 (1.4)	HU + microalbuminuria: 104.7 (7.1) HU + microalbuminurea at baseline: 92.1 (7.0)	NR	NR	NR	HU with no microalbuminuria: 16 of 17 remained free from microalbuminuria during treatment HU + microalbuminuria: 4 of 9 normalized microalbuminuria during treatment
Odievre, 2008 ⁴⁶	Children/cross-sectional	On HU and had vaso-occlusive events (26) Non-HU and had vaso-occlusive events (20) Never had vaso-occlusive events 28 Non-SCD (controls) 27	On HU: 11.6 Non-HU: 6.5 Never had vaso-occlusive events: 8.8 Non-SCD: 0.2	NR	On HU: 87 Non-HU: 79 Never had vaso-occlusive events: 80 Non-SCD: 129	On HU: 87.6 Non-HU: 84.2 Never had vaso-occlusive events: 78.7 Non-SCD: 82.1	NR	NR	NR	On HU: Polymorphonuclear leukocytes (PMNs)+++ 2.3, platelets 246, RBCs 4.7, reticulocytes 50.85, hematocrit (Hct) 39.9 Non-HU: PMN 5.7, platelets 478, RBCs 3.1, reticulocytes 231.68, Hct 4.7 Never had vaso-occlusive events: PMN 5.5, platelets 434, RBCs 2.9, reticulocytes 303.45, Hct 24.3 Non-SCD: PMN 4, platelets 431, RBCs 2.8, reticulocytes 227.98, Hct 26.6
Olivieri, 1998 ⁴⁷	Children/prospective	Post-HU 17 Pre-HU NR	Post-HU: 16.7 (1.8) Pre-HU: 7.6 (1.6)	NR	Post-HU: 10.2 (3.6) Pre-HU: 8.9 (4.3)	Post-HU: 104 (3) Pre-HU: 87 (7)	NR	Post-HU: 1.2/yr (0.4) Pre-HU: 3.1/yr (0.5)	Post-HU: 1.7/yr (2.0) Pre-HU: 6.7/yr (2.8)	ACS rate declined from 1.3/yr to 0.2/yr. No difference in number of pitted RBCs (<i>n</i> =12 children) was observed
Pashankar, 2008 ⁴⁸	Children/prospective	HU 6 Non-HU 4	NR	NR	HU: 7.98	NR	NR	NR	NR	TRV and right ventricle pressure (RVP) decreased (40.16 to 23.6 mmHg) after 9–12 mo of therapy. O ₂ saturation increased from 90 to 93%

Author	Patients/design	Study arm (N)	HbF%	%F cells	Hemoglobin (g/dL)	MCV (fL)	White blood cell (WBC) count (/μL)	Pain crises	Hospital admissions	Comments
Puffer, 2007 ⁴⁹	Children/cross-sectional	HU 15 No HU 50	NR	NR	NR	NR	NR	NR	HU: Mean 7.40 within 12 mo No HU: Mean 3.18 within 12 mo	The HU group showed higher mean scores on all of the cognitive measures relative to the comparison group though the differences were not all statistically significant. Given that the HU group was typically older and had lower household incomes, one might expect their observed scores to be somewhat lower than the comparison group
Rigano, 2001 ⁵⁰	Adults/prospective	Post-HU 22 Pre-HU NR	Post-HU: 25.2 (5.2) [†] Pre-HU: 7.5 (5.3)	NR	Post-HU: 10 (1.5) Pre-HU: 6 (1.3)	Post-HU: 96.4 (7.2) [†] Pre-HU: 73.9	Post-HU: 10,200 (3,900) Pre-HU: 11,400 (3,900)	Post-HU: 1.1 (1.8)/yr median =0.5 [†] Pre-HU: 7/yr median=9 (all crises including pain)	Post-HU: 0.5 (1.6) [†] ; hospital days 1.2 (2.3) [†] Pre-HU: Hospital days 22.4	NR
Santos, 2002 ⁵¹	Children/prospective	HU 21	15.1 ^{§§}	NR	NR	NR	NR	NR	NR	10 patients had improvement in splenic function
Scott, 1996 ⁵³	Children/prospective	Post-HU 15 Pre-HU NR	Post-HU: 15.2 (9.8.) [4.1–31] [¶] Pre-HU: 6.9 (6.2)	NR	Post-HU: 9.5 (1.5) [7.7–13.1] Pre-HU: 8.2 (1.0)	Post-HU: 100 (15) [80–127] [†] Pre-HU: 85 (11)	NR	NR	Post-HU: 3/yr (4) Pre-HU: 7/yr (2.4)	NR
Singh, 2010 ⁵⁴	NR/prospective	HU 24	Before HU 9.15, after 1 yr 9.98	NR	NR	Before HU 82.57, after 1 yr 89.87	NR	NR	NR	NR
Svarch, 2006 ⁵⁵	Children/retrospective	HU 51 Baseline (pre-HU) NR	HU: 12.4 (7.9) [†] Baseline: 6.4	NR	HU: 8.5 (1) <i>p</i> =.0001 Baseline: 7.8	NR	HU: 9,800 (2,100) <i>p</i> =.12 Baseline: 10,900	HU: Median 0.8/yr [0–2] Baseline: Median 3/yr	HU: 0.5 [0–4] Baseline: 4 [0–6]	HU: Resource-poor environment
Thornburg, 2009 ⁵⁶	Children/prospective	HU 14	25.9 (6.6)	NR	9.5 (1)	99 (12)	NR	NR	NR	NR
Thornburg, 2010 ⁵⁷	Children/prospective	HU 75	8% increase [6.2–9.8]	NR	1.3 [1.0–1.5]	NR	NR	NR	NR	1,699 cells/mm ³ decrease in absolute neutrophil count
Vicari, 2005 ⁵⁸	Adults/prospective	Post-HU 22 Pre-HU NR	Post-HU: 10.2 (5) [*] Pre-HU: 5 (3)	NR	Post-HU: 8.6 (1.1) [‡] Pre-HU: 7.9 (0.9)	NR	NR	NR	NR	Post-HU: Outcomes reported by haplotype
Voskaridou, 1995 ⁵⁹	Adults/prospective	Post-HU 14 Pre-HU NR	Post-HU: 22.9 (7.7) Pre-HU: 3.6 (2.1)	NR	Post-HU: 9 (1.3) Pre-HU: 9 (1.2)	Post-HU: 95 (14.1) Pre-HU: 71.9 (5.7)	NR	NR	NR	NR

Author	Patients/design	Study arm (N)	HbF%	%F cells	Hemoglobin (g/dL)	MCV (fL)	White blood cell (WBC) count (/μL)	Pain crises	Hospital admissions	Comments
Voskaridou, 2010 ⁶⁰	Adults/prospective	HU 131 Non-HU 199	HU: 17.4 [0.8–38.3] Non-HU: 4.9 [0.8–38.3]	NR	HU: 9.5 [6.3–13] Non-HU: 9.1 [5.5–13.6]	HU: 96.8 [79.8–127.2] Non-HU: 71.1 [62.8–99.2]	NR	HU: 0.025 (0.026) >95% reduction	HU: 0.041 (0.018)	Some outcome data not reported for non-HU arm. Some outcomes were reported per yr
Wang, 2001 ⁶¹	Children/prospective	Post-HU 28 Pre-HU CSSCD NR	Post-HU: 20.3 (4.9) Pre-HU: 21.8 (7.8) CSSCD: 10.9 (7.9)	Post-HU: 76.2 (12.4) Pre-HU: 80.6 (14.1) CSSCD: 65.4 (11.2)	Post-HU: 8.8 (1.2) Pre-HU: 8.5 (1.2) CSSCD: 7.7 (1.0)	Post-HU: 90 (9.6) Pre-HU: 81.7 (8.0) CSSCD: 84.1 (10.1)	Post-HU: 10,100 (3,200) Pre-HU: 12,600 (4,400) CSSCD: 14,300 (2,400)	NR	NR	Post-HU: Outcomes are for 21 patients who completed 2 yr of treatment (not necessarily on MTD)
Ware, 2002 ⁶²	Children/prospective	Post-HU 68 Pre-HU NR	Post-HU: Median=17.6, [2.9–32.4] Pre-HU: 6.7	NR	Pre-HU: 7.7	Pre-HU: 85.7	Pre-HU: 14,000	NR	NR	HbF% was predicted by HbF% at baseline ($p=.001$) and Hb at baseline ($p=.01$); HbF% was negatively associated with number of pills returned ($p=.02$), positively with change in Hb ($p<.0001$), MCV ($p=.01$) and decline in reticulocytes ($p=.01$), and decline in WBC count ($p=.006$)
Ware, 2004 ⁶³	Children/prospective	HU 35	18.6 (6.6)	NR	9.2 (1.4)	112 (9)	7,300 (2,500)	NR	NR	Data collected on 2 groups; patients initiating HU after an abrupt halt to transfusion therapy, and patients initiating HU before transfusion therapy was completely halted. Pooled data were presented here. Stroke recurrence rate 5 of 7/100 patient-yr (7 children, 4 of whom were noncompliant with HU)
Zimmerman, 2004 ⁶⁴	Children/prospective	Post-HU (122) Pre-HU NR	Post-HU: 19.7 (8.5) [‡] Pre-HU: 7.6	NR	Post-HU: 9.7 (1.3) [‡] Pre-HU: 8.2	Post-HU: 105.8 (13.8) [‡] Pre-HU: 84.4 (8.5)	Post-HU: 7.0 Pre-HU: 12,400	NR	NR	Efficacy (in Hb, MCV, % HbF, WBC count, ANC, reticulocyte, bilirubin) maintained over 7 yr of followup
Zimmerman, 2007 ⁶⁵	Children/prospective	Patients with increased TCD velocities post-HU 37 Patients with increased TCD velocities pre-HU NR	Patients with increased TCD velocities post-HU: 22.7 (7.9) median= 23.3 [†] Patients with increased TCD velocities pre-HU: 10.3	NR	Patients with increased TCD velocities post-HU: 9.4 (1.1) median = 9.4 [†] Patients with increased TCD velocities pre-HU: 7.8	Patients with increased TCD velocities post-HU: 104 (9) median [†] Patients with increased TCD velocities pre-HU: 86 (8)	NR	NR	NR	Patients with increased TCD velocities post-HU: Significant decline in TCD of RMCA, LMCA, RACA, LACA, and LPCA, but not RPCA. Stroke rate on treatment 0.52/100 patient-yr, RMCA on treatment 134 cm/s, $p<.0001$. Patients with increased TCD velocities pre-HU: RMCA 162 cm/s

* $p=.0002$

$p\leq.005$

† $p \leq .0001$

‡ $p \leq .001$

†† $p \leq .00001$

§ $p \leq$ not significant

$p = .057$

|| $p \leq .01$

§§ Change from baseline

†† $p \leq .002$

Table 10. Toxicities of Hydroxyurea in Observational Studies in Sickle Cell Disease

Author	Group (number)	Primarily toxicity study	Deaths, <i>n</i> (per patient/yr)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other toxicities
Berthaut, 2008 ¹⁴	HU (44)	Yes	0	0	0	0	0	0	Before HU: Volume of ejaculate 3.08±1.67 mL, spermatozoa concentration 38.55±43.12 ×10 ⁶ /mL, total sperm count 114.17±124.12 ×10 ⁶ , initial forward motility 28.66±18.38% of motile, spermatozoa morphology 21.92±14.63% of normal, vitality 59.75±21.61% of living During HU: Volume of ejaculate 2.68±1.28 mL, spermatozoa concentration 2.66±3.75 ×10 ⁶ /mL, total sperm count 7.02±10.18 ×10 ⁶ , initial forward motility 30.00±5.77% of motile, spermatozoa morphology 34.50±21.92% of normal, vitality 52.00±14.23% of living After HU: Volume of ejaculate 2.99±2.85 mL, spermatozoa concentration 18.46±26.86 ×10 ⁶ /mL, total sperm count 61.12±107.37 ×10 ⁶ , initial forward motility 29.46±20.13% of motile, spermatozoa morphology 19.16±16.3% of normal, vitality 44.40±20.12% of living
Chaîne, 2001 ¹⁵	HU (17)	Yes	NR	NR	NR	NR	5	13	Prior leg ulcer associated with ulcer on treatment (<i>p</i> <.005); patients with ulcer were older than those without (<i>p</i> <.001); 3 of 5 resolved with holding HU
Charache, 1992 ¹⁶	HU (49)	NR	NR	17	1	NR	NR	NR	No unusual infections; karyotypic analysis showed no difference in % abnormal chromosomes pre- and posttreatment
de Montalembert, 1997 ¹⁹	HU (35)	NR	NR	NR	NR	NR	NR	5	NR
de Montalembert, 1999 ²⁰	HU (101)	Yes	NR	2 with ANC 500–1,000/μL ,3 with ANC 1,000–1,500/μL	4 with 90–100,000/μl	1	1	8	NR
de Montalembert, 2006 ²¹	HU (225)	Yes	1	8	8	1 (same patient as in earlier study) ¹⁹	NR	NR	81 patients discontinued therapy, mostly for lack of efficacy
el-Hazmi, 1992 ²²	HU (21)	NR	NR	NR	NR	NR	NR	NR	6 with leukopenia (WBC <4,500/μL)
Ferguson, 2002 ²³	HU≥24 mo (30) HU<24 mo (30)	NR	NR	NR	NR	NR	NR	NR	HU ≥24 mo: Stated no adverse events HU <24 mo
Gulbis, 2005 ²⁷	HU (109)	NR	1 (0.23/100)	NR	NR	NR	NR	NR	Transient hematological toxicity in 1.4/100 patient-yr

Author	Group (number)	Primarily toxicity study	Deaths, <i>n</i> (per patient/yr)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other toxicities
Hanft, 2000 ²⁸	HU and no HU (SCD and MPD) (95)	Yes	NR	NR	NR	NR	NR	NR	HPRT cloning efficiency and VDJ recombination events described in text
Hankins, 2005 ²⁹	HU (21)	NR	1	21 episodes in 10 patients in yr 3, 21 episodes in 9 patients in yr 4	2 in year 5, 1 in year 6	NR	NR	NR	Severe anemia 3 times in 3 patients in yr 3; 4 times in 1 patient in yr 4
Italia, 2008 ³⁴	HU (77)	No	NR	1	NR	NR	NR	NR	NR
Khayat, 2006 ³⁵	HU (8)	Yes	NR	NR	NR	NR	NR	NR	There was no significant difference in mitotic index ($p>.05$). There was no significant difference in chromosomal aberrations ($p>.05$) pre- and posttreatment
Kinney, 1999 ³⁶	HU (84)	Yes	NR	56 with ANC <2,000/ μ L	7	NR	NR	5	NR
Loukopoulos, 2000 ⁴¹	HU (69)	NR	NR	NR	NR	NR	3	0	2 with severe anemia; 0 of 40 with oncogenes; 0 of 10 with cytogenetic abnormalities
Olivieri, 1998 ⁴⁷	HU (17)	Yes	0	9	3	NR	NR	1	NR
Scott, 1996 ⁵³	HU (15)	NR	1	NR	NR	NR	NR	1	Anemia in 3 of 13 completing study
Schultz, 2003 ⁵²	Patients with SCD and cancer (49) Patients on HU with cancer (3)	Patients with SCD and cancer: Yes	NR	NR	NR	Patients with SCD and cancer: 7 of 16,613; not all on HU Patients on HU with cancer: 1	NR	NR	Patients with SCD and cancer: 49 cancers in patients with SCD described, in survey of providers Patients on HU with cancer: Unknown number taking HU, but among 49 patients, 3 were on HU, including 1 with leukemia
Thornburg, 2009 ⁵⁶	HU (14)	Yes	NR	11	4	NR	NR	NR	2 patients had combined cytopenias
Thornburg, 2010 ⁵⁷	HU (75)	No	NR	Mean change in neutrophil count: -1,699 cells/ mm^3 ; 95% CI, -2,513-885; $P<.0001$	NR	NR	NR	NR	NR
Vicari, 2005 ⁵⁸	HU (22)	NR	NR	3	NR	NR	NR	NR	NR
Voskaridou, 1995 ⁵⁹	HU (14)	NR	NR	NR	NR	NR	NR	NR	Leukopenia or thrombocytopenia in 6; rapidly reversed by holding therapy
Wang, 2001 ⁶¹	HU (28)	NR	1	17 with ANC <1,500/ μ L 6 with ANC <500/ μ L	1 with <80,000/ μ L	NR	NR	NR	NR
Zimmerman, 2004 ⁶⁴	HU (122)	NR	(2/455)	NR	NR	NR	NR	NR	No increase in the acquired illegitimate VDJ rearrangements

Table 11. Toxicities of Hydroxyurea Reported in Multiarm Observational Studies in Sickle Cell Disease Published After 2007

Author	Group (number)	Primarily toxicity study	Deaths, <i>n</i> per patient/yr	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other toxicities
Little, 2006 ³⁹	A: High-risk SCD with HU intolerance (5) B: High-risk SCD with relative renal insufficiency (5) C: Misc (3)	No	NR	NR	NR	NR	NR	NR	Twelve of the 13 patients treated with EPO did not experience worsening of symptomatic SCD, changes in ophthalmologic symptoms, or clinical thromboses while on HU and EPO. There was no evidence for pure red cell aplasia or systemic hypertension
Lukusa, 2009 ⁴²	HU (4) Hematopoietic stem cell transplantation (HSCT) (6)	Yes	NR	NR	NR	NR	NR	NR	HU: 2 patients were azoospermic HSCT: 3 patients were azoospermic
Voskaridou, 2010 ⁶⁰	HU (131) Non-HU(199)	Yes	HU: 13 Non-HU: 49	HU: 9	HU: 8	NR	NR	HU: 1	HU: 2 patients developed red cell aplasia; 2 patients developed alopecia

Table 12. Toxicity Results From Case Reports in Hydroxyurea Treatment of Sickle Cell Disease Only*

Outcome	Number of case reports	Females/Males	Mean age at toxicity	Median number of weeks on HU until toxicity	Number of case reports with certain causality**	Number of reports with probable causality**	Number of reports with possible causality**	Level of evidence for this outcome (1, 2, 3)**
Leg ulcer	1	1/0	45	104	0	0	1	3
Leukemia	3	3/0	32	288	0	0	3	3
Cytopenia	1	1/0	26	153	0	1	0	3
Avascular necrosis	3	2/1	19	NR	0	0	3	3
Splenomegaly	1	1/0	32	NR	0	0	1	3
Cryptosporidial infection	1	1/0	36	80	0	0	1	3
Intracranial hemorrhage/thrombosis	2	0/2	21.5	52	0	0	2	3
Hodgkin's lymphoma	3	0/3	8	26	0	1	2	3
Low sperm count/motility decrease	4	0/4	31	128	0	0	4	3
Acute myocardial infarction	1	0/1	28	NR	0	0	1	3
Hyperpigmentation of skin	2	1/1	16	75	0	0	2	3
Mild transient myelotoxicity	1	1/0	4	NR	1	0	0	NR
Azoospermia	3	0/3	29	17	0	1	2	NR

* Explanation of differences from this report and the NHLBI HU Consensus Conference Report by Segal et al.⁶⁷ Level of evidence column was removed due to universal low level of evidence; toxicity of mild transient myelotoxicity and azoospermia were added to the summary.

For case reports published before July 2007, certain modifications were made to the table format to fit these purposes. Please refer to the original NHLBI HU Consensus Conference Report by Segal et al.⁶⁷ For case reports published after July 2007, please refer to articles cited in ⁶⁸⁻⁷².

** WHO causality assessment: A reaction was rated as "certain" if all 4 criteria for causality were fulfilled: (1) a plausible time relationship between drug administration and an event; (2) an absence of a concurrent disease that might have caused the event; (3) a reasonable response to drug withdrawal; and (4) existence of a rechallenge or a demonstrated biological explanation. A reaction was rated as "probable" if criteria 1, 2, and 3 were fulfilled and "possible" if only criterion 1 was met and information on criterion 3 was lacking or unclear. A reaction was rated as "unlikely" if criterion 1 was not met and if other drugs, chemicals, or underlying disease provided a plausible explanation for the reaction.

1. Is the time relationship from drug administration to the event *plausible* for causality to be established?
2. Is there an absence of concurrent diseases or other drugs that may have caused the event?
3. Is there a reasonable response to drug withdrawal?
4. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease

Author, year	Location	Inclusion and exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Group 1 Outcome	Group 1 Result	Group 2 Outcome	Group 2 Result	Group 3 Outcome	Group 3 Result
Athanassiou, 2006 ⁷³	Europe	Inclusion: Unclear	Group 1: SCA Group 2: SCA treated with HU Group 3: Healthy Donors (NO SCD or HU)	NR	60 mo	Index of rigidity (IR)	HU: 31.9±12.2* SCD or HU: 46.1±13.08 NO SCD or HU: 13.15±0.5	Mean elastic shear modulus (u x 10 ⁻³ dyn/cm)	HU: 15±1.3 [†] SCD or HU: 21.1±2.1	NR	NR
Flanagan, 2010 ²⁵	North America	Inclusion: Children with SCD on HU	HU	NR	NR	Micronuclei (MN) in RBCs	Exposure to HU was associated with significantly increased frequencies of MN-CD71+ and MN-RBC compared to baseline. The increases were evident by 3 mo of therapy, and did not escalate further with up to 12 yr of continuous drug exposure; also there was no association between MN production and HU dose	NR	NR	NR	NR
Gambero, 2007 ⁷⁴	South America	Inclusion: HbSS or HbSα-thal, not in crisis, had not received blood transfusions in the preceding 3 mo, and patients on HU therapy had been taking 20–30 mg/kg/d for at least 3 mo	Group 1: Sickle cell on HU Group 2: Sickle cell Non-HU Group 3: Healthy individuals and non-splenectomised hereditary spherocytosis patients were used as controls	NR	NR	Adherence to fibronectin	RBCs from patients on HU therapy have a decreased ability to adhere to fibronectin in comparison with RBCs from patients not on HU	Reticulocytes count	Slightly lower than that of HbSS patients not on HU, significantly higher (<i>P</i> <.001) than that of normal RBCs	Adhesion molecules	HU is more likely to have an indirect effect on sickle RBC adhesion (i.e., mediated by decreased gene expression) rather than a direct effect on the affinity of the adhesion molecules already expressed on the RBC surface

Author, year	Location	Inclusion and exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Group 1 Outcome	Group 1 Result	Group 2 Outcome	Group 2 Result	Group 3 Outcome	Group 3 Result
Harrod, 2007 ³²	North America	Inclusion: Pediatric patients with sickle cell, HbSS or HbSC, ages 0–19 yr	HU	NR	NR	Howell-Jolly Bodies	HJB was significantly influenced by HU exposure	CD71+ reticulocytes	HU exposure in children with HbSS was associated with a significantly lower % of CD71+ reticulocytes, presumably reflecting the mild marrow suppression	NR	NR
Heeney, 2003 ⁷⁵	North America	Inclusion: Children; SCA; HbSβ ⁰ -thal; HbSβ ⁰ -thal Exclusion: HU before age 5 yr; No labs before HU; <12 mo of HU; Unknown or rare UGT1A genotype	UGT1A 6/6 UGT1A 6/7 UGT1A 7/7	UGT1A 6/6: 15–20 mg/kg/d: every 8 weeks to maximum of 30–35 mg/kg/d UGT1A 6/7: 15–20 mg/kg/d: every 8 weeks to maximum of 30–35 mg/kg/d UGT1A 7/7: 15–20 mg/kg/d: every 8 weeks to maximum of 30–35 mg/kg/d	At least 12 mo	HbF (%) [‡]	UGT1A 6/6: 16.4 UGT1A 6/7: 12.1 UGT1A 7/7: 13.5	Hb (g/dL) [‡]	UGT1A 6/6: 1.7 UGT1A 6/7: 1.5 UGT1A 7/7: 1.9	Total bilirubin (mg/dL) [‡]	UGT1A 6/6: -1.4 UGT1A 6/7: -1.3 UGT1A 7/7: -2.8
Italia, 2009 ³⁴	United States	Inclusion: Frequent VOCs (>5/yr), CNS affected at least once in the past, acute chest syndrome > twice in the past, avascular necrosis of femoral head along with any of the above	HU	10–15 mg/kg/d	2 yr	Xmn I polymorphism	50 patients from groups I and II were Xmn I +/+, and 4 were +/-, while 8 patients from group III were Xmn I +/+, 14 were +/-, and 1 was -/-. The latter had HbF level of 25.0% before and 28.0% after therapy. Patients with Xmn I +/+ had a mean HbF level of 17.0±6% before and 24.0±7% after therapy, while those with Xmn I +/- had a mean HbF level of 16.0±10% before and 26.0±12% after therapy	γ mRNA expression	A significant increase in γ gene mRNA levels was seen after therapy, which correlated with an increase in HbF levels studied among 10 patients	(AT)x(T)y motif	3 different motifs, (AT) 9(T)5, (AT)8 (T)9 and (AT) 7(T)7 were found in 4 different genotypes

Author, year	Location	Inclusion and exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Group 1 Outcome	Group 1 Result	Group 2 Outcome	Group 2 Result	Group 3 Outcome	Group 3 Result
Iyamu, 2005 ⁷⁶	North America	Inclusion: Age 8–21; SCA; in steady state Exclusion: Transfusion in last 6 mo; smoking; substance abuse	Group 1: steady-state (intervention = HU) Group 2: steady-state (no HU intervention) Group 3: African American HbAA	HU steady-state: 15–30 mg/kg/d No HU steady-state: No HU African American HbAA: No HU	HU steady-state: cross-sectional	HU steady-state: HbF %	HU steady-state: 13.8 No HU steady-state: 6.8	HU steady-state: Nitric oxide synthase No HU steady-state: (nmol/mL/min)	HU steady-state: 0.50 No HU steady-state: 0.27 African American HbAA: 0.32	HU steady-state: Arginase (U/nmol/1) No HU steady-state: 0 ⁸ cells ± SEM)	HU steady-state: 1.36± 0.20 [†] No HU steady-state: 3.31± 0.29 African American HbAA: 0.23
Lapoumeroulie, 2005 ⁷⁷	Europe	Inclusion: Children, SCA in steady-state	SS children with clinical events (8 on HU, 10 untreated) SS children in steady state, (no intervention) SS children in steady state, (intervention = HU) Healthy African American controls (no intervention)	NR	>12 mo	Endothelin -1 (pg/mL ± SEM)	Clinical events (8 on HU, 10 untreated): 1.32± 0.17 Steady state, No HU: 0.65±0.11 Steady state, HU: 0.37±0.05 [†] Healthy African American: 0.65± 0.07	NR	NR	NR	NR
Maluf, 2009 ⁷⁸	South America	Inclusion: HbSS, on HU at least 6 mo	Sickle cell on HU Nonsickle cell	NR	NR	Micronucleus frequency	Sickle cell on HU: 4.74 Nonsickle cell: 3.47	Frequency of nucleoplasmic bridges/ nuclear buds	There was no significant difference between the 2 groups	NR	NR
Nahavandi, 2002 ⁷⁹	North America	Inclusion: SCA Exclusion: Transfusion within 3 mo; significant renal insufficiency; infection; PHT	HU Non-HU steady- state HU during VOC Non-HU during VOC	HU: 1,200 mg/d Non-HU steady-state: No HU HU during VOC: 1,200 mg/d Non-HU during VOC: No HU	HU: 35	HU: HbF% (range)	HU: 17 (6.7–28) Non-HU steady- state: 3.6, (1.7–6) [§] HU during VOC: 19 (7–31) Non-HU during VOC: 4.2 (1.5–6.7) [§]	HU: Cyclic granule membrane protein (GMP) (pmol/mL ± SEM)	HU: 2.45±0.32 Non-HU steady-state: 1.75±0.42 HU during VOC: 2.56±0.3 Non-HU during VOC: 1.56±0.1 [§]	HU: Nitric oxide metabolite Non-HU steady-state: s (microM ± SEM)	HU: 29± 2.5 Non-HU steady-state: 19±1.8 [§] HU during VOC: 32±5 Non-HU during VOC: 17±1.7 [§]
Nahavandi, 2003 ⁸⁰	North America	Inclusion: Age 18–48; SCA Exclusion: ACS; transfused in last 3 mo; renal insufficiency; infection; hypoxemia	HU, no VOC No HU no VOC HU and VOC No HU, VOC	HU, no VOC: 1,000–1,500 mg/d HU and VOC: 1,000–1,500 mg/d	NR	Venous oxyhemoglobin (%)	HU, no VOC: 65 No HU no VOC: 60 HU and VOC: 81 No HU, VOC: 73	Venous reduced Hb (%)	HU, no VOC: 28 No HU no VOC: 36 HU and VOC: 13 No HU, VOC: 22	Nitric Oxide Metabolites (µM)	HU, no VOC: 17±9 [§]

Author, year	Location	Inclusion and exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Group 1 Outcome	Group 1 Result	Group 2 Outcome	Group 2 Result	Group 3 Outcome	Group 3 Result
Odievre, 2008 ⁴⁶	Europe	Inclusion: Children, HbSS	On HU and had vaso-occlusive events Non-HU and had vaso-occlusive events Never had vaso-occlusive events Non-SCD (controls)	NR	NR	Adhesion molecules	Reticulocytes and/or RBCs from the children with SCD showed significantly higher expression of CD36, $\alpha 4\beta 1$, Lu/BCAM than those from controls, whatever the severity of the disease, as well as less marked increases in expression of ICAM-4, CD47, and CD147. Under HU treatment, the expression of CD36, $\alpha 4\beta 1$, and ICAM-4 (to a lesser extent) was decreased, but surprisingly the expression of Lu/BCAM (and also CD47 and CD147 to a lesser extent) was significantly increased	NR	NR	NR	NR
Tavakkoli, 2004 ⁸¹	North America	Inclusion: SCA Exclusion: Transfusion in last 3 mo	HU Steady-state condition, not on HU VOC, on HU VOC, not on HU	HU: 1,000–1,500 mg: NA VOC, on HU: 1,000–1,500 mg: NA	NR	TNF- α (pm/mL)	HU: 4.89 Steady state condition, not on HU: 3.78 VOC, on HU: 6.45 VOC, not on HU: 5.86	NR	NR	NR	NR
Teixeira, 2003 ⁸²	South America/ Mexico	Inclusion: SCA; HbS β^+ -thal; HbS β^0 -thal; HbS α^+ -thal; HbSC; Age >12	HU No HU	NR	2–60 mo	HbF (%)	HU: 14.2 \pm 8.3 [§] No HU: 8.8 \pm 4.1	HU: Hb (g/dL)	HU: 9.6 \pm 2.2 [§] No HU: 8.1 \pm 0.9	NR	NR
Ulug, 2008 ⁸³	Europe	Inclusion: HbSS	10 patients were analyzed before and while taking ('on' and 'off') HU Not taking HU (n=115)	On-HU: 500 mg/d	On-HU: NR	Plasma cfDNA levels	On-HU: Mean 804 Off-HU: Mean 2,481 Non-HU: Mean 975	HbF increase/ MCV increase	On-HU: Mean 16.07/mean 103.01 Off-HU: Mean 7.08/mean 84.56 Non-HU: NR	Total Hb increase	On-HU: Mean 8.95 Off-HU: Mean 8.00 Non-HU: NR

* $p=.02$

† $p=.03$

‡ $p<.001$

§ $p<.05$

Table 14. Patient Characteristics in Studies Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease†

Author, year	Intervention (N)	Age, mean (SD) [range]*	Male, n (%)	Genotype/haplotype (%)	Last observation
Athanassiou, 2006 ⁷³	HU (22) SCD no HU (14) NO SCD or HU (5)	HU: Median, 30; [20–46] SCD no HU: Median, 32; [25–42] No SCD or HU: Mean, similar age	HU: 14 SCD no HU: 5 No SCD or HU: 40	NR	NR
Flanagan, 2010 ²⁵	HU (105)	NR	NR	NR	NR
Gambero, 2007 ⁷⁴	Sickle cell on HU (14) Sickle cell non-HU (28) Nonsickle cell	Sickle cell on HU: 31.9 Sickle cell non-HU: 32	Sickle cell on HU: 8 Sickle cell non-HU: 9	HbSS or HbS α -thal	NR
Harrod, 2007 ³²	HU (57)	11.8	NR	HbSS	NR
Heeney, 2003 ⁷⁵	HU UGT1A 6/6 (17) HU UGT1A 6/7 (24) HU UGT1A 7/7 (18)	HU UGT1A 6/6: Mean, 11.4 HU UGT1A 6/7: Mean, 11.3 HU UGT1A 7/7: Mean, 12.6	HU UGT1A 6/6: 13 HU UGT1A 6/7: 15 HU UGT1A 7/7: 11	NR	At least 12 mo
Iyamu, 2005 ⁷⁶	HU, steady state (23) No HU, steady state (12) African American HbAA (10)	HU, steady state: 13.5 [9–21] No HU, steady state: 12.5 [(8–19) 15.6 [11–21]	NR	HU, steady state: HbSS (100) No HU, steady state: HbSS (100) African American HbAA: HbAA (100)	Cross-sectional once
Lapoumeroulie, 2005 ⁷⁷	Clinical events; HbSS 8 HU, 10 none (18) HbSS, no HU (17) HbSS, HU (16) NI African American, controls none (26)	Clinical events; HbSS 8 HU, 10 none: [2.9–13.2] HbSS, no HU: [3.0–14.9] HbSS, HU [3.5–15.1] NI African American, controls none [2.6–15.8]	NR	HbSS (100)	NR
Maluf, 2009 ⁷⁸	Sickle cell on HU (35) Nonsickle cell (34)	26.3	Sickle cell on HU: 43%	Sickle cell on HU: HbSS	NR
Nahavandi, 2002 ⁷⁹	HU (12) Non-HU steady-state (26) HU during VOC (14) Non-HU during VOC (12)	HU: 32 [18–47] Non-HU steady-state: 34 [18–53] HU during VOC: 34 [18–48] Non-HU during VOC: 31 [18–45]	HU: 9 8 8 NR	HbSS (100)	NR
Nahavandi, 2003 ⁸⁰	HU (12) HU untreated, with VOC (12) HU treated, with VOC (14) HU untreated control, no VOC (31)	HU: 32 [18–47] HU untreated, with VOC: 31 [18–45] HU treated, with VOC: 34 [18–48] HU untreated control, no VOC: 34 [18–53]	HU: 9 HU untreated, with VOC: 8 HU treated, with VOC: 8 HU untreated control, no VOC: NR	HbSS (100)	NR
Odievre, 2008 ⁴⁶	On HU and had vaso-occlusive events (26) Non-HU and had vaso-occlusive events (20) Never had vaso-occlusive events (28) Non-SCD (controls) (27)	On HU and had vaso-occlusive events: Median=10; [4.0–19.0] Non-HU and had vaso-occlusive events: Median=9.5; [6.0–17.0] Never had vaso-occlusive events: Median=10.5; [5.0–20.0] Non-SCD: HbAS: Median=41 [7.0–66.0]; HbAA: Median=17 [10.0–36.0]	NR	On HU and had vaso-occlusive events; non-HU and had vaso-occlusive events; and never had vaso-occlusive events: HbSS Non-SCD: HbAS n=21, HbAA n=6	NR

Author, year	Intervention (N)	Age, mean (SD) [range]*	Male, n (%)	Genotype/haplotype (%)	Last observation
Tavakkoli, 2004 ⁸¹	HU (10) Steady-state condition, not on HU VOC, on HU (10) VOC, not on HU (10) No HU (30)	HU: 32 [18–47] VOC, on HU: 34 [15–53] VOC, not on HU: 34 [18–48] No HU: 31 [18–45]	NR	HbSS (100)	NR
Teixeira, 2003 ⁸²	HU (31) No HU (30)	NR	NR	NR	NR
Ulug, 2008 ⁸³	10 patients were analyzed while 'on' and 'off' HU Non-HU (115)	On/Off-HU: NR Non-HU: NR	On/Off-HU: NR Non-HU, 40	All HbSS	NR

* Unless otherwise specified.

† Recruitment start and end dates as well as race of patients were unreported for all studies in this table.

Table 15. Adequacy of Reporting in Biomarker Studies in Sickle Cell Disease

Author, year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Adjustment when reporting outcome comparisons	Objective outcome	Losses to followup	Quality score
Athanassiou, 2006 ⁷³	0.5	0.5	1	0	0	0	2	NA	29
Gambero, 2007 ⁷⁴	1	1	1	1	NA	NA	2	NA	33
Harrod, 2007 ³²	1	2	1	NA	NA	NA	2	NA	33
Heeney, 2003 ⁷⁵	1	2	1.5	2	0	0	2	NA	57
Iyamu, 2005 ⁷⁶	0	0.5	1	1	0	0	2	NA	32
Lapoumeroulie, 2005 ⁷⁷	1	0	1	0	0	NA	2	NA	29
Maluf, 2009 ⁷⁸	1	1	1	NA	NA	NA	2	NA	28
Nahavandi, 2002 ⁷⁹	0.5	1	1	1	0	0	2	NA	39
Nahavandi, 2003 ⁸⁰	1.5	1.5	2	1	0	0	2	0	50
Odievre, 2008 ⁴⁶	2	1	1	1	NA	NA	2	NA	39
Tavakkoli, 2004 ⁸¹	1	1	1.5	1.5	NA	0	2	NA	58
Teixeira, 2003 ⁸²	1	0	0.5	0.5	0	0	1.5	NA	23
Ulug, 2008 ⁸³	2	2	2	2	1	NA	2	NA	61

NA = Not applicable to this question

The scale used in this table is described in detail in a footnote for Table 7.

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease

Author, year	Intervention (N)	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other toxicities, n (%)
Bloch, 2006 ⁸⁴	Indinavir, ritonavir, ddl, and either stavudine or lamiduvine + HU (35) Indinavir, ritonavir, ddl, and either stavudine or lamivudine (33)	NR	NR	NR	NR	Indinavir, ritonavir, ddl, and either stavudine or lamivudine + HU: 1 Indinavir, ritonavir, ddl, and either stavudine or lamivudine: 0	NR	NR	NR	NR	Indinavir, ritonavir, ddl, and either stavudine or lamivudine + HU: CMV esophagitis, (3); renal colic, (20); pneumonia, (3) Indinavir, ritonavir, ddl, and either stavudine or lamivudine: neuropathy, (3); rectal tear, (3); renal colic, (3)
Broustet, 1991 ⁸⁵	HU (26) IFN (24)	HU: D: 20.4 mo IFN: D: 13.9 mo	NR	NR	NR	HU: 0 IFN: 1	NR	NR	NR	HU: 0 IFN: 1	IFN: Flu-like, 1; CNS disturbance, 2; thyroid insufficiency, 2
Burnett, 2007 ⁸⁶	HU (99) Low-dose cytarabine (103) HU (8 weeks) (38) Low-dose cytarabine (8 weeks) (40)	HU and low-dose cytarabine: Unclear HU and low-dose cytarabine (8 weeks): (8 weeks)	HU: 26 (26) Low-dose cytarabine: 27 (26) HU (8 weeks): 14 (38) Low-dose cytarabine (8 weeks): 16 (39)	NR	NR	NR	NR	NR	NR	NR	HU: ***** (Nausea/emesis 0.6, alopecia 0.2, oral 0.5, diarrhea 0.5, cardiac 0.5) HU (8 weeks): Infection n=8; hemorrhage n=1; stroke n=0; cardiac n=1; renal n=1; other n=3; resistant/progressive disease n=14 Low-dose cytarabine (8 weeks): Infection n=18; hemorrhage n=2; stroke n=1; cardiac n=0; renal n=2; other n=3; resistant/progressive disease n=14
Cortelazzo, 1995 ⁸⁷	HU (56) None (58)	HU: D: 27 mo	NR	NR	HU: 0 None: 0	NR	HU: 0 None: 0	NR	NR	HU: 0 None: 0	NR
Finazzi, 2000 ⁸⁸	HU (56) No myelosuppressive agent at randomization (58)	HU: Median F: 73 mo (3–93) No myelosuppressive agent at randomization: Median F: 73 mo (12–94)	NR	NR	NR	NR	NR	HU: 7 (13) No myelosuppressive agent at randomization: 1 (1.7)	NR	NR	NR

Author, year	Intervention (N)	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other toxicities, n (%)
Frank, 2004 ⁸⁹	didanosine (ddl) monotherapy (28) HU (low dose) with/without ddl (53) HU (high dose) with/without ddl (50)	ddl mono: D: 6 mo	NR	ddl mono: 3 (11) HU (low dose) with/without ddl: 10 (19) HU (high dose) with/without ddl: 20 (40)*	ddl mono: 0 HU (low dose) with/without ddl: 1 (2) HU (high dose) with/without ddl: 9 (18) [†]	ddl mono: 0 HU (low dose) with/without ddl: 0 HU (high dose) with/without ddl: 3 (6)	NR	NR	NR	NR	ddl mono: Grade 3 chemistry or more, 3 (11) HU (low dose) with/without ddl: Grade 3 chemistry or more, 7 (13) HU (high dose) with/without ddl: Grade 3 chemistry or more, 4 (8)
Harrison, 2005 ⁹⁰	Aspirin + HU (404) Anagrelide + aspirin (405)	Aspirin + HU: Median F: 39 mo (12–72)	Aspirin + HU: 4 ^{§§§§} Anagrelide + aspirin: 3	NR	NR	NR	Aspirin + HU: 6 Anagrelide + aspirin: 4	NR	NR	NR	Aspirin + HU: Myelofibrosis, 5 Anagrelide + aspirin: Myelofibrosis, 16
Havlic, 2001 ⁹¹	IDV, ddl, d4T, + HU (68) IDV, ddl, d4T + placebo (68) IDV, ZDV (or d4T), 3TC (lamivudine) (66) ABC, EFV, ddl (24)	IDV, ddl, d4T, + HU: F: 40 weeks	IDV, ddl, d4T, + HU: 3 IDV, ddl, d4T + placebo: 0 IDV, ZDV (or d4T), 3TC: 0	NR	NR	NR	NR	NR	NR	ABC, EFV, ddl: 3	IDV, ddl, d4T, + HU: GI upset, 2; pancreatitis, 4; asymptomatic amylase elevation, 2 IDV, ddl, d4T + placebo: GI upset, 1; pancreatitis, 3. ABC, EFV, ddl: GI upset, 10; neurological/psychiatric, 12; nasal symptoms, 2; endocrine or metabolic, 3; arthralgia, 1; fatigue, 2; neuropathy, 1
Hehlmann, 1993 ⁹²	HU (216) Busulfan (225)	HU: Median F: 2.03 yr	NR	NR	NR	NR	NR	NR	NR	NR	HU: Long-lasting bone marrow aplasia, 0 (denominator=209) Long-lasting bone marrow aplasia, unknown (denominator=204)
Hehlmann, 1994 ⁹³	HU (194) IFN (133) Busulfan (186)	HU: Median F: 3.4 yr	NR	NR	NR	NR	NR	HU: 1 (0.5) IFN: 2 (1.5) Busulfan: 2 (1.0)	NR	NR	HU: Fever, 1 (0.5)
Hehlmann, 2003 ⁹⁴	HU (308) IFN + HU (226)	HU: F: 7.3 yr IFN + HU: Followup: 7.9 yr	NR	NR	NR	NR	NR	NR	NR	HU: 29/30 (9.4) IFN + HU: 64/22 (28.3)	HU: GI upset, 60 (19.5) (denominator=304); flu-like, 38 (12.3); neurological/psychiatric, 19 (6.2); cardiac/pulmonary symptoms, infections, wt loss, lab findings, BM aplasia, 53 (17.2) IFN + HU: GI upset, 88 (38.9) (denominator=222); flu-like, 146 (64.6); neurological/psychiatric, 82 (36.3); cardiac/pulmonary symptoms, infections, wt loss, lab findings, BM aplasia, 92 (40.7)

Author, year	Intervention (N)	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other toxicities, n (%)
Kiladjan, 2006 ⁹⁵	HU (123) Pipobroman (134)	HU: Followup: 14 yr Pipobroman: Followup: 11 yr	NR	NR	NR	NR	HU: 15 ⁺⁺⁺ Pipobroman: 25 ⁺⁺⁺	NR	NR	NR	NR
Loening, 1981 ⁹⁶	HU (40) Cyclophosphamide (43) Methyl-CCNU (38)	HU: NR	NR	NR	HU: 2/28 (7) Cyclophosphamide: 2/34 (5) Methyl-CCNU: 11/27 (41)	HU: 8/28 (29) Cyclophosphamide: 11/34 (26) Methyl-CCNU: 9/27 (33)	NR	NR	NR	NR	HU: GI upset, 13 (46) (denominator=28) Cyclophosphamide: GI upset, 20 (46) (denominator=43) Methyl-CCNU: GI upset, 11(41) (denominator=27)
Najejan, 1997 ⁹⁷	HU (150) Pipobroman (142)	HU: F: 1–17 yr	NR	NR	NR	NR	HU: NR by arm ^{sss} Pipobroman: NR by arm ^{ttt}	HU: 10 ^{lll} Pipobroman: 6 ^{ttt}	HU: 12 (9) Pipobroman: 1	HU: 10 (7) Pipobroman: 5 (4)	HU: GI upset, 9 (7); myelofibrosis, 26, 40% at the 16th yr; cystitis, 3 (2); stomatitis, 13 (10) Pipobroman: GI upset, 19 (17); myelofibrosis, 3; stomatitis, 4 (4)
No author, 1998 ⁹⁸	HU alone (95) IFN and HU if needed (100)	HU alone: F: 51 mo	NR	NR	NR	NR	NR	NR	NR	HU alone: 1 IFN and HU if needed: 3	HU alone: Fever, 2; accelerated disease/blast crisis, 52 IFN and HU if needed: Flu-like, 7; neurological/psychiatric, 6; vasculitis, 1; accelerated disease/blast crisis, 37
Rutschmann, 1998 ⁹⁹	ddl, stavudine + HU (72) ddl, stavudine + placebo (72)	ddl, stavudine + HU: F: 24 weeks	NR	ddl, stavudine + HU: 14 [±] ddl, stavudine + placebo: 3/25	ddl, stavudine + HU: 8 [§] ddl, stavudine + placebo: 3	NR	NR	NR	NR	ddl, stavudine + HU: 5 ^{ll} ddl, stavudine + placebo: 4	ddl, stavudine + HU: GI upset, 16; fatigue, 10; neuropathy, 18 ^{ll} diarrhea, 15 ddl, stavudine + placebo: GI upset, 11; fatigue, 2; neuropathy, 10; diarrhea, 9
Rutschmann, 1998 ¹⁰⁰	ddl, stavudine + HU (72) ddl, stavudine + placebo (72)	ddl, stavudine + HU: D: 12–48 weeks F: 48 weeks	NR	ddl, stavudine + HU: 11/unclear ddl, stavudine + placebo: 3**	ddl, stavudine + HU: 7 ddl, stavudine + placebo: 1 ^{††}	NR	NR	NR	NR	NR	ddl, stavudine + HU: Fatigue, 10; diarrhea, 15; paraesthesia, 29 ddl, stavudine + placebo: Fatigue, 2 [±] diarrhea, 9 ^{§§} paraesthesia, 14 ^{ll}
Rutschmann, 2000 ¹⁰¹	ddl, stavudine + HU (72) ddl, stavudine + placebo (72)	ddl, stavudine + HU: F: 24 mo	NR	ddl, stavudine + HU: 18 ^{¶¶} ddl, stavudine + placebo: 8	ddl, stavudine + HU: 29 ^{##} ddl, stavudine + placebo: 8	NR	NR	ddl, stavudine + HU: 4 Kaposi's sarcoma ^{***} ddl, stavudine + placebo: 1 Kaposi's sarcoma	NR	ddl, stavudine + HU: 8 ddl, stavudine + placebo: 5	ddl, stavudine + HU: GI upset, 20 ^{†††} hair loss, 1; fatigue, 16; neuropathy, 28 ^{±±} diarrhea, 23; mucositis, 5 ddl, stavudine + placebo: GI upset, 6; hair loss, 1; fatigue, 5; neuropathy, 10; diarrhea, 15

Author, year	Intervention (N)	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other toxicities, n (%)
Seminari, 1999 ¹⁰²	ddl + HU (40) ddl (21)	ddl + HU: F: 40 weeks ddl: D: 24 weeks	NR	ddl + HU: 1 ddl: 0	ddl + HU: 1 ddl: 0	ddl + HU: 1 ddl: 0	NR	NR	NR	NR	ddl + HU: Hair loss, 2; hyperamylasemia, 1; hypertriglyceridemia, 1 ddl: GI upset, 1; hyperamylasemia, 1; hypertriglyceridemia, 1
Swindells, 2005 ¹⁰³	ABC, EFV, ddl + HU (30)	ABC, EFV, ddl + HU: F: 48 weeks	NR	NR	NR	NR	NR	NR	NR	ABC, EFV, ddl + HU: 5	ABC, EFV, ddl + HU: GI upset, 28; neurological/psychiatric, 23; endocrine or metabolic, 7; arthralgia, 2; fatigue, 6; neuropathy, 4
Stephens, 1984 ¹⁰⁴	HU (69) Adriamycin + cyclophosphamide (68)	HU: NR Adriamycin + cyclophosphamide: NR	NR	NR	HU: 11/68 (16) Adriamycin + cyclophosphamide: 9/68 (14)	NR	NR	NR	NR	NR	NR

* $p=.007$ (comparing arms 2 and 3)

*** $p=.2$

† $p=NS$ ††† $p=.006$

‡ $p=.04$ for grade 1, ns for 2, 3, (denominator=36) §§§ Risk=10% at 13th yr (denominator=150)

§ $p=.03$ for grade 1, ns for 2 and 3 |||| Risk=15% at 14th yr, Risk=1.1%/yr

|| $p=.7$ ¶¶¶ Risk =10% at 13th yr (denominator=142)

¶ $p=.09$ #### Risk=15% at 14th yr, Risk=1.1%/yr

n =original assignments, please see associated text for number of patients that crossed over.

†††† 6 (40%) occurred after the 12th yr of followup, (denominator=123)

** $p=.04$, (denominator for this outcome unclear given crossover)

†††† 11 (44%) after the 12th yr of followup (denominator=134)

†† $p=.03$ §§§§ Death from transformation

‡‡ $p=.02$

|||| It is unclear why this only represents 157 patients when it is a followup of the §§ $p=0.2$ original study 123. No information on patients lost to followup is given.

|| $p=.008$

¶¶¶¶ (OR 0.67, CI, 0.20–0.33) $p=NS$

¶¶ $p=.08$

(OR 2.92, CI, 1.24–6.86) $p=.01$

$p=.001$

***** the severity of toxicity according to National Cancer Institute

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease*

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months [†]	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other toxicities, n (%)
Ansari, 2007 ¹⁰⁵	HU (21)	F: 24 mo	1	NR	NR	NR	NR	NR	NR	NR	4 mild myelo-suppression, 2 diarrhea
Bernasconi, 2002 ¹⁰⁶	HU only (23) Pipobroman (106) No treatment (26)	Median F: 104 mo (range, 8–240) for all 3 groups	NR	NR	NR	NR	HU only: 4 Pipobroman: 4 ^{¶¶} No treatment : 0	NR	NR	NR	NR
Chim, 2005 ¹⁰⁷	HU alone (224) Melphalan + HU (4) Phosphorus + HU (3)	F: 10 yr	NR	NR	NR	NR	HU alone: 3 (1.3) Melphalan + HU: 2 Phosphorus + HU: 0	NR	NR	NR	HU alone: Myelofibrosis, 6 Melphalan + HU: Myelofibrosis, 1
D'Adda, 2008 ¹⁰⁸	HU (13)	F: 57 mo [15–219]	NR	8 (62)	NR	NR	NR	NR	2 (15)	NR	Thrombocytosis: 2 patients
Donovan, 1984 ¹⁰⁹	HU no prior treatment (59) HU after prior myelo-suppressive therapy (59)	HU no prior treatment: F: 61 weeks to 171 weeks HU after prior myelo-suppressive therapy: F: 193 weeks	NR	NR	NR	NR	HU no prior treatment: 2 HU after prior myelo-suppressive therapy: 1	NR	NR	NR	NR
Duletic-Nacinovic, 2000 ¹¹⁰	HU (72) Busulfan (109) 8 varieties prior chemo: 2 patients had no prior therapy (10)	HU: F: Median=32 mo Busulfan: F: Median=31 mo	NR	HU: 2 Busulfan: 8	NR	HU: 0 Busulfan: 2	NR	NR	NR	HU: 0 Busulfan: 2	Busulfan: Lung fibrosis, 3; amenorrhea, 2
Finazzi, 2005 ¹¹¹	HU only (742) Any other cytoreductive drug (227) No drug or interferon α only (669)	NR	NR	NR	NR	NR	HU only: 6 Any other cytoreductive drug: 11 No drug or interferon α only: 5	NR	NR	NR	NR
Fruchtman, 1997 ¹¹²	HU (51) Phlebotomy (134)	HU: F: 795 weeks Phlebotomy: NR	HU: 16 (31.4) ^{‡‡} Phlebotomy: 54 (40.3)	NR	NR	NR	HU: 5 (9.8) ^{§§} Phlebotomy: 5 (3.7)	NR	NR	NR	HU: Spent phase, 4 Phlebotomy: Spent phase, 15
Gangat, 2007 ¹¹³	HU only (165) Anegralide or IFN α only (63) Exposure to single agent cytotoxics other than HU (21) No drug exposure (181) Anagrelide or IFN + HU (128) Other cytotoxics + HU (47)	HU only: Median F: 84 mo (0–424)	NR	NR	NR	NR	HU only: 5 Anegralide or IFN α only: 1 Exposure to single agent cytotoxics other than HU: 3 No drug exposure: 4 Anagrelide or IFN + HU: 2 Other cytotoxics + HU 5	NR	NR	NR	NR

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months [†]	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other toxicities, n (%)
Italia, 2009 ¹¹⁴	HU (79)	Median F: 22 mo [20–24]	NR	16 (20)	NR	NR	NR	NR	NR	NR	NR
Italia, 2010 ¹¹⁵	HU (13)	Median F: 20 mo [17–23]	NR	Incidence NR	NR	NR	NR	NR	NR	NR	NR
Kaplan, 1986 ¹¹⁶	HU (51) Phlebotomy (134)	HU: D: Median 245 weeks (range: 5–389 weeks) Phlebotomy: NR	NR	NR	NR	NR	HU: 3 (5.9) Phlebotomy: 2 (1.5) ^{±±}	NR	NR	NR	NR
Koren, 2008 ¹¹⁷	HU (18)	D: 46±26 mo, (range: 6–96)	NR	3	NR	NR	NR	NR	NR	NR	NR
Kosaryan, 2009 ¹¹⁸	HU (297)	D: 5.2±2 yr [0.5–9]	NR	NR	NR	NR	NR	NR	NR	NR	Nausea 3, palpitation 9, transient leukopenia 18
Latagliata, 2009 ¹¹⁹	HU (symptomatic patients) (32) HU (>70 yr of age) (33) HU (≥4 points on study scoring system for risk, score increase) (32) HU (<4 points after 28 d of diagnosis) (24) Non-HU (47)	F: 106 mo [59.9–135.6]	16 (9.5)	NR	NR	NR	4 (3.3) Non-HU: 1 (2.1)	9 (7.4) Non-HU: 1 (2.1)	5 (4.1)	NR	HU: Thrombosis: 5 (7) HU (>70 yr of age): Thrombosis: 4 (12.5) HU (> or = 4 points on study scoring system for risk, score increase): Thrombosis: 4 (12.5) HU (<4 points after 28 d of diagnosis): Thrombosis: 5 (7)
Lim, 2009 ¹²⁰	INF-α (40) HU (26) Imatinib mesylate (22) 2-Chlorodeoxy-adenosine (22)	INF-α: D: 12 mo (median) [1–65] HU: D: 31.5 mo (median) [5–50] Imatinib mesylate: D: 19.6 mo (median) [6–96] 2-Chlorodeoxy-adenosine: Median D: 11 mo [3–74]	NR	NR	INF-α: Was a major toxicity. Otherwise not specified	NR	NR	NR	NR	NR	INF-α: Major toxicity included fatigue and depression HU: Major toxicity was myelosuppression Imatinib mesylate: Major toxicity included: diarrhea and edema 2-Chlorodeoxy-adenosine: Major toxicity included infection and myelo-suppression
Mavrogianni, 2002 ¹²¹	PV: HU therapy (34) ET: HU therapy (30) PV: HU and busulfan (1) ET: INF-α (4)	PV: HU therapy: D: 86 [36–195] mo ET: HU therapy: D: 79 [36–162] mo PV: HU and busulfan: D: 44 mo on HU followed by 86 mo on busulfan ET: INF-α: D: 105 [91–123] mo	NR	NR	NR	NR	PV: HU therapy : 2 (5.7) ET: HU therapy: 1 (3.3)	NR	NR	PV: HU and busulfan: 1	NR
Mtvarelidze, 2008 ¹²²	HU (6)	F: 60 mo	0	0	0	0	0	0	0	0	Erythropoietin toxic reaction: 1

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months [†]	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other toxicities, n (%)
Najejan, 1996 ¹²³	HU only [§] (104) Pipobroman (98) Radioactive phosphorous (32P) + HU maintenance (174) 32P without maintenance (221)	HU only [§] : Median followup: 6.7 yr Pipobroman: median followup: 6.7 yr 32P+HU maintenance: D: 1–15 yr Median 10.5 yr 32P without maintenance: D: 1–15 yr, Median 10.5 yr	NR	NR	NR	NR	HU only [§] : 13% at 12-yr followup Pipobroman: 14% at 12-yr followup 32P+HU maintenance: 19% at 10-yr followup [#] 32P without maintenance: 10% at 10-yr followup	HU only [§] : 9% at 10-yr followup Pipobroman: 9% at 10-yr followup 32P+HU maintenance: 29% at 12-yr followup 32P without maintenance: 15% at 12-yr followup **	NR	NR	HU only [§] : Myelo-fibrosis, 17% at 12-yr followup 32P+HU maintenance: Myelo-fibrosis, 16% at 10-yr followup; 23% at 14-yr followup 32P without maintenance: Myelo-fibrosis, 10% at 10-yr followup; 19 at 14-yr followup
Nielsen, 2003 ¹²⁴	HU (36) No drug treatment (21) Busulfan alone (4) Busulfan + HU (18) Anagrelide + HU (1) Busulfan, IFN + HU (1) Busulfan, anagrelide + HU (1) IFN + HU (1)	HU: F: 7.8 yr (followup for all patients who received HU) No drug treatment: F: 10.5 yr (this is followup for all patients who did not receive HU) Busulfan, IFN + HU: 62 Busulfan, anagrelide + HU: 84 IFN + HU: 21	NR	NR	NR	NR	HU: 5 No drug treatment: 1 Busulfan alone: 0 Busulfan + HU: 4 Anagrelide + HU: 0 Busulfan, IFN + HU 1 Busulfan, anagrelide + HU: 1 IFN + HU: 1	NR	NR	NR	NR
Ogbogu, 2009 ¹²⁵	Steroids (179) HU (64) INF- α (46) Cyclosporine (11) Imatinib (68)	Steroids: D: 2 mo to 20 yr HU: NR INF- α : NR Cyclosporine: NR Imatinib: NR	Steroids: 4	NR	NR	NR	NR	NR	NR	NR	NR
Palandri, 2009 ¹²⁶	HU (205) Non-HU (133)	F: Median=9.5 yr [3–28.5]	NR	NR	NR	NR	NR	NR	NR	HU: 3 (1.4) Non-HU: 2 (1.5)	HU: Extrahematological toxicity, 6 ; Hypertransaminasemia, 3 ; Hematological toxicity, 5. Non-HU: Extra-hematological toxicity, 6 ; hypertransaminasemia, 3 ; hematological toxicity, 5

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other toxicities, n (%)
Radaelli, 2008 ¹²⁷	HU only (116) Alkylating agents (ALK) (busulfan or melphalan) (38) ALK followed by HU (40) No treatment (137)	F: Median=108 mo	NR	NR	NR	NR	NR	NR	NR	NR	HU only: second malignancies, 13 Alkylating agents (ALK) (busulfan or melphalan): second malignancies, 10 ALK followed by HU: second malignancies, 10 No treatment: second malignancies, 10
Randi, 2005 ¹²⁸	HU (152)	Median 4.33 yr aspirin (n=88), ticlopicine (n=11), oral anticoagulants (n=12), 8.13 yr	3 (1.97)	NR	NR	5 (0.03 29)	3, (1.97)	NR	4 (2.6)	NR	Cutaneous allergic reaction and mild pancytopenia, 1; allergic reaction and transient liver failure, 1; fever above 39°C, 2
Randi, 2005 ¹²⁹	HU (129)	F: 7.18 yr	NR	NR	NR	2/129	3	1	4	3	CV complications, 4; coronary complications, 5; fever above 39°C, 2
Randi, 2008 ¹³⁰	HU (27) Non-HU (27)	HU: F: [24–144] mo Non-HU: F: [12–216] mo	HU, 2 Non-HU, 1	NR	NR	NR	NR	NR	NR	NR	HU: In 5 patients, “major” HU side effects occurred and tx was stopped
Ranjan, 2007 ¹³¹	HU (15) Methotrexate (15)	F: 12 weeks	NR	NR	NR	NR	NR	NR	NR	HU: 2 (13) Methotrexate: 5 (33)	The side effects in both groups were mild and did not re-quire d/c of therapy. No patient developed hepatic or hematologic toxicity due to any of the drugs
Sterkers, 1998 ¹³²	HU alone (201) HU + other agents (50) 32P alone (29) 32P + other agents (11) Busulfan alone (35) Busulfan + other agents (6) Pipobroman alone (12) Pipobroman + other agents (31) No treatment (31)	HU alone: Median F: 98 mo (22–265)	NR	NR	NR	NR	HU alone: 7 (3.5) HU + other agents: 7 (14) 32P alone: 2 (7) 32P + other agents: 1 (9) Busulfan alone: 1 (3) Busulfan + other agents: 1 (17) Pipobroman alone: 0 Pipobroman + other agents: 5 (16) No treatment: 0	NR	NR	NR	NR

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months [†]	Death, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other toxicities, n (%)
Taher, 2010 ¹³³	Non-HU (382) HU (202)	NR	NR	NR	NR	NR	NR	NR	Non-HU: 44 (11.5) HU: 2 (1)	NR	Non-HU: Extra-medullary hematopoiesis, 91 (23.8%); PHTN, 53 (13.9%); 2 ^o heart failure, 12 (3.1%); thrombosis, 65 (17%); cholelithiasis, 80 (20.9%); abnormal LFTs, 36 (9.4%); DM, 99 (2.6%); osteoporosis, 132 (34.6%); hypogonadism, 44 (11.5%) HU: Extramedullary hematopoiesis, 33 (16.3%); PHTN, 11 (5.4%); secondary heart failure, 13 (6.4%); thrombosis, 17 (8.4%); cholelithiasis 20, (9.9%); abnormal LFTs, 21 (10.4%); hypogonadism 57 (28.2%)
Urabe, 1990 ¹³⁴	HU (134)	NR	NR	NR	NR	NR	NR	NR	NR	1	Liver dysfunction, 1 GI upset, 1
Vassallo, 2001 ¹³⁵	HU (158)	D: Median=38 mo	NR	NR	NR	NR	NR	5	NR	21 [‡]	NR
Weinfeld, 1994 ¹³⁶	PV: HU (30) ET: HU (10) MF: HU (10)	NR	NR	NR	PV: HU: (30) ET: HU: (30)	NR	PV: HU: 3 ET: HU: 1 MF: HU: 3	NR	NR	NR	PV: HU: Chromosomal anomalies, 4/11; platelet count >6x10 ⁹ /L ET: HU: Chromosomal anomalies, 1/5; platelet count >6x10 ⁹ /L MF: HU: Chromosomal anomalies, 2/3
West, 1987 ¹³⁷	HU only (100)	D: 3–216 mo, mean 64.9 [3–21] F: 20 yr observation	NR	NR	NR	NR	2 (2)	1 (1)	NR	1	Splenic infarction, 1 Myelofibrosis, 6
Yin, 2006 ¹³⁸	15-HU 1-imatinib (16)	D: HU, 2 weeks to 31 mo before translocation; D: imatinib alone, 3 mo	8/15	NR	NR	NR	NR	NR	NR	NR	NR
Zamani, 2009 ¹³⁹	HU (49)	F: 60 mo	NR	1 (2)	NR	NR	NR	NR	NR	NR	NR

* Denominators = N unless otherwise specified.

[†] Unless otherwise specified

[‡] HU therapy was discontinued in all 21 patients showing toxicity, and all cutaneous ulcers healed within a median period of 9 mo. [§] 12 patients originally assigned to the HU arm were switched to pipobroman, and 5 patients on the pipobroman arm were switched to the HU arm. ^{||} Actuarial risk [¶] Observed risk [#] Reported as “significant” when compared to no maintenance arm ^{**} p<.01 at 10 yr followup compared to Arm 3

^{††} p>.25

^{‡‡} p=.0718

^{§§} p=.0973

^{|||} Incidence rate ratio (IRR) HU v PI 6.15, CI, 1.4–26.99, 5-yr CI=8.09%, 10-yr CI=15.53%, 15-yr CI=22.37% (where Cul is cumulative incidence, p for IRR=0.0198)

^{¶¶} 5-yr Cul=1.97%, 10-yr Cul=3.89%, 15-yr Cul=5.78%

Table 18. Hydroxyurea Toxicity Results From Case Reports in Diseases Other Than Sickle Cell Disease*

Outcome	Number of case reports	Females/males	Underlying disease %	Median weeks on HU until toxicity	Number of case reports with certain causality	Number of reports with probable causality**	Number of reports with possible causality**	Number of reports with unlikely causality**
Alopecia	1	1/0	CML: 100	16	0	0	1	0
Alveolitis	2	0/2	CML: 50, MPD: 50	4	0	1	1	0
Arthritis	1	0/1	CML: 100	12	0	0	1	0
Azoospermia or decreased sperm motility	4	0/4	ET: 50, PV: 50	470, 338	2	1	1	0
Behcet's disease	2	2/0	CML :100	91	0	0	1	1
Colitis	1	0/1	CML: 100	2	0	1	0	0
Cytopenia	5	3/2	HIV: 40, PV: 20, MPD: 40	12, 312	0	1	4	0
Eyelid changes	1	0/1	CML: 100	NR	0	1	0	0
Falsely elevated HbA1c	1	0/1	PV: 100	NR	0	0	0	1
Fever	16	7/9	ET: 69, CML 13, other: 13, MPD: 6	3, 676	14	0	2	0
Gangrene of toes	2	1/1	CML: 100	175	0	0	2	0
Glioblastoma multiforme	1	1/0	MPD: 100	150	0	0	1	0
Hemolytic anemia	2	1/1	ET: 50, MPD: 50	413	0	1	1	0
Hepatitis	6	2/4	ET: 33, PV: 33, Psoriasis: 33	27	3	1	2	0
Interstitial Pneumonitis	5	1/4	CML: 40, ET: 40, MPD: 20	16	1	3	1	0
Leg ulcer	74	31/42, 1 unclear	CML: 43, ET 22; PV: 24, MPD: 8, 1 unclear	220, 182	6	35	33	0
Leukemia	36	17/19	ET: 61, PV: 22, MPD: 12, Hypereosinophilia: 6	300, 260	0	0	33	3
Limbal stem cell deficiency (cornea)	1	0/1	CML: 100	104	1	0	0	0
Lymphoma	2	1/1	ET: 50, Hypereosinophilia: 50	450	0	0	2	0
Melanoma	1	0/1	ET: 100	64	0	0	1	0
Meningioma	1	1/0	ET: 100	520	0	0	1	0
Multiple myeloma	1	1/0	ET: 100	360	0	0	1	0
Nail change	15	11/4	CML: 33, ET: 20, Psoriasis: 7, MPD: 40	104, 45.5	0	6	9	0
Neuromuscular disorder	1	0/1	CML: 100	4	0	0	1	0
Oral ulcers	4	0/4	ET: 25, Leukemia: 75	116	0	2	2	0
Pruritis	1	1/0	PV:100	5	1	0	0	0

Outcome	Number of case reports	Females/males	Underlying disease %	Median weeks on HU until toxicity	Number of case reports with certain causality	Number of reports with probable causality**	Number of reports with possible causality**	Number of reports with unlikely causality**
Pulmonary Fibrosis	1	1/0	PV: 100	16	0	0	1	0
Dermatological changes	35	20/15	CML: 66, ET: 6, PV: 24, Leukemia: 3, MPD: 3	222, 780 (Females/Males)	0	19	16	0
Sarcoidosis	1	0/1	ET: 100	16	0	0	1	0
Sarcoma	1	0/1	ET: 100	0	0	0	1	0
Skin cancer	29	10/19	CML: 38, ET: 27, PV: 27, MPD: 7	376, 403 (Females/Males)	1	6	22	0
Systemic lupus erythematosus	1	1/0	Psoriasis: 100	160	0	1	0	0
Soft-tissue Nodule	1	0/1	MPD: 100	32	0	1	0	0
Thrombotic microangiopathy	1	1/0	CML: 100	72	0	0	1	0
Tumorlysis	4	1/3	CML: 25, Leukemia: 50, PV: 25	0.56	0	0	4	0
Ulcer (surgical site)	1	1/0	PV: 100	300	0	1	0	0
elevations in liver function tests	1	0/1	PV:100	1	1	0	0	0
neutropenia	2	1/1	SE: 100	Unclear	0	0	1	0
Decreased platelet count	1	1/0	SE:100	Unclear	0	0	1	0
Erythema induratum (Bazin disease) in legs/erythematous maculopapular rash	1	1/0	ET: 100	260	0	1	0	0
Dermatomyositis	1, 1	1/1	MPD: 100	442	0	1	1	0

* Explanation of differences from this report and the NHLBI HU Consensus Conference Report by Segal et al.⁶⁷ Level of evidence column was removed due to universal low level of evidence; toxicity of elevations in liver function tests, neutropenia, decreased platelet count, erythema induratum (Bazin disease) in legs/erythematous maculopapular rash, and dermatomyositis were added to the summary.

For case reports published before July 2007, certain modifications were made to the table format to fit these purposes. Please refer to the original NHLBI HU Consensus Conference Report by Segal et al.⁶⁷ For case reports published after July 2007, please refer to articles cited in ^{72,141-158}

** WHO causality assessment: A reaction was rated as “certain” if all 4 criteria for causality were fulfilled: (1) a plausible time relationship between drug administration and an event; (2) an absence of a concurrent disease that might have caused the event; (3) a reasonable response to drug withdrawal; and (4) existence of a rechallenge or a demonstrated biological explanation. A reaction was rated as “probable” if criteria 1, 2, and 3 were fulfilled and “possible” if only criterion 1 was met and information on criterion 3 was lacking or unclear. A reaction was rated as “unlikely” if criterion 1 was not met and if other drugs, chemicals, or underlying disease provided a plausible explanation for the reaction.

1. Is the time relationship from drug administration to the event plausible for causality to be established?
2. Is there an absence of concurrent diseases or other drugs that may have caused the event?
3. Is there a reasonable response to drug withdrawal?
4. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease

Author, year	Outcome measurement	Study population/location	N	Barriers	Facilitators	Neither	Primary results
Armstrong, 1992 ¹⁴⁰	Provider provision of pain medication provider report	Physicians (pediatric residents), nurses/unknown	92	Hospital visits	NR	Provider attitudes, professional experience, and training	Nurses, but not pediatric residents, recommended lower pain medication doses for frequently, as opposed to occasionally, hospitalized children as described in hypothetical history vignettes. However, there were no differences in pain ratings between nurses and residents across the vignettes. There were no significant correlations between nurse or resident pain ratings or medication decisions and their attitudes and beliefs about pain in children
Barakat, 2002 ¹⁴¹	General adherence to treatment regimens Provider report, patient report, family report, administrative data	Patients (children/caregivers)/unknown	81	NR	Greater parental/family knowledge, family problem-solving effort, higher family income	NR	In multivariate models, greater SCD knowledge ($p=.032$) and greater family effort in solving family problems ($p=.037$) were significantly associated with higher medical staff rating of patient/family adherence to treatment regimens. Greater family income was marginally associated with higher medical staff ratings of adherence ($p=.053$)
Belgrave, 1994 ¹⁴²	Appointment-keeping Patient report	Patients (adults)/ Washington, DC, United States	49	NR	Social support	NR	Social support, defined in this study as the frequency of supportive and helpful behaviors performed by others, was positively correlated with self-report of medical appointment keeping ($r=0.47$, $p<.05$). Patients with greater social support had better self-reported rates of keeping medical appointments
Crosby, 2009 ¹⁴³	Examining perceived barriers to clinic attendance and strategies to overcome these barriers	Patients (children, adolescents)/Midwest, United States	45	Competing activities involving school or peers; birthdays, homework	Education about the importance of attending routine clinic visits; interventions to decrease forgetting (e.g., phone call reminders or text messaging); scheduling appointments to accommodate busy schedules/scheduling conflicts; providing teen-friendly clinic environments; and using technology	NR	Adolescents identified competing activities, health status, patient-provider relationships, adverse clinic experiences, and forgetting as barriers to clinic attendance. Calendars/reminders and parent reminders were the most commonly reported strategies to facilitate clinic attendance. Adolescents also reported the need for flexible scheduling and improved patient-provider communication
Elliot, 2001 ¹⁴⁴	Patient adherence to prophylactic antibiotics family report, administrative records	Patients (children/caregivers)/unknown location	50	More children at home	More adults at home, having a car	Patient age, parental education	A higher number of adults living in the home and having a car were positively associated with compliance ($p<.01$). A higher number of children in the home was negatively associated with compliance ($p<.01$). The number of days between refills tended to increase as the child's age increased ($p=.15$). Maternal education was not significantly associated with compliance ($p=.25$). The authors assessed the utility of the Health Belief Model in predicting parental compliance with prophylactic penicillin administration and did not find that any of the assessed variables (parent's perceptions of the seriousness of infection in young children with SCD, the perceived susceptibility of their child to infection, the perceived benefit of prophylactic penicillin in preventing infection, and the perceived burden of penicillin administration) were significantly associated with compliance after adjustment for demographic factors ($p=.61$)

Author, year	Outcome measurement	Study population/location	N	Barriers	Facilitators	Neither	Primary results
Hankins, 2007 ³⁰	Patient decision to initiate HU Patient report, family report	Patients (children/caregivers)/Memphis, TN, United States	30	NR	Perceived safety and efficacy	Parental age, sex, number of children, parent's rating of child's health-related quality of life, frequency of VOC in prior 2 yr	In this study of patient and parental treatment decisions, after hearing nonbiased information about all 3 potential treatments, the majority of patients and parents (70%) chose HU therapy over chronic transfusion (17%) and stem cell transplantation (10%) ($p < .001$). The perceived efficacy and perceived safety of potential treatment options were the 2 most commonly cited factors affecting parental treatment preferences for their kids (~80% of respondents each). Health-related quality of life and number of VOC events were not associated with treatment preference. There was disagreement over treatment preference in 3 out of 7 patient-parent dyads
Haque, 2000 ¹⁴⁵	Use of routine health services Patient report, administrative data	Patients (adults and children/caregivers)/North Carolina, United States	1,189	Greater community socioeconomic distress	Rural geographic region	Distance to clinic, interference of disease in daily life, level of medical problems	Patients living in rural areas were estimated to have greater utilization of comprehensive sickle cell services than patients living in urban areas after adjustment for socioeconomic distress, interference of sickle cell disease in their daily lives, their self-reported level of medical problems, their distance to a comprehensive clinic, and a term representing the interaction of distance to a clinic and their level of socioeconomic distress ($p < .001$). In this same model, patients living in areas with more socioeconomic distress were estimated to have less utilization of services ($p = .04$) after adjustment for the other factors. None of the other variables in the model were significantly associated with utilization
Jensen, 2005 ¹⁴⁶	Patient adherence to prophylactic antibiotics family report	Patients (children/caregivers) United States	97	NR	Caregiver knowledge for children <11 yr, no child history of transfusions	History of stroke, hospital visits, number of missed appointments	In the overall sample, caregiver knowledge of SCD did not correlate with adherence with recommended SCD preventative behaviors ($r = 0.16$, $p = .12$). In post hoc analyses, however, the authors found that caregiver knowledge of SCD was positively associated with adherence for children 11 yr of age and younger, but not for children 12 and older ($p < .05$)
Labbe, 2005 ¹⁴⁷	Provider provision of pain medication provider report	Physicians 7 federally funded comprehensive SCD centers in the United States	109	Negative provider attitudes	Fewer provider years in practice, provider female gender	NR	Physician characteristics and attitudes may affect the quality of pain management delivered to patients with SCD. The earlier the year of graduation from medical school, the more likely a physician was to believe that opioids play major role in the development of addiction ($r = -0.32$, $p < .001$), and also that drug addiction should be a primary concern when treating patients with SCD ($r = -0.26$, $p < .008$). Female physicians were more likely than male physicians to believe that the primary focus of treatment for a sickle cell crisis should be adequate pain relief ($r = -0.20$, $p < .04$). Physicians who believed drug addiction should be a primary concern were less likely to believe the primary focus of treatment should be adequate pain relief ($r = -0.20$, $p < .0037$)
Lanzkron, 2008 ¹⁴⁸	Providers' awareness of the NHLBI recommendations regarding HU prescribing, whether these recommendations have changed providers' practices and how these providers prescribed HU	Health care providers (adult patients)/location unclear	48	Provider concerns to prescribe HU, lack of time and resources to adequately explain the risks and benefits	NR	NR	94% heard about the NHLBI recommendations, 81% read it, 76% of those who read it either somewhat or completely agreed with it, while 19% either somewhat or completely disagreed with it, and 5% had no opinion. 45% did not change their practice, 29% moderately changed, 13% significantly changed

Author, year	Outcome measurement	Study population/location	N	Barriers	Facilitators	Neither	Primary results
Logan, 2002 ¹⁴⁹	Use of routine health services patient report, family report, administrative data	Patients (children/caregivers)/unknown	70	NR	Illness-related stress, greater parental/family knowledge	Parent/adolescent relationship, disease severity, stressful life events, clinical maladjustment	The authors developed a multivariate model predicting the use of routine health services (scheduled clinic visits, calls to clinic, information seeking from clinic, management of pain symptoms at home). The frequency of illness-related stress accounted for the largest individual portion of the explained variance in routine service use (partial $r=0.41$, $p<.001$). Having more frequent illness-related stress was associated with greater use of routine services. Greater parental knowledge of SCD also accounted for a significant portion of the variance in routine service use and predicted more use of routine services (partial $r=0.33$, $p<.001$). Parental reports of the parent-adolescent relationship, disease severity, stressful life events, and clinical maladjustment were not significant predictors of routine service use
Modi, 2009 ¹⁵⁰	Barriers and facilitators to adherence to treatment and routine care	Caregivers and adolescent patients/Ohio, United States	102 (71 caregivers, 31 patients)	Forgetting, loss of medication, discomfort, pain from treatment, taste aversions, side effects, embarrassment	Reminders, peer support, flavor supplements, physician encouragement, use of pills	NR	Caregiver reminders were identified by both caregivers and adolescents as the primary facilitators for pain management, oral antibiotics, chelation therapy, and vitamin and mineral supplements. In addition, support from peers was identified as the primary strategy to facilitate exercise. Caregivers identified several unique facilitators including flavor supplements for hydration, physicians encouraging chelation therapy, and use of pills compared to liquids to assist in HU adherence
Newland, 2008 ¹⁵¹	Factors influencing independence in adolescents with SCD	Patients (children, young adults)/United States	74	Good family relationships	Less knowledge about the disease, poorer family relationships, and more severe disease	NR	The prediction model was statistically significant but accounted for only 25% of the variance for independence. According to the model, adolescents with SCD that have less knowledge about their disease, poorer family relationships, and more severe disease will be more independent
Pejaver, 1997 ¹⁵²	Patient adherence to prophylactic antibiotics family report, presence of penicillin in urine	Patients (children/caregivers)/Saudi Arabia (armed forces hospital)	41	NR	NR	Patient/caregiver knowledge, patient age, patient sex, number of children in family, years on therapy, number of inpatient admissions	1/4 (24%) of parents demonstrated good knowledge of the reasons and need for penicillin prophylaxis; however knowledge was not associated with compliance levels in this study
Pence, 2007 ¹⁵³	Patient use of pain medication patient report, family report	Patients (children/caregivers)/North Carolina, United States	27	NR	Dispositional optimism	Patient age, patient sex, parent education	For adolescent patients with SCD, pain severity was positively associated with opioid use such that high pain predicted higher use ($p<.001$), and pain severity uniquely accounted for the largest proportion of the variance in opioid use (partial $r^2=0.19$). Dispositional optimism was found to moderate the relationship between pain severity and use of opioids ($p<.05$). Specifically, at medium and high levels of optimism, pain severity was positively associated with opioid use. At low levels of optimism, pain severity was not associated with opioid use. At low levels of optimism, an intermediate level of opioids was used consistently regardless of whether pain severity was low or high. Additionally, maternal education was found to be marginally associated with adolescent opioid use ($p=.08$). Higher maternal education predicted more opioid use, while lower maternal education predicted more nonopioid use
Shankar, 2008 ¹⁵⁴	The impact of proximity to comprehensive SCD center on utilization of healthcare services	Patients (children)/United States	1,214	NR	NR	Proximity to a comprehensive sickle cell center	The cohort consisted of 1,214 children with 6,393 person-yr of followup. 56% of patients resided in the region with the CSCC. This region had the highest overall rates of hospitalization for all children ($P<.001$), while ED and outpatient visits were higher in other areas. The death rates ranged from 1.8 to 4.3/1,000 person-yr in the 4 regions and did not represent statistically significant differences

Author, year	Outcome measurement	Study population/location	N	Barriers	Facilitators	Neither	Primary results
Sox, 2003 ¹⁵⁵	Receipt of prophylactic antibiotics administrative data	Patients (children/caregivers)/Tennessee, Washington State, United States	261	NR	Private insurance, hospital visits	Patient sex, patient age, urban residence, cost-sharing, nonpreventive outpatient care visits	Publicly insured children may receive an inadequate amount of prophylactic antibiotics against pneumococcal infections, as the children in this sample were dispensed an average of only 148.4 d of cover-age out of a 365-d period (SD: 121.4, median:114, IQR 39–247). The number of outpatient visits for preventive care and the number of ED visits experienced by children were significantly associated with in-creased provision of prophylactic antibiotics. Each visit for preventive care was associated with 12 additional d of prophylactic antibiotic coverage (95% CI 2.3–21.7). Each ED visit was associated with 10 additional d of coverage (95% CI 1.2–18.8)
Teach, 1998 ¹⁵⁶	Patient adherence to prophylactic antibiotics patient report, family report, biologic outcome (urine assay)	Patients (children/caregivers)/ Buffalo, NY, United States	123	NR	Private insurance, younger patient age	Patient sex, SCD type	Measured compliance was significantly greater in patients <5 yr of age than in those >5 (64% vs. 34%, $p=.004$). Patients with private insurance ($p=.02$) had better measured compliance than patients with public insurance. Sex, type of hemoglobinopathy, recruitment site (ED vs. clinic), and chief complaint in ED (fever vs. VOC) were not significantly associated with measured compliance
Telfair, 2003 ¹⁵⁷	Use of routine health services patient report, administrative data	Patients (adults and children/caregivers)/ Alabama, United States	662	NR	Rural geographic region	Community socio-economic distress, physical functioning, number of medical problems, distance to a clinic	In bivariate analyses, patients with SCD living in rural areas had lower utilization of comprehensive sickle cell services than patients living in urban areas (significance not reported). However, utilization of comprehensive sickle cell services is predicted to be higher for SCD patients in rural areas compared to those in urban areas after adjustment for distance to a clinic, community socioeconomic distress, physical functioning, and a medical problem index ($p=.003$). While the model results suggested that utilization of services increased with increasing socioeconomic distress, the p -value for the result ($p=.011$) did not reach the author's threshold for statistical significance
Thornburg, 2010 ⁵⁷	Association between treatment adherence and HbF %	Patients (children), caregivers/Durham, NC, United States	75	Clinic visits, prescription refills	Visual analog scale, Morisky score, medical provider report	Age, length of treatment	Good adherence was estimated at 82% with visual analog scale, 84% with Morisky score, 85% with medical provider report, 77% with clinic visits, and 49% on the basis of pharmacy refills. Increase in HbF was moderately associated with good adherence as measured with the parent/proxy Morisky score ($r = -0.39$; 95% CI, -0.58 – 0.17 ; $P<.01$) and prescription refills ($r=0.39$; 95% CI, 0.16 – 0.57 ; $P<.01$)
Thornburg, 2010 ¹⁵⁸	Adherence to medication and study visits and to evaluate socioeconomic factors influencing measurement of adherence	Patients (children), caregivers/United States	191	NR	Allowing the families to have flexible scheduling options within the clinic, recognizing warning signs such as conflicts between family members about study participation	Socioeconomic factors (SES: higher education level of the primary caregiver and household income)	MedAd (median study medication) data were available on 153 of the 191 subjects who started randomized study medication. MedAd was 101.7% of volume prescribed, with 88.9% of subjects taking at least 80% of doses. VAd (mean visit adherence) data were available on 185 of the 191 subjects who started randomized study medication. VAd was 97.3%, with 82.2% of subjects having no missed visits. During dose titration, subjects had on average 12.9% higher medication adherence than subjects who were on a stable dose and had less frequent study visits. MedAd and VAd were not significantly associated with SES

Author, year	Outcome measurement	Study population/location	N	Barriers	Facilitators	Neither	Primary results
Treadwell, 2005 ¹⁵⁹	Patient adherence to chelation therapy patient or caregiver report, physical examination, administrative records	Patients (children, caregivers)/California, United States	15	Family stress	Child-parent shares responsibility	Convenience of the regimen, behavioral/psychological adjustment, patient/caregiver knowledge, satisfaction with regimen, child cognitive disability	The developmentally appropriate sharing of responsibilities for chelation therapy between parents and their children with SCD contributes to better adherence to home deferoxamine administration ($p < .05$). Low family stress was marginally related to better adherence ($p = .07$). There was no difference between the most and least adherent group in the perception of the inconvenience of the deferoxamine regimen (significance not shown). The child's behavioral and psychological adjustment was not associated with adherence (significance not shown). The primary hypothesis, that greater child cognitive disability would be a risk factor for nonadherence, was not supported by the data (significance not shown)
Witherspoon, 2006 ¹⁶⁰	Patient adherence to prophylactic antibiotics Provider report, family report, administrative data	Patients (children/caregivers)/ United States	30	NR	Caregiver knowledge, intent to adhere, perceived benefits, family employment	NR	Based on pharmacy records, 1/3 of caregivers had poor (14–30 d/mo not “covered” with antibiotic) and 1/3 had less than optimal (2–7 d/mo “uncovered” with antibiotics) levels of adherence to penicillin prophylaxis. Caregiver knowledge of infection and intent to adhere positively predict adherence. Caregivers with better adherence had more knowledge of infection, greater intent to adhere or greater belief in the importance of the medication ($p < .05$), and reported fewer barriers to adherence ($p < .01$). Families with better adherence rates were more likely to be employed ($p < .01$) and reported fewer barriers to adherence ($p < .05$)
Wojciechowski, 2002 ¹⁶¹	Transition to adult care Patient report, provider report	Patients (adults and children/caregivers)/ unknown	18	NR	Self-efficacy, female sex	Receipt of preparation for the transfer to adult care	In this study of adolescents and young adults making the transition to adult-centered care, patients with greater SCD self-efficacy kept a higher percentage of their care appointments ($p < .05$ using Spearman rho test). Females exhibited better compliance with medical regimens than did males as indicated by higher scores on a scale assessing compliance. There was no significant association between receipt of preparation for the transfer to adult-centered care and compliance with medical regimens
Wurst, 2004 ¹⁶²	Provider provision of prophylactic antibiotics/ provider report	Physicians (hematologists, heme/onco, pediatricians)/North Carolina, United States	142	Academic medical center setting	Provider knowledge, provider specialty	Provider years in practice, provider gender	Pediatricians were more likely than hematologists to answer correctly 5 or 6 out of 6 questions on SCD antibiotics guidelines ($p < .001$). Pediatricians were significantly more likely than hematologists to be 100% adherent in prescribing antibiotic prophylaxis ($p = .001$). Physician knowledge of antibiotic prophylaxis-prescribing guidelines was associated with better physician adherence to prescribing antibiotics ($p = .031$). Physicians in a medical school or university setting were significantly less likely than physicians in other settings to be 100% adherent ($p = .033$)

Table 20. Summary of Barriers and Facilitators

Subgroup	Factor	Facilitator	Neutral	Barrier
Health care providers	Knowledge and experience	2	1	0
Health care provider	Attitude	2	1	1
Health care provider	Female gender	1	1	0
Health care provider	Concerns about HU harms	0	0	1
Health care provider	Lack of time to offer counseling	0	0	1
Caregivers	Knowledge & education	4	3	1
Caregivers	Poor socioeconomic status	1	3	3
Caregivers	Family support	3	1	1
Caregivers	Perceived safety & efficacy	2	0	0
Caregivers	Frequency of hospital visits	1	1	2
Patients	Peer activities	0	0	1
Patients	Prescription refills	0	0	1
Patients	Appointment reminders	2	0	0
Patients	More children at home	0	1	1
Patients	More adults at home	1	0	0
Patients	Young age	1	4	0
Patients	Gender	0	3	0
Patients	Disease severity	1	2	0
Patients	Forgetting	0	0	1
Patients	Loss of medication	0	0	1
Patients	Rural region	2	1	0
System	Private insurance	2	0	0
System	Distance to clinic	0	3	0

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers

Author, year	Study design	Study population/location	N	Barriers identified	Primary results
Acharya, 2009 ⁶⁶	Quantitative survey	Patients' parents, caregivers	53	Misinformation about what it means to be a carrier and its health and reproductive implications	There was significant misunderstanding about sickle cell inheritance (mean score, 68%), but parents who have a child with SCD have better knowledge compared to those without a child with SCD (78% vs. 58%, $p=.002$). Respondents perceive minimal stigma associated with sickle cell trait. Unless there is an affected proband, individuals with sickle cell trait rarely receive counseling or education outside of the family
Alleyne, 1995 ¹⁶³	Qualitative: indepth, semistructured, individual and group interviews	Nurses (inpatient), patients (adults)/ United Kingdom	20 [†]	Negative provider attitudes, patient race	All 10 patients and 4 nurses expressed dissatisfaction with pain management. Patients (7) reported they had to demand painkillers and wait at least 30 min. Patients (8) believed the nurses doubt the genuine nature of the pain, all patients reported lack of involvement in pain control, and all reported that nurses were not sympathetic to pain, telling them, "you'll have to wait." 1 patient said, "I've got the feeling that some of them purposely pro-long it." 1 nurse suggested that there might be a link between young Black people and drug-taking, which caused nursing staff to be suspicious of the patients' request for pethidine. Nurses reported frustration with relying on physician orders for narcotics, and 2 nurses reported that patients could not be "trusted to be responsible" with patient-controlled analgesia
Booker, 2006 ¹⁶⁴	Qualitative: focus groups	Patients (adults)/ United Kingdom	10	Negative provider attitudes	Participants likened dealing with health care professionals to a battle. They felt that they had to work hard to convince the doctors that they were in genuine pain and need of help. Some patients felt so disbelieved that they actively avoided consulting when in crisis, for fear of being perceived as opioid dependent. Many patients felt that doctors did not have sufficient knowledge of sickle cell disease to make valid treatment decisions
Burnes, 2008 ¹⁶⁵	Qualitative survey	Caregivers (mother)/ Canada	10	Lack of research and resources for SCD, lack of knowledge and skills about SCD, racism, fear for children's safety	Mothers commonly reported several daily coping challenges: fear of their children's death, separation anxiety, loss of control over life, helplessness, and loneliness/isolation. SCD stigma interacted with racism, contributed to social isolation, and prevented families from organizing as a group. They also expressed frustration at lack of public awareness of the disease and its stigma. Lack of research. Knowledge and skills were the main health care system related barriers
Butler, 1993 ¹⁶⁶	Qualitative: authors' reports of themes that arose in a SCD support group that included medical residents	Patients (adults)/ United States	24	Negative provider attitudes	During their lives, each member of the group had experienced many negative interactions with health care providers, including routinely being treated with suspicion and distrust. Patients expressed extreme frustration in attempting to convince health professionals of their distress
Chestnut, 1994 ¹⁶⁷	Qualitative: structured interview and service perception test (SPT) in which subjects had to choose patients (via pictures) who they felt would receive better care	Nurses, doctors (hematologists), medical staff, patients (children/ caregivers)/United States	29 [§]	Patient race, patient sex, patient age	Family respondents perceived that younger children get the best care (regardless of gender or race), that Whites get better service than Blacks (regardless of age or gender), and that females get better care than males. Medical staff also perceived that children, Whites, and females get better care than adults, Blacks, and males
Crosby, 2009 ¹⁴³	Qualitative survey, using 2 phases: 1 is a focus group and the other is an individual semistructured interview	Patients' parent, caregivers/Midwest, United States	45	Competing activities involving school or peers; birthdays, homework	Adolescents identified competing activities, health status, patient-provider relationships, adverse clinic experiences, and forgetting as barriers to clinic attendance. Calendars/reminders and parent reminders were the most commonly reported strategies to facilitate clinic attendance. Adolescents also reported the need for flexible scheduling and improved patient-provider communication
Harris, 1998 ¹⁶⁸	Qualitative: standardized, structured, open-ended interviews	Patients (adults)/ United Kingdom	27	Negative provider attitudes	Study participants were satisfied with pain relief (78%), but 30% stated pain control would be improved with more prompt administration of meds. Overall hospital service was reported as "satisfactory to good" by 63%, but 44% made a complaint about the staff's negative attitude to people with SCD, 26% felt staff generally lacked knowledge and understanding of SCD and pain crises, 22% said staff did not believe or appreciate that they were in pain ("they treat us like liars") and 19% said nurses were slow to give analgesia and attended to other "less urgent" tasks (such as "pillows")

Author, year	Study design	Study population/location	N	Barriers identified	Primary results
Labbe, 2005 ¹⁴⁷	Quantitative: questionnaires	Doctors/Alabama, United States	109	Negative provider attitudes, inadequate pain assessment tools	Physicians hold a number of beliefs and attitudes which may affect the quality of pain management delivered to patients with SCD. While the patient's self-report of pain was the tool most commonly used by physicians in assessing the severity of pain (92% of respondents), 86% of the physicians "somewhat disagreed to dis-agreed" that the most reliable indicator of the existence and intensity of pain is the patient's self-report. Physiological and behavioral measures were also commonly cited tools used to assess pain severity. The top 5 barriers to optimal pain management in SCD as reported by these physicians were lack of psychological support from patient's family and the medical profession, fear that the patient is a drug abuser, reluctance to prescribe opioids, disbelief in patient's report of pain severity, and inadequate pain assessment tools
Lanzkron, 2008 ¹⁴⁸	Quantitative: 45-item questionnaire sent to members of the Sickie Cell Adult Provider Network (SCAPN).	Physicians, nurse practitioners, physician assistants, and other providers/ location unknown	48	Provider concerns to prescribe HU, lack of time/resources to adequately explain the risks/benefits	Providers were concerned about: Patient will not be compliant with needed blood tests, 74% Patient will not use appropriate contraception, 63% Patient will not be compliant with HU, 50% Patient does not have enough information about HU, 43% Patient's anticipation of side effects, 35% Patient is too young, 18% Concern about carcinogenic potential, 17% Provider lacks the time/resources to adequately explain the risks and benefits of HU, 13% Concern over cost, 11% Patient is too old, 2%
Maxwell, 1999 ¹⁶⁹	Qualitative: 18 semistructured interviews with 15 individuals and 8 focus groups	Patients (adults)/ London, United Kingdom	57	Negative provider attitudes	In focus groups, patients reported negative experiences with hospital care. These were characterized by mistrust (being suspected by health professionals of exaggerating pain), stigmatization (treated differently from other inpatients—"drug addicts"), control (health professionals exerted control and failed to involve patients in decisionmaking), neglect (of personal care, monitoring of vital signs, and psychosocial support due to under-staffing or low priority). A minority of patients responded to unsatisfactory care by self-discharging from 1 hospital and going to another
Modi, 2009 ¹⁵⁰	Quantitative: questionnaire about HU and routine care barriers and facilitators	Caregivers and adolescent patients/Ohio, United States	102	Forgetting, loss of medication, discomfort, treatment pain, taste aversions, side effects, embarrassment	Forgetting to take medication or loss of medication was the primary barrier identified by both caregivers and adolescents for pain management, hydroxyurea, and vitamin and mineral supplements, whereas fatigue was the primary barrier for exercise. Both caregivers and adolescents endorsed treatment pain or discomfort as barriers to chelation therapy and exercise, and taste aversions or side effects (e.g., nausea, racing heart) as barriers to pain medication and oral antibiotics. However, adolescents also uniquely identified side effects as barriers to transfusions (e.g., fever, chills), hydration (e.g., bloating), and vitamin and mineral supplements (e.g., constipation), along with taste aversions for the latter 2 treatments. Adolescents also reported questioning medication efficacy and a desire to be "normal" as barriers to oral antibiotics. In contrast, caregivers uniquely reported difficulty incorporating transfusions, hydration, and vitamin and mineral supplements into daily life, worry and anxiety about receiving transfusions, and embarrassment of doing chelation therapy (e.g., subcutaneous or intravenous injections) in front of others (e.g., friends, family) at home
Murray, 1988 ¹⁷⁰	Quantitative: questionnaires	Patients (adults)/ United Kingdom	102	Negative provider attitudes	Of the 88 patients who went to the hospital for care, 18 thought they were seen quickly, 33 thought the delay was too long, 17 were concerned about side effects of medications, 40 said pain relief "was there when needed," but only 23 routinely received analgesics on demand, and 57 patients thought staff did not appreciate the amount of pain they were having
Pack-Mabien, 2001 ¹⁷¹	Quantitative: questionnaires (written 31-item multiple choice survey about nurses' attitudes and perceived barriers to opioid pain management of pain episodes in patients with SCD)	Nurses/ United States	200	Negative provider attitudes, lack of provider knowledge, lack of time, inadequate pain assessment tools	Many nurses believed that drug addiction frequently develops in patients with sickle cell (63%) and reported (49%) that they did not have broad knowledge of sickle cell disease. Inadequate pain assessment tools were reported by 59% as the greatest barrier in the management of pain episodes. Lack of time for psychological support of patients (58%), nurse reluctance to provide opioids (37%), a narrow range of available analgesics (37%), physicians' reluctance to prescribe opioids (33%), and the belief that most patients with sickle cell are drug addicts (32%) were also reported barriers

Author, year	Study design	Study population/location	N	Barriers identified	Primary results
Pejaver, 1997 ¹⁵²	Quantitative: questionnaires	Patients (children/caregivers)/ Saudi Arabia	41	Forgetting, disliking taste, concern about side effects	Common reasons given for noncompliance with penicillin were forgetting to give the medicine, forgetting to re-new the supply of medicine, the child not liking the medicine, and the feeling that daily medication could have ill effects
Rouse, 2004 ¹⁷²	Qualitative: observations made while performing anthropological research on 2 children's hospitals	Nurses, doctors, patients (adults)/California and Pennsylvania, United States	NR	Negative provider attitudes	In the wards, residents and nurses dismissed patients' demands for pain relief as drug addiction, malingering, or manipulation. Furthermore, several staff members stated that "patients were being denied proper medical care, unfairly accused of drug use or criminal behavior, transferred to adult care clinics at an early age, and generally treated with less respect than the cancer patients who occupied the same floor in the hospital." With few exceptions, the nurses' perceptions of their patients with SCD were overwhelmingly negative. During 1 session, it was revealed that while nurses believe cancer patients' self-reporting of pain, they generally believed that their patients with sickle cell inflated their level of pain. 1 nurse said, "One of the problems with patients with SCD, I believe, is that health care professionals make a connection between African Americans using drugs and existing stereotypes; and that is coupled with health care professionals' lack of knowledge about sickle cell disease"
Shelley, 1994 ¹⁷³	Qualitative: phone interviews	Patients (adults, SCD self-help group leaders)/ United States	11	Negative provider attitudes, lack of provider knowledge	Patients perceived problems in health care services delivery. Inadequate staff training and high turnover in the ED, health providers' fears of drug addiction, negative attitudes of physicians to patients, delays in ED, un-familiarity of staff with SCD, routine accusations of drug-seeking, insensitivity of physicians to patients' pain, and negative reactions by physicians to patient attempts to be involved in the course of their own care were all reported. Most group leaders cited the unfamiliarity of ER staff with SCD as a factor which contributes to delays in treatment of VOCs. Several group leaders also cited provider insensitivity to patients' pain as a problem. Almost half of group leaders reported negative reactions on the part of some physicians to patients, including ignoring a patient, blunt remarks about the doctor's amount of knowledge vs. the "lay" patient. Group leaders reported that these sorts of incidents keep some SCD patients from the ED, even when they are in pain
Strickland, 2001 ¹⁷⁴	Qualitative: focus groups	Patients (adults), family members/United States	21 [†]	Negative provider attitudes	In focus group sessions, adults with SCD stated the belief that nurses would not give them pain medications when needed because the nurses believed that persons with SCD are addicts. Adults with SCD also stated the belief that some medical providers are intimidated when patients demonstrate knowledge about their disease or their pain control
Telfair, 1998 ¹⁷⁵	Quantitative: questionnaires (providers were asked to agree or disagree with 3 questions about (1) quality of health care provided to persons with SCD, (2) decisions about the administration of pain medication, (3) quality of interpersonal relationships between health care providers and patients)	Nurses, doctors, physician assistants, social workers/ United States	227	Patient race	Providers generally disagreed that race influences delivery of health care to individuals with SCD (52% dis-agree that quality is influenced, 77% disagree that pain medication decisions are influenced, 52% disagree that quality of interpersonal relationships are influenced). In bivariate analyses, 76% African American vs. 35% Caucasians ($p<.00$) agreed that race is an influence on quality, and 30–54% females vs. 12–37% males ($p<.01$) agreed with all 3 statements regarding race as an influence on health care provision. More urban providers (26%) vs. rural providers (11%) agree that race influences pain medication decisions ($p<.02$). In multivariate analysis, African American provider race was associated with all 3 questions ($p<.01$): quality (or 5.6, 95% CI: 2.80,11.22); pain medication decisions (or 3.1, 95%CI: 1.54,6.19); quality of relationships (or 3.9, 95% CI: 2.02,7.38)
Thornburg, 2010 ⁵⁷	Quantitative: Single institution cross-sectional prospective study. Care-givers were given a questionnaire to fill out on factors that may affect adherence	Patients (children)/ Durham, NC, United States	75	Clinic visits, prescription refills	The proportion of subjects with good adherence was 75% with 4 of 5 measures. Although there was significant increase in HbF, there was variability in response, which was partially explained by lack of adherence on the basis of pharmacy prescription refills and Modified Morisky Score
Tucker, 1995 ¹⁷⁶	Qualitative: Focus groups	Patients (adults)/ California, United States	NR	Negative provider attitudes, lack of provider knowledge	In 12 support group sessions of 2–8 patients each, patients all agreed on 2 major problem areas: (1) obtaining appropriate medical care in the ER (time to admission, feeling "forgotten," would delay hospital visits out of "dread") and (2) difficulty relating to members of the health care team (poor communication, "providers did not believe them," pain medication "not strong enough," discharged "too soon," being told "the pain is all in your head." Also, patients noted lack of knowledge by providers, felt "they are encouraged to 'act out' the pain" in order to be taken seriously and medicated appropriately. Several group members said that "they would do everything possible" to keep from coming to the hospital because they dreaded the admission procedures

Author, year	Study design	Study population/location	N	Barriers identified	Primary results
Vichinsky, 1999 ¹⁷⁷	Quantitative: Questionnaires (directors and associates of SCD centers were asked to comment on provision of care by community physicians using a survey tool developed for this study)	Directors and associates of SCD centers/United States, Canada	21	Lack of provider knowledge	In most categories, over 90% of respondents stated that care provided by physicians from their centers complied with NIH guidelines, as compared to many fewer (50% or less) who reported that care by community physicians complied with NIH guidelines in all categories except care related to infection (60%) and contraception and pregnancy care (59%). Most respondents (72%) believed that lack of knowledge or training was the reason that community physicians failed to follow NIH guidelines
Walters, 1996 ¹⁷⁸	Quantitative: Questionnaires (bone marrow consortium participants were asked to report on barriers at their institutions)	Physicians/United States (multicenter study)	315	Lack of donor, lack of financial/psychosocial support, parental refusal, physician refusal, history of non-compliance	315 out of 4,848 patients from 22 centers were reported to be eligible for BMT. Of the 315, 187 did not undergo HLA typing. The reasons for this included lack of HLA matching donor (76/187), lack of support (33/187), parental refusal (30/187), and physician refusal (13/187). Among those who had an HLA-identical donor (44), parental refusal was the most frequent reason for not performing a BMT
Waters, 1995 ¹⁷⁹	Mixed: Questionnaires (self-administered in presence of research coordinator) with qualitative analysis of open-ended responses	Nurses (inpatient), patients (adults)/ United Kingdom	26*	Negative provider attitudes, lack of provider knowledge, lack of time	Factors reported by the subset of 13 nurses who felt they could better relieve sickle cell pain were time (4/13), lack of knowledge of narcotic analgesia (4/13), fears of overdosing and addiction (4/13), and lack of experience with patients with sickle cell (2/13). Most patients (7/9) felt less in control of pain while in the hospital as compared to at home and wanted to be more involved in management of pain while on the ward. All patients stated they had to ask if they wanted more analgesia although the "majority" of nurses said they assessed pain continually. The majority of patients considered nurses' knowledge of sickle cell crisis and sympathy towards them as a patient group to be poor. Evidence of unsatisfactory pain management evidenced by a comment from the patient: "You can just tell sometimes that they don't agree with having to give you the injection"
Witherspoon, 2006 ¹⁶⁰	Quantitative: Questionnaires	Patients (children/caregivers)/United States	30	Caregiver being busy, forgetting to administer medications, child falling asleep, running out of medication	Commonly reported barriers to adherence were the caregiver being busy (26.7%), forgetting to administer the medication (23%), the child falling asleep (20%), and running out of medication (16.7%)
Zumberg, 2005 ¹⁸⁰	Quantitative: Questionnaires (27-item, 4-page, self-administered questionnaire)	Doctors (hematologists)/ Florida, North Carolina, United States	184	Patient compliance, lack of contraception, patient anticipation of side effects, patient age, provider concern about side effects, provider doubting effectiveness, cost	There were differences in HU prescribing between community and academic physicians showed differences in HU prescribing in the treatment of ACS (43% vs. 70%, $p=.006$), stroke (40% vs. 60%, $p=.04$), and PHTN (7% vs. 23%, $p=.008$). Community physicians less frequently monitored compliance by pill count (7% vs. 20% in academic physicians, $p=.03$) and MCV measurements (36% vs. 90%, $p<.0001$). Concerns that were identified as "important" or "very important" barriers to the use of HU were patient compliance (90%), lack of contraception (79%), patients' anticipation of side effects (82%), patient's age (50%), cost (59%), concern about carcinogenic potential (40%), and doubting effectiveness (40%)

* 9 patients and 17 nurses

† 10 nurses and 10 patients

‡ 10 patients and 11 family members

§ 22 patients and 7 staff

Table 22. Description of Interventions To Improve Patient Care in Sickle Cell Disease

Author, year	Study design	Study population/study location	N	Intervention objective Main intervention components	Intervention description
Benjamin, 2000 ¹⁸¹	CCT, pre-post	Nurses, doctors, social workers, patients/ Bronx, NY, United States	144	To decrease the load of the ED and study the value of a dedicated facility with knowledgeable staff applying principle-based individualized care/establishment of day hospital	Establishment of a day hospital with comprehensive assessment and treatment protocol (assessment and initial treatment within 15–20 min of arrival followed by assessment with established instruments every 30 min). Protocol included assessment, individualized drug management, medication titration to relief, maintenance of relief, use of combination drugs to enhance efficacy/toxicity ratio, monitoring of adverse events, identifying and treating precipitating factors, and appropriate disposition
Berkovitch, 1998 ¹⁸²	RCT	Patients (children/caregivers)/ Toronto, Canada	23	To establish a simple method of improving compliance with antibiotics in children with SCD/education and followup by medical professionals	Intervention subjects attended slide show (describing pathophysiology of SCD, risk of infections, importance of antibiotics), received stickers and a calendar to document compliance, and got a weekly phone call from social worker (asking questions about treatment, general health, other meds, family problems). Control and intervention subjects were invited to clinics every 8 weeks, where meds were dispensed and compliance evaluated. At end of 6 mo, parents in both groups completed a questionnaire to determine knowledge and understanding of SCD
Brookoff, 1992 ¹⁸³	Pre-post	Nurses, doctors, patients(adults)/ Philadelphia, PA, United States	50/yr	To determine if providing adequate pain control (using continuous morphine infusions and sustained courses of orally administered, controlled-release morphine) for the treatment of SCD in adults can decrease hospital visits and admissions for sickle cell pain/clinical protocol/pathway	Intravenous and oral controlled-release morphine was used instead of intramuscular meperidone and short-acting opioids in treatment of pain
Co, 2003 ¹⁸⁴	Pre-post, CCT	Patients (children/caregivers)/ Baltimore, MD, United States	369	To improve the care for pediatric SC VOCs/clinical protocol/pathway	Clinical pathway for the treatment of children aged 2–19 yr with VOC requiring hospitalization. Use of IV fluids, incentive spirometry, and pain service consultation were main check points for the pathway
Cooper, 2000 ¹⁸⁵	CCT, pre-post	Nurses, doctors Cleveland, Ohio, United States	67	To develop individualized pain management protocols; (2) discourage the use of meperidine in favor of morphine, hydromorphone, and levorphanol; (3) use buprenorphine for patients with known or suspected narcotic dependence/clinical protocol/pathway	The intervention was developed by establishing consensus concerning guidelines for care of SCD patients, and then educating physicians, nurses and house staff on new guidelines via grand rounds, conferences, medical management conferences, informal presentations, audiotapes, and mailings. Patients were identified via admitting diagnosis, and a care manager or physician made recommendations based on guidelines. Individualized care plans were constructed for “frequently admitted” patients with SCD and were entered into mainframe for access by all physicians
Day, 1997 ¹⁸⁶	Pre-post	Nurses, doctors, patients United Kingdom	18	To retrospectively audit admissions of SCD patients to identify problems with pain management and look for improvements after the care guide-lines were introduced to department/audit and feedback	1 nurse audited 10 admissions prior to implementation and 8 admissions after implementation to evaluate time to receive analgesia, what was prescribed, dose and method of administration, whether the pain management team was called, whether patient-controlled analgesia was used, and to which ward patient was admitted. Data from the initial audit were shared with providers
Fertleman, 1997 ¹⁸⁷	Pre-post	Nurses, doctors, patients (children/caregivers)/ London, United Kingdom	72	To evaluate the efficacy of a fast-track system in which children with SCD are directly admitted to the ward after a telephone call from parent, assessed immediately, and given intramuscular pethidine, if indicated (dose pre-prescribed)/establishment of fast track admission procedures	A fast-track system in which children with SCD are directly admitted to the ward after a telephone call from a parent, assessed immediately, and given a (pre-prescribed, documented) dose of intramuscular pethidine, if indicated. Time to treatment pre- (1994) and postimplementation (1995) were compared. Parents (25) whose children had used both systems completed questionnaires about both

Author, year	Study design	Study population/study location	N	Intervention objective Main intervention components	Intervention description
Jamison, 2002 ¹⁸⁸	Pre-post	Nurses, doctors, patients/ Greensboro, NC, United States	204	(1) To improve overall satisfaction of patients with SCD who were cared for at the study hospital (tertiary care hospital in the southeast); (2) reduce the length of stay of patients with SCD; (3) reduce the costs associated with hospital treatment of patients with SCD/clinical protocol/pathway with sensitivity training	The Intervention included staff education (sensitivity training, information about SCD, pain management, and other treatment interventions); nurse education about complementary therapies and other diversional activities; and a protocol to be used that included standing orders to evaluate and treat crises. Patients who did not have adequate control within 8 h and who were moved to inpatient area were all admitted to the oncology ward rather than diverse departments. Patient education materials, safety guidelines for admission, identification cards, and discharge instructions (including document with education and resources) were developed
Ketchen, 2006 ¹⁸⁹	RCT	Patients (children/caregivers)/ United States, Canada	37	To evaluate the efficacy of the home version of Starbright World, a Web-based computer network designed to connect chronically ill children, on increasing knowledge of SCD, in-creasing engagement in health-promoting activities, and improving psychosocial functioning/education and peer support	Access to Starbright World with weekly assignments (educational and social activities and those that encouraged child-parent participation). A staff member called caregivers weekly
LaVista, 2009 ¹⁹⁰	Qualitative: observational study	Patients, physicians/ United States	58	To develop and evaluate an intervention to empower patients and their families to discuss with their physician the risks and benefits of HU/educational video	Video content was developed based on gaps in patient knowledge discovered during patient interviews and observed by physicians caring for patients with SCD. A 15-min DVD entitled "Hydroxyurea: Is it Your Hope for Better Days?" included patients discussing experiences with HU and SCD experts discussing risks and benefits of HU and potential questions for patients to ask physicians
Mitchell, 2002 ¹⁹¹	Pre-post	Nurses, doctors, social workers, patients/ Philadelphia, PA, United States	27	To improve the consistency and quality of care for patients with SCD having a VOC at a 200-bed community hospital/clinical protocol/pathway	Implementation of new mandatory pain management protocol emphasizing aggressive pain management in the ED (using morphine sulfate or dilaudid rather than meperidine), admission to the medical-surgical unit if the crisis was not resolved in 8 h, and continued PCA, IV fluids, and oxygen. Physicians and nurses received in-service training related to the new protocol. 1 case manager was also assigned to coordinate all care
Patik, 2006 ¹⁹²	Pre-post	Patients (children/caregivers)/ Pittsburgh, PA, United States	202	To determine the feasibility and acceptance of the intervention for families with a child with SCD and the impact of the intervention on adherence to comprehensive care/education and nonmedical followup support	Telephone-delivered, structured followup, support, and education by nonmedical personnel (graduate student researcher). The semistructured script included questions related to patients' well-being and health-related behaviors and was administered at 3-mo intervals from the last contact
Thornburg, 2010 ¹⁵⁸	Prospective RCT	Patients (children), caregivers/United States	191	To increase adherence/efforts by study personnel to reinforce the importance of adherence and implement creative solutions to overcome barriers	NA, observational study
Treadwell, 2001 ¹⁹³	Pre-post	Patients (children/caregivers)/ California, United States	11	To increase patients' knowledge of the disease and treatment regimen within a setting that encouraged and assisted peer interactions, and ultimately to enhance treatment adherence/education and peer support	Desferel Day Camp provided peer support and education for 4 d each summer
Treadwell, 2002 ¹⁹⁴	Pre-post	Hospital staff, patients (children/caregivers)/ United States	235	To implement developmentally appropriate pain assessment guidelines for pediatric inpatients/clinical protocol/pathway	Staff were educated on the use of pediatric pain assessment tools, and a standardized pain assessment protocol was put into practice

Table 23. Results of Interventions To Improve Patient Care in Sickle Cell Disease

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Benjamin, 2008 ¹⁹⁵	Utilization, pain management quality (direct)	Administrative data were used	Walk-in day hospital patients discharged to home increased from 70% in first 2 yr to 90–94% in last 3 yr. The average length of stay in day hospital was 4.5 h (range 2–7 h) vs. 13 h (range 11 min to 90 h) in the ED. Treatment time in the ED before transfer to day hospital was 16 h in yr 1 vs. 8 h in yr 5. Visits resulting in admission were lower for day hospital patients (8%) vs. ED patients (51%). Admission rate in patients with uncomplicated pain was 776/1,818 (42.7%) ED patients vs. 168/2,033 (8.3%) day hospital patients. The use of meperidine decreased from 90% in yr 1 to 63% in yr 5, while the use of hydromorphone increased from 3% (yr 1) to 33% (yr 5). There were no <i>p</i> -values reported	Potential improvement
Berkovitch, 1998 ¹⁸²	Patient adherence (direct)	Family reports, administrative data, and medication event monitoring system were used. At 6 mo, parents in both groups completed questionnaire	Compliance at 2–4 mo was 79.0% (±31.4%) in the intervention group vs. 66.0 (±20.2%) in control group (<i>p</i> =.297). Compliance at 4–6 mo was 82.0 (±34.7%) in the intervention group vs. 65.8 (±25.3) in the control group (<i>p</i> =.366). There were no significant differences in admission rates or in measures of parent knowledge of SCD	No improvement
Brookoff, 1992 ¹⁸³	Utilization (indirect)	Administrative data and patient reports were used. Data on admissions and duration of hospital stay were collected for patients with SCD for all admissions from Jan. 1 to June 30 in the yr 1985 to 1990. ED visit data were collected for Jan. 1 to June 30, 1988–1990. The new protocol was implemented in 1989	Following this intervention, the total number of ED visits declined by 67% (426 to 138), the number of admissions declined by 44% (115 to 65), and the duration of hospital stay decreased by 23% (7.12 d to 5.45 d). There were no <i>p</i> -values reported. The new protocol “met with strong resistance by a few patients” but this was eased by allowing these patients to “participate in developing their own analgesic plan”	Potential improvement
Co, 2003 ¹⁸⁴	Pain management quality (direct)	Administrative data (use of IV fluids, incentive spirometry, and pain service consultation) were used	Of 369 patients, 139 were admitted before the pathway, and 230 were admitted after the pathway. Physicians used the pathway 43% of the time after the pathway became available. Pathway patients were more likely than nonpathway patients to have received IV fluids (OR=1.15, 95% CI 1.07–1.23); incentive spirometry (OR=2.49 95% CI 2.02–3.07); and pain service consult (OR=1.33, 95% CI 1.18–1.50). Pathway patients had longer length of stay (<i>p</i> =.01) and time on oral pain medication (<i>p</i> <.001) than nonpathway admissions. No difference in re-admission rates	Improvement
Cooper, 2000 ¹⁸⁵	Utilization, costs, pain management quality (direct)	Administrative data were used	Of 58 care-managed admissions (study group) and 9 noncare-managed admissions (control group), the median unadjusted hospital length of stay was 3.5 d in the study group vs. 4 d in the control group (<i>p</i> =.54). Costs were \$2,920 in the study group vs. \$3,157 in the control group (<i>p</i> =.32). The use of nonguideline narcotic meperidine decreased from 82% preimplementation to 18% postimplementation (<i>p</i> <.001)	Improvement
Crosby, 2009 ¹⁴³	Patient awareness (direct)	Pre-post surveys	Patients expressed a strong desire after viewing the video to learn about potential benefits of HU. Furthermore, the video was useful in heightening the intent of patients to ask their health care providers about HU therapy	Improvement
Day, 1997 ¹⁸⁶	Pain management quality (direct)	Administrative data were used	After the intervention, the use of intramuscular pethidine decreased from 8/10 to 0/8 and the use of patient-controlled analgesia with morphine increased from 1/10 to 7/8. The incidence of calling the pain team promptly at admission increased from 1/10 to 8/8. The author reports that the time to see a physician was “often . . . not immediate” prior to the intervention, but changed to “all . . . seen by a doctor immediately upon arrival” after the intervention	Potential improvement
Fertleman, 1997 ¹⁸⁷	Pain management quality, patient ratings (direct)	Family reports and administrative data were used	Median time to pethidine decreased from 38 min to 5 min (<i>p</i> <.001). 21 of 25 questionnaires were returned and all parents preferred the fast-track system. Parents “added that the ward staff knew more about SCD, knew their children, and did not ask irrelevant questions before giving pethidine”	Improvement
Jamison, 2002 ¹⁸⁸	Patient ratings, utilization, costs (direct)	Patient reports, administrative data were used	A pain management questionnaire administered to 9 patients at the beginning of implementation and to 10 patients 6 mo later showed “marked improvement in the followup 6-mo survey.” Patient satisfaction postquestionnaire that asked patients about satisfaction pre- and postimplementation was administered to 18 patients, and suggested that satisfaction overall improved. There was an overall trend in decreasing LOS postimplementation. Admissions to the ED or inpatient departments decreased >50% postimplementation. There was an 18.5% decrease in inpatient costs and 29.6% decrease in costs of observation stays. There was no significance testing reported in the article	Potential improvement

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Ketchen, 2006 ¹⁸⁹	Health promotion activities, parent-child relationships, child quality of life, child depression (direct)	Patient/family reports were used. Data collection occurred preintervention and 2 mo postintervention of SCD	Intervention and control groups did not differ with respect to demographic, disease severity, prestudy computer ownership, or exposure to health-education programs. Children in the intervention group had significant improvements in quality of life [child quality of life (lower scores better): pre: 32.70 (17.64) in intervention vs. 35.27 (17.08) in control; post: 29.90 (15.34) in intervention vs. 31.44 (25.05) in control time. Children in the intervention group showed improvements in parent-child relationships (pre: 14.50 (6.19) in intervention vs. 17.82 (4.28) in control, and post: 16.04 (4.75) in intervention vs. 17.18 (5.00) in control time). There was a nonsignificant trend toward children in the intervention group having improvements in depression scores. There were no significant differences between intervention and control groups in health promotion activities or child knowledge of SCD	Partial Improvement
Mitchell, 2002 ¹⁹¹	Utilization (indirect)	Administrative data were used. Outcomes were measured 6 mo before and 6 mo after protocol	There were 235 visits to the ED with 76 admissions (68% treat-and-release) preintervention compared to 188 visits to the ED with 46 admissions (76% treat-and-release) postintervention. The average length of stay decreased from 4.9 d to 3.8 d. The authors report that there were no patient complaints during the intervention and that patients commented that "pain was being managed more efficiently." There was no significance testing reported in the article	Potential improvement
Patik, 2006 ¹⁹²	Rate of patient nonattendance at clinic for 2 yr (direct)	Cross-sectional patient survey prior to the start of the intervention and repeated 18 mo later	147 of the 202 patients (73.6%) were available and willing to talk. 64% of patients requested a service during the phone call (e.g., prescription refill, information, appointment scheduling). The proportion of patients who had not attended clinic for >2 yr decreased from 19.7% to 9.9% ($p=.002$) following intervention, and TCD compliance increased from 34% to 49% ($p=.05$)	Improvement
Treadwell, 2001 ¹⁹³	Patient adherence (direct)	Patient reports were used	Participation in Desferal Day Camp did not result in increases in measures of patient knowledge, peer support, or adherence to therapy	No improvement
Treadwell, 2002 ¹⁹⁴	Pain management quality, patient ratings (direct)	Patient report, family report, administrative data	Patients, families, and staff reported increased pain assessment, improved staff responsiveness to patients' pain, and greater satisfaction with assessment tools postintervention (all p -values $<.05$). Increased compliance with the assessment guidelines was confirmed by chart audit	Improvement

Table 24. Outcome Data Stratified by Dosage in Adults

Study label	Study arm (N)	HbF%*	%F cells*	Hemoglobin (g/dL)	MCV (fL)	WBC count (/μL)	Pain crises*	Hospital admissions*	Comments
MTD: Al-Jam'a, 2002 ¹¹	Post-HU (27) Pre-HU (27)	Post-HU: 25.7 (7.3) median= 25 [#] Pre-HU: 12.6 (5.4)	NR	Post-HU: 10.7 (1.4) median= 10.8 [#] Pre-HU: 9.71 (1.2)	NR	Post-HU: 6,260 (2,580) Median= 5,600 [#] Pre-HU: 8,990 (3,480)	Pre-HU: 6.5/yr(2.8)	Post-HU: 0.93 (2.2) Median=0 [†] ; hospital days 5.1 (13.5) median=0 [#] Pre-HU: Hospital days 33.9 (26.1)	NR
MTD: Charache. 1992 ¹⁶	Post-HU (32) Pre-HU (49)	Post-HU: 15 (6) [†] Pre-HU: 4 (2)	Post-HU: 73 (17) [†] Pre-HU: 28 (14)	Post-HU: 9.7 (1.8) [†] Pre-HU: 8.4 (1.4)	Post-HU: 117 (15) [†] Pre-HU: 94 (8)	Post-HU: 8,400 (1400) [†] Pre-HU: 13,400 (3,200)	Post-HU: 1.3 (2)/6 mo [0–9] Pre-HU: 4 [0–20]/6 mo	NR	Post-HU: Mean=4.3 kg weight gain [†]
MTD: Voskaridou, 2010 ⁶⁰	HU (131) Non-HU (199)	HU: 17.4 [0.8–38.3] Non-HU: 4.9 [0.8–38.3]	NR	HU: 9.5 [6.3–13] Non-HU: 9.1 [5.5–13.6]	HU: 96.8 [79.8–127.2] Non-HU: 71.1 [62.8–99.2]	Pre-HU median: 10.7, r 3.0 - 33.8*10 ⁹ /L Post-HU median: 8.0, r 2.9 - 39.6*10 ⁹ /L	HU: 0.025 (0.026) >95% reduction	HU: 0.041 (0.018)	HU: Some outcome data were not reported for non-HU arm. Some outcomes were reported per year
Non-MTD: Berthaut, 2008 ¹⁴	Before HU (34) During HU (5) After HU (8)	NR	NR	NR	NR	NR	NR	NR	Before HU: Volume of ejaculate 3.08±1.67 mL; spermatozoa concentration 38.55±43.12 ×10 ⁶ /mL; total sperm count 114.17±124.12 ×10 ⁶ ; initial forward motility 28.66±18.38 % of motile; spermatozoa morph-ology 21.92±14.63% of normal; vitality 59.75±21.61% of living During HU: Volume of ejaculate 2.68±1.28 mL; spermatozoa concentration 2.66±3.75 ×10 ⁶ /mL; total sperm count 7.02±10.18 ×10 ⁶ ; initial forward motility 30.00±5.77 % of motile; spermatozoa morph-ology 34.50±21.92% of normal; vitality 52.00±14.23 % of living After HU: Volume of ejaculate 2.99±2.85 mL; spermatozoa concentration 18.46 ± 26.86 ×10 ⁶ /mL; total sperm count 61.12±107.37 ×10 ⁶ ; initial forward motility 29.46±20.13% of motile; spermatozoa morphology 19.16±16.3% of normal; vitality 44.40±20.12% of living
Non-MTD: Dahoui, 2010 ¹⁸	Normal TRV (58) PHTN (27)	NR	NR	NR	NR	NR	NR	NR	Normal TRV: Patients on HU had a higher prevalence of PHTN and HU was not able to stop PHTN from developing in 5 patients
Non-MTD: el-Hazmi, 1992 ²²	Post-HU (21)	Post-HU: 19.8 (4) [†]	NR	Post-HU: NR [†]	Post-HU: NR [†]	Post-HU: 6,629 (2,603) [†]	NR	NR	Post-HU: P-value relative to baseline

Study label	Study arm (N)	HbF%*	%F cells*	Hemoglobin (g/dL)	MCV (fL)	WBC count (/μL)	Pain crises*	Hospital admissions*	Comments
Non-MTD: Italia, 2009 ³⁴	Adult HbSS (29) Adults HbSβ ⁰ -thal (23)	Adult HbSS: 23.1 (5.2) Adults HbSβ ⁰ -thal: 26.9 (10)	Adult HbSS: 82.7 (8.7) Adults HbSβ ⁰ -thal: 70.3 (18.2)	Adult HbSS: 10.7 (1.5) Adults HbSβ ⁰ -thal: 9.8 (1.7)	Adult HbSS: 95.4 (11.8) Adults HbSβ ⁰ -thal: 77.2 (12)	Adult HbSS: 8 (2) Adults HbSβ ⁰ -thal: 8.2 (3.3)	Adult HbSS: 0–1/yr: 83% 2–3/yr: 17% Adults HbSβ ⁰ -thal: 0–1/yr: 87% 2–3/yr: 13%	Adult HbSS: 0: 97% 1–2/yr: 3% Adults HbSβ ⁰ -thal: None: 100%	NR
Non-MTD: Lefevre, 2008 ³⁸	HU (80) Non-HU (39)	HU: NR	NR	NR	NR	NR	NR	NR	HU: 2 presented stroke; 4 patients with a previous history of stroke, but only 1 presented a new episode; recurrence rate of stroke was 2.9/100 patient-yr; incidence of first stroke 0.36/100 patient-yr Non-HU: Velocity increases with age to a maximum ages 6–9
Non-MTD: Little, 2006 ³⁹	A: High-risk SCD with HU intolerance (5) B: High-risk SCD with relative renal insufficiency (5) C: Misc (3)	A: High-risk SCD with HU intolerance: 13.5 [3.1–21], up from 5 [1.6–14]	A: High-risk SCD with HU in-tolerance: 47.5 [24–75], up from 22 [13–66]	A: High-risk SCD with HU intolerance: 8.5 [6.7–11.5], up from 6.4 [4.7–8.6]	NR	NR	NR	NR	NR
Non-MTD: Loukopoulos, 1998 ⁴⁰	Post-HU (44) Pre-HU	Post-HU: 23.1 (9.2) Pre-HU: 6.7(4.7)	NR	Post-HU: 9.3 Pre-HU: 8.9	Post-HU: 98.1 (15) Pre-HU 75.7 (11)	NR	NR	NR	NR
Non-MTD: Loukopoulos, 2000 ⁴¹	HbSS (14) HbSβ ⁰ -thal (35) HbSβ ⁺ -thal (20)	HbSS: M: 28 (6.5), F: 26.6 (6.7) HbSβ ⁰ -thal: M: 34.2 (12.8), F: 27.9 (14.3) HbSβ ⁺ -thal: M: 25 (6.3), F: 25.2 (6.4)	NR	HbSS: M: 10.7 (0.8), F: 9.4 (1.5) HbSβ ⁰ -thal: M: 9.8 (1.7), F: 8.8 (0.8) HbSβ ⁺ -thal: M: 9.2 (1.7), F: 9.1 (1.1)	HbSS M: 121.5 (17.3), F: 125.4 (8.3) HbSβ ⁰ -thal: M: 100.4 (12.3) F: 100 (9.4) HbSβ ⁺ -thal: M: 90.9 (11.1) F: 88.7 (12.4)	NR	NR	NR	Mean clinical severity score of 81.7 over 12,018 patient-weeks was down from baseline score of 1,182 (arbitrary scale) Outcomes measured at maximum HbF concentrations. HbF% difference was very significant ($P<.001$) in all but female HbSS patients. Hb difference was very significant ($P<.001$) only in male HbSβ ⁰ -thal patients
Non-MTD: Rigano, 2001 ⁵⁰	Post-HU (22) Pre-HU	Post-HU: 25.2 (5.2) [†] Pre-HU: 7.5 (5.3)	NR	Post-HU: 10 (1.5) Pre-HU: 6 (1.3)	Post-HU: 96.4 (7.2) [†] Pre-HU: 73.9	Post-HU: 10,200 (3,900) Pre-HU: 11,400 (3900)	Post-HU: 1.1 (1.8)/yr median= 0.5 [‡] Pre-HU: 7/yr median=9 (all crises including pain)	Post-HU: 0.5 (1.6) [†] ; hospital days 1.2 (2.3) [†] Pre-HU: hospital days 22.4	NR

* Mean, (SD) [range] unless otherwise noted # $p\leq.005$

[†] $p\leq.0001$ ^{**} $p=.0002$

[‡] $p\leq.001$ ^{††} $p\leq.00001$ [§] $p\leq$ not significant

^{‡‡} $p=.057$ ^{||} $p\leq.01$

^{§§} Change from baseline [¶] $p\leq.002$

Table 25. Outcome Data Stratified by Dosage in Children

Study label	Study arm (N)	HbF%*	%F cells*	Hemoglobin (g/dL)	MCV (fL)	WBC count (/μL)	Pain crises*	Hospital admissions*	Comments
MTD: Al-Jam'a, 2002 ¹¹	Post-HU (27) Pre-HU	Post-HU: 25.7 (7.3) median=25 [#] Pre-HU: 12.6 (5.4)	NR	Post-HU: 10.7 (1.4) median=10.8 [#] Pre-HU: 9.71 (1.2)	NR	Post-HU: 6,260 (2,580) median 5,600 [#] Pre-HU: 8,990 (3,480)	Pre-HU: 6.5/yr (2.8)	Post-HU: 0.93 (2.2) median=0 [†] ; hospital days 5.1 (13.5) median 0 [#] Pre-HU: Hospital days 33.9 (26.1)	NR
MTD: de Montalembert, 1997 ¹⁹	Post-HU (35) Pre-HU (35)	Post-HU: 13.7 [3.2- 27.0] [†] Pre-HU: 4 [0.8513.9]	NR	Post-HU: 9 (1.4) <i>p</i> =.03 Pre-HU: 8.4 (1.2)	NR	NR	NR	NR	All but 2 patients had decreased frequency or termination of crises. No clear difference in weight or height velocity
MTD: Flanagan, 2010 ²⁵	HU (37)	Baseline Median =5.9 MTD Median=19.1	NR	Baseline Median=8.1 MTD Median=9.1	Baseline: 86.2 MTD: 104.2 Difference: 17.3 (all median values)	Baseline Median=12.4 MTD Median=8.5	NR	NR	Red blood cell count (baseline median=2.7 MTD median=2.5); platelet count (baseline median=495 MTD median=364); absolute neutrophil count (baseline median=5,989 MTD median=3,510); absolute reticulocyte count (baseline median=246 MTD median=126)
MTD: Hankins, 2005 ²⁹	Post-HU (21) Pre-HU (21)	Post-HU: 23.7 (7.4) [‡] Pre-HU: 21.8 (7.8)	Post-HU: 82.6 (7.9) [‡] Pre-HU: 80.6 (14.1)	Post-HU: 9.1 (1.4) [‡] Pre-HU: 8.5 (1.2)	Post-HU: 95.1 (10.4) [‡] Pre-HU: 81.7 (8.0)	Post-HU: 10,100 (5,000) [‡] Pre-HU: 12,600 (4,400)	Post-HU: 33.8/100 patient-yr compared to 32.4/100 patient-yr in CSSCD [§]	NR	Outcomes are for 17 children after 4 yr of therapy
MTD: Hankins, 2007 ³⁰	HU (52)	NR	NR	NR	NR	NR	NR	NR	6 patients had recovery of splenic function; 24/25 had stable brain MRIs
MTD: Hankins, 2008 ³¹	HU (52)	Patients whose spleen function recovered or was preserved (before HU=9.3, during HU=22.3) Patients whose spleen function had no effect from HU (before HU=4.0, during HU=18.2)	NR	Patients whose spleen function recovered or was preserved (before HU=9.1, during HU=11.1) Patients whose spleen function had no effect from HU (before HU=8.6, during HU=9.2)	Patients whose spleen function recovered or was preserved (before HU=86; during HU=104) Patients whose spleen function had no effect from HU (before HU=86; during HU=107)	Patients whose spleen function recovered or was preserved (before HU=13.5; during HU=8.7) Patients whose spleen function had no effect from HU (before HU=15.9; during HU=8.1)	NR	NR	Patients whose spleen function recovered or was preserved (<i>n</i> =8) Patients whose spleen function had no effect from HU (<i>n</i> =35) Patients whose brain function showed improvement on MRI (<i>n</i> =24) Patients whose brain function worsened on MRI (<i>n</i> =1) (patient had a new punctate hemorrhagic area in the right deep frontal white matter) Patients whose brain function was stable on MRA (<i>n</i> =24) Patients whose brain function showed improvement on MRA (<i>n</i> =1)
MTD: Kinney, 1999 ³⁶	Post-HU (84) Pre-HU	Post-HU: 17.8 (7.2) [†] Pre-HU: 7.3	Post-HU: 66.5 (19.6) [†] Pre-HU: 34.6 (17.8)	Post-HU: 9 (1.4) [†] Pre-HU: 7.8	Post-HU: 101.3 (10.2) [†] Pre-HU: 85.9 (6.6)	Post-HU: 9,200 (3,200) [†] Pre-HU: 13,600	NR	NR	Hematological effects were attained by 6 mo (even before MTD). There was little difference between 6- and 12-mo data. Continued weight gain and linear growth
MTD: Kratovil, 2006 ³⁷	HU (24) No HU	HU: 11.79, [3.8 - 25.4] relative to untreated	NR	HU: 8.2 [5.2 10.6] ^{±±} relative to untreated	NR	NR	NR	NR	HU: Mean of maximum TCD=111.2 cm/s No HU: Mean of maximum TCD=124 cm/s

Study label	Study arm (N)	HbF%*	%F cells*	Hemoglobin (g/dL)	MCV (fL)	WBC count (μL)	Pain crises*	Hospital admissions*	Comments
MTD: Maier-Redelsperger, 1998 ⁴³	Post-HU (29) Pre-HU (29)	Post-HU: 13 (9.4) Pre-HU: 4 [0.8513.9]	Post-HU: 54.2 (22.1) Pre-HU: 24.4	Post-HU: 9.1 (0.9) Pre-HU: 8.4 (1.2)	Post-HU: 101.8 (15.9) Pre-HU: 84.5	NR	NR	NR	NR
MTD: Olivieri, 1998 ⁴⁷	Post-HU (17) Pre-HU (17)	Post-HU: 16.7 (1.8) Pre-HU: 7.6 (1.6)	NR	Post-HU: 10.2 (3.6) Pre-HU: 8.9 (4.3)	Post-HU: Post-HU: 104 (3) Pre-HU: 87 (7)	NR	Post-HU: 1.2/yr (0.4) Pre-HU: 3.1/yr (0.5)	Post-HU: 1.7/yr (2.0) Pre-HU: 6.7/yr (2.8)	ACS rate declined from 1.3/yr to 0.2/yr. No difference in number of pitted RBCs (n=12 children) was observed
MTD: Santos, 2002 ⁵¹	HU (21)	15.1 ^{§§}	NR	NR	NR	NR	NR	NR	10 patients had improvement in splenic function
MTD: Thornburg, 2009 ⁵⁶	HU (14)	25.9 (6.6)	NR	9.5 (1)	99 (12)	NR	NR	NR	NR
MTD: Thornburg, 2010 ⁵⁷	HU (75)	8% inc' [6.2–9.8]	NR	1.3 [1.0–1.5]	NR	NR	NR	NR	1,699 cells/mm ³ decrease in absolute neutrophil count
MTD: Ware, 2002 ⁶²	Post-HU (68, 53 with sufficient data) Pre-HU	Post-HU: Median=17.6, [2.9-32.4] Pre-HU: 6.7	NR	Pre-HU: 7.7	Pre-HU: 85.7	Pre-HU: 14,000	NR	NR	HbF% was predicted by HbF% at baseline (p=.001) and Hb at baseline (p=.01); HbF% was negatively associated with number of pills re-turned (p=.02), positively with change in Hb (p<.0001), MCV (p=.01) and decline in reticulocytes (p=.01), and decline in WBC (p=.006)
MTD: Ware, 2004 ⁶³	HU (35)	18.6 (6.6)	NR	9.2(1.4)	112(9)	7,300 (2,500)	NR	NR	Data collected on 2 groups; patients initiating HU after an abrupt halt to transfusion therapy, and patients initiating HU before transfusion therapy was completely halted. Pooled data were presented here. Stroke recurrence rate 5/7/100 patient-yr (7 children, 4 of whom were noncompliant with HU)
MTD: Zimmerman, 2004 ⁶⁴	Post-HU (122) Pre-HU (122)	Post-HU: 19.7 (8.5) [‡] Pre-HU: 7.6	NR	Post-HU: 9.7 (1.3) [‡] Pre-HU: 8.2	Post-HU: 105.8 (13.8) [‡] Pre-HU: 84.4 (8.5)	Post-HU: 7.0 Pre-HU: 12,400	NR	NR	Efficacy (in Hb, MCV, % HbF, WBC count, ANC, reticulocyte, bilirubin) maintained over 7 yr of followup
MTD: Zimmerman, 2007 ⁶⁵	Patients with increased TCD velocities post-HU (37) Patients with increased TCD velocities pre-HU	Patients with increased TCD velocities post-HU: 22.7 (7.9) median=23.3 [†] Patients with increased TCD velocities pre-HU: 10.3	NR	Patients with increased TCD velocities post-HU: 9.4 (1.1) median=9.4 [†] Patients with increased TCD velocities pre-HU: 7.8	Patients with increased TCD velocities post-HU: 104 (9) median [†] Patients with increased TCD velocities pre-HU: 86 (8)	NR	NR	NR	Significant decline in TCD of RMCA, LMCA, RACA, LACA, and LPCA, but not RPCA. Stroke rate on treatment 0.52/100 patient-yr, RMCA on treatment 134 cm/s, p<.001
Non-MTD: Bakanay, 2005 ¹³	HU (226)	NR	NR	NR	NR	NR	NR	NR	Very little description of study population and treatment, also had concern about confounding by indication
Non-MTD: Dahoui, 2010 ¹⁸	Normal TRV (58) PHTN (27)	NR	NR	NR	NR	NR	NR	NR	Patients on HU had a higher prevalence of PHTN, and HU was not able to stop PHTN from developing in 5 patients

Study label	Study arm (N)	HbF%*	%F cells*	Hemoglobin (g/dL)	MCV (fL)	WBC count (/μL)	Pain crises*	Hospital admissions*	Comments
Non-MTD: Italia, 2009 ³⁴	Children HbSS (25)	HbSS: 24.4 (6.3)	HbSS: 84.4 (10.8)	HbSS: 9.4 (1.9)	HbSS: 94.5 (10.6)	HbSS: 9.1 (3.4)	HbSS: 0–1/yr: 64% 2–3/yr: 36%	HbSS: None: 96% 1–2/yr: 4%	NR
Non-MTD: Odievre, 2008 ⁴⁶	On HU and had vaso-occlusive events (26) Non-HU and had vaso-occlusive events (20) Never had vaso-occlusive events (28) Non-SCD (controls) (27)	On HU and had vaso-occlusive events: 11.6 Non-HU and had vaso-occlusive events: 6.5 Never had vaso-occlusive events: 8.8 Non-SCD (controls): 0.2	NR	On HU and had vaso-occlusive events: 87 Non-HU and had vaso-occlusive events: 79 Never had vaso-occlusive events: 80 Non-SCD (controls): 129	On HU and had vaso-occlusive events: 87.6 Non-HU and had vaso-occlusive events: 84.2 Never had vaso-occlusive events: 78.7 Non-SCD (controls): 82.1	NR	NR	NR	On HU and had vaso-occlusive events: PMN+++ 2.3, platelets 246, RBCs 4.7, reticulocytes 50.85, Hct 39.9 Non-HU and had vaso-occlusive events: PMN 5.7, platelets 478, RBCs 3.1, reticulocytes 231.68, Hct 4.7 Never had vaso-occlusive events: PMN 5.5, platelets 434, RBCs 2.9, reticulocytes 303.45, Hct 24.3 Non-SCD (controls): PMN 4, platelets 431, RBCs 2.8, reticulocytes 227.98, Hct 26.6
Non-MTD: Pashankar, 2008 ⁴⁸	HU (6) Non-HU (4)	NR	NR	HU: 7.98	NR	NR	NR	NR	HU: TRV and RVP decreased (40.16 to 23.6 mmHg) after 9–12 mo of therapy. O ₂ sat increased from 90 to 93%
Non-MTD: Scott, 1996 ⁵³	Post-HU (15) Pre-HU (15)	Post-HU: 15.2 (9.8) [4.1–31] [¶] Pre-HU: 6.9 (6.2)	NR	Post-HU: 9.5 (1.5) [7.7–13.1] Pre-HU: 8.2 (1.0)	Post-HU: 100 (15) [80–127] [†] Pre-HU: 85 (11)	NR	NR	Post-HU: 3/yr (4) Pre-HU: 7/yr (2.4)	NR
Non-MTD: Svarch, 2006 ⁵⁵	HU (51) Pre-HU (51)	HU: 12.4 (7.9) [†] Pre-HU: 6.4	NR	HU: 8.5 (1) <i>p</i> =.0001 Pre-HU: 7.8	NR	HU: 9,800 (2,100) <i>p</i> =.12 Pre-HU: 10,900	HU: Median 0.8/yr [0–2] Pre-HU: Median 3/yr	HU: 0.5 [04] Pre-HU: 4 [0–6]	HU: Resource-poor environment
Non-MTD: Wang, 2001 ⁶¹	Post-HU (28) Pre-HU CSSCD	Post-HU: 20.3 (4.9) Pre-HU: 21.8 (7.8) CSSCD: 10.9 (7.9)	Post-HU: 76.2 (12.4) Pre-HU: 80.6 (14.1) CSSCD: 65.4 (11.2)	Post-HU: 8.8 (1.2) Pre-HU: 8.5 (1.2) CSSCD: 7.7 (1.0)	Post-HU: 90 (9.6) Pre-HU: 81.7 (8.0) CSSCD: 84.1 (10.1)	Post-HU: 10,100 (3,200) Pre-HU: 12,600 (4,400) CSSCD: 14,300 (2,400)	NR	NR	Post-HU: Outcomes are for 21 patients who completed 2 yr of treatment (not necessarily on MTD)

* Mean, (SD) [range] unless otherwise noted

p≤.005

† *p*≤.0001

** *p*=.0002

‡ *p*≤.001

†† *p*≤.00001

§ *p*≤ not significant

‡‡ *p*=.057

|| *p*≤.01

§§ Change from baseline

¶ *p*≤.002

Table 26. Randomized Controlled Trials Identified Through Supplemental Search (June 1, 2010–July 11, 2014)*

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)
Jain, 2012 ¹⁹⁶	India	NR	Children with severe sickle cell anemia (SCA) (more than 3 hospitalizations per year for vaso-occlusive crisis (VOC) or 3 transfusions per year)	HU 10 mg/kg/day or placebo	18 mo	HU (30) Placebo (30)	12 (5–18)	47	NR	Moderate risk of bias Double-blinded (unclear who was blinded), unclear allocation concealment and loss to followup	Compared to placebo, HU group had significantly decreased VOC frequency, increased hemoglobin and hemoglobin F percentage ($p<0.001$ for all 3 outcomes) Side effects: No serious events, no leucopenia, neutropenia, renal or hepatic toxicity
Ware, 2012 (SWITCH trial) ¹⁹⁷	United States	NR	Children with SCA, previous stroke, and ≥ 18 months of transfusions with documented iron overload	Hydroxyurea 20 mg/kg/d with escalation to maximum tolerated dose (MTD) + transfusions for 4 to 9 mo during an overlap phase + phlebotomy with a target of 10 mL/kg (maximum volume 500 mL) removed monthly Standard treatment: Monthly transfusions to maintain $\geq 30\%$ HbS, with local discretion regarding transfusion type + daily iron chelation typically with deferasirox	30 mo	HU + phlebotomy (67) Transfusion and chelation (66)	13	54	SS	Low to moderate risk of bias Investigators and outcome assessors were blinded and allocation concealed; one patient lost to followup trial stopped early for futility	7/67 strokes in hydroxyurea/phlebotomy group compared with 0/66 in transfusions/chelation group; rate difference within the noninferiority margin but liver iron content (LIC) values were not superior on hydroxyurea/phlebotomy so the study was stopped

* 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 two being relevant to the HU chapter. Only trials of interventions that addressed the management of SCD or related complications were included.

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** For case reports published before July 2007, please refer to evidence reports reviewed by Segal et al.⁶⁷ (Segal JB, Strouse JJ, Beach MC, Haywood C, Witkop C, Park HS, et al. Hydroxyurea for the treatment of sickle cell disease. Evidence Report/Technology Assessment No. 165. (Prepared by Johns Hopkins University Evidence-based Practice Center under contract No. 290-02-0018). AHRQ Publication No. 08-E007. Rockville, MD. Agency for Healthcare Research and Quality, February 2008.) with 198 aggregated case reports. There are 214 articles directly referenced in this evidence table, adding up to a total of 412 included studies.

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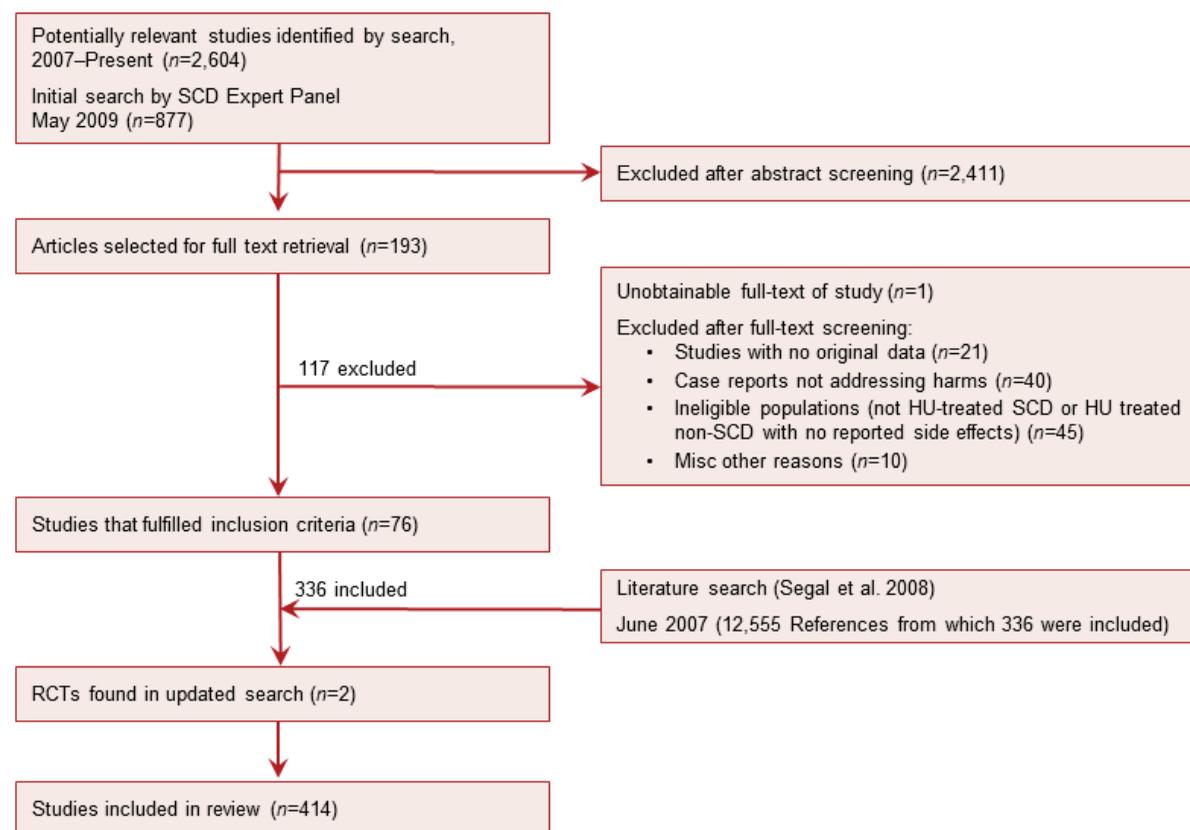
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Appendix A. Study Selection Process^{††}



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 interviewer agreement was observed (kappa statistic ≥ 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.

^{††} The 414 studies include the 76 new articles plus 336 existing articles in the Segal et al.⁶⁷ review in 2008, plus 2 randomized controlled identified in an updated search from June 2010 through July 2014. Among the 336 articles, 118 are described in detail, while 218 (mostly case reports and case series) are described in aggregate (for full citation, see Segal et al.⁶⁷ at <http://www.ahrq.gov/research/findings/evidence-based-reports/hydscd-evidence-report.pdf>). Thus, the 197 direct references contain 76 new articles, 118 detailed articles, the 1 systematic review by Segal et al.,⁶⁷ and 2 RCTs from a supplemental search.

Appendix B. Methods

The Critical Question of the Systematic Review (PICOS)*

Patients:

- Patients with sickle cell disease (SCD)
(For hydroxyurea harms, studies in non-SCD patients are included.)

Intervention:

- Hydroxyurea (HU)

Comparison:

- Usual care without HU

Outcomes:

- Benefits of HU (death, stroke, pain crises, need for transfusion, hemoglobin, and hemoglobin F levels)
- Harms of HU (adverse effects)
- Barriers to implementation of HU treatment and interventions to overcome barriers
- Treatment protocols and monitoring parameters

Study design:

Randomized or nonrandomized design including case reports of rare complications

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

Appendix C. Data Sources and Search Strategies

A comprehensive search of several databases (from 1970 to January 2011, 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, EBSCO Cumulative Index to Nursing and Allied Health Literature, TOXLINE, 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 define the concept areas: sickle cell disease, hydroxyurea, its efficacy, barriers to use, and adverse effects. Additional references were identified by consulting with experts in the field.

Database(s): EMBASE, Ovid MEDLINE(R), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR)

Search Strategy

Number	Searches	Results
1	exp Anemia, Sickle Cell/	25,696
2	(sickle cell or "hemoglobin s" or drepanocytemia or "drepanocytic anemia" or drepanocytosis or "hemoglobin ss" or meniscocytosis or "sickle anemia" or "ss disease").mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	29,336
3	1 or 2	29,430
4	thrombocytopenia.mp. or exp Thrombocytosis/	9,347
5	exp thrombocytopenia/	5,951
6	thrombocytosis.mp.	6,949
7	4 or 5 or 6	10,958
8	exp hydroxyurea/	17,378
9	(biosuppressin or hydrea or "hydroxy carbamid*" or "hydroxy urea" or hydroxycarbamid* or litalir or "nsc 32065" or oncocarbide or oxycarbamid* or oxyurea).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	673
10	8 or 9	17,493
11	(3 or 7) and 10	2,836
12	exp Drug Toxicity/	46,407
13	exp Neoplasms/	3,552,247
14	exp Ulcer/	84,952
15	exp Nausea/	102,675
16	exp Alopecia/	28,960
17	exp Safety/	138,286
18	macrocytosis.mp.	1,008
19	exp Gangrene/	9,997
20	exp Erythema/	53,632
21	myelosuppression.mp.	12,055
22	exp Hyperpigmentation/	22,762
23	(atrophy or scaling or rash or rashes).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	225,030
24	exp Exanthema/	40,375
25	exp Nail Diseases/ or melanonychia.mp.	15,621
26	exp Keratosis/	28,064

Number	Searches	Results
27	(keratosis or keratoses).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	15,081
28	poikilodermat*.mp.	138
29	exp Telangiectasis/	15,763
30	telangiectas*.mp.	20,518
31	exp Polycythemia/ or polycythemia.mp.	15,343
32	exp Dermatitis/ or dermatitis.mp.	140,319
33	lesion*.mp.	891,820
34	exp Lichen Planus/	8,726
35	(lichen adj2 planus).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	9,939
36	exp Diarrhea/ or diarrhea.mp.	164,704
37	constipation.mp. or exp Constipation/	48,722
38	exp Anorexia/ or anorexia.mp.	56,910
39	exp Vomiting/	93,915
40	vomit*.mp.	148,294
41	mucositis.mp. or exp Mucositis/	20,234
42	exp Stomatitis/ or stomatitis.mp.	40,713
43	exp Pancreatitis/ or pancreatitis.mp.	79,457
44	leukopenia.mp. or exp Leukopenia/	113,435
45	subarachnoid hemorrhage.mp. or exp Subarachnoid Hemorrhage/	32,201
46	exp Fever/	99,952
47	fever*.mp.	248,249
48	azotemia.mp. or exp Azotemia/	11,604
49	respiratory failure.mp. or exp Respiratory Insufficiency/	86,802
50	exp Myelodysplastic Syndromes/	24,786
51	Myelodysplastic Syndrome*.mp.	23,046
52	exp Chromosome Aberrations/	191,807
53	(abnormal* adj2 chromosome*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	11,612
54	reticulocytopenia.mp.	338
55	exp Hepatitis/	204,588
56	hepatotoxicity.mp.	18,399
57	systemic lupus erythematosus.mp. or Lupus Erythematosus, Systemic/	76,250
58	drowsiness.mp. or exp Sleep Stages/	38,115
59	exp Dizziness/	24,491
60	(dizziness or dizzy).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	40,333
61	exp Seizures/	80,509
62	seizure*.mp.	162,610
63	exp Headache/	97,287
64	(headache* or migraine*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	184,185

Number	Searches	Results
65	peripheral neuropathy.mp. or exp Peripheral Nervous System Diseases/	135,561
66	Blepharitis.mp. or exp Blepharitis/	2,508
67	(flaky or flakiness).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	280
68	exp Confusion/	19,786
69	(confusion or disorient*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	48,406
70	exp Hallucinations/	21,007
71	hallucinat*.mp.	26,605
72	exp Cystitis/ or cystitis.mp.	19,057
73	dysuria.mp. or exp Dysuria/	7,057
74	exp Kidney Diseases/	641,332
75	(kidney or renal).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	1,144,814
76	pulmonary fibrosis.mp. or exp Pulmonary Fibrosis/	36,959
77	exp Lung Diseases, Interstitial/	59,629
78	interstitial lung disease*.mp.	8,645
79	exp Dyspnea/ or dyspnea.mp.	72,682
80	exp Cough/ or cough.mp.	72,130
81	exp Fetal Diseases/	90,950
82	(fetal or maternal).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	557,083
83	(toxicity or harm or "adverse event*" or neoplasm* or malignanc* or cancer* or ulcer* or nausea or vomit* or alopecia or "hair loss" or (delay* and (development* or growth)) or teratogen* or safety or leukemia* or gangrene or hyperpigmentation or Erythema or Exanthema or nail or nails or carcinoma*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	4,770,421
84	or/12-83	8,651,154
85	10 and 84	12,052
86	exp Hydroxyurea/to [Toxicity]	545
87	85 or 86	12,182
88	exp Health Policy/	129,475
89	(health adj2 policy).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	115,896
90	exp Ethics/	194,560
91	ethic*.mp.	176,494
92	exp "Delivery of Health Care"/	1,423,835
93	(delivery adj2 "health care").mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	109,544
94	exp Social Support/	59,598
95	social support.mp.	69,380
96	exp Psychology/	103,885
97	psychology.mp.	261,540
98	bias.mp.	113,650
99	exp "Costs and Cost Analysis"/	288,705
100	(cost or costs).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	580,700
101	exp Health Behavior/	169,022

Number	Searches	Results
102	health behavior*.mp.	47,181
103	exp Communication/ or communication.mp.	607,854
104	barrier*.mp.	207,479
105	patient satisfaction.mp. or exp Patient Satisfaction/	100,829
106	comorbidity.mp. or exp Comorbidity/	126,237
107	exp Depression/ or depression.mp.	449,513
108	socioeconomic status.mp. or exp Social Class/	55,564
109	social class.mp.	37,828
110	social support.mp. or exp Social Support/	69,380
111	family support.mp.	3,716
112	exp Patient Education as Topic/	93,519
113	education.mp. or exp Education/	969,403
114	exp Insurance, Health/	163,289
115	insurance.mp.	131,371
116	exp "Quality of Health Care"/	4,968,725
117	(quality adj3 care).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	179,772
118	practice pattern.mp.	582
119	disease severity.mp.	245,657
120	burden.mp.	109,792
121	cognitive ability.mp.	3,681
122	respect.mp.	357,536
123	exp Religion/	56,517
124	(religion or religious).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	54,626
125	exp Spirituality/	19,416
126	spiritual*.mp.	13,819
127	internal-external control.mp. or exp Internal-External Control/	222,315
128	exp control/	208,113
129	or/88-128	8,374,314
130	3 and 129	9,336
131	11 or 87 or 130	21,680
132	limit 131 to (meta analysis or "review") [Limit not valid in EMBASE,CDSR; records were retained]	4,076
133	131 not 132	17,604
134	"review"/	2,509,536
135	meta analysis/	63,328
136	133 not 134 not 135	17,517
137	limit 136 to english language [Limit not valid in CCTR,CDSR; records were retained]	16,014
138	limit 137 to human [Limit not valid in CCTR,CDSR; records were retained]	14,422
139	limit 138 to yr = "2007 -Current"	3,210
140	limit 139 to humans [Limit not valid in CCTR,CDSR; records were retained]	3,210
141	remove duplicates from 140	2,514

Toxline

1. hydroxyurea or biosupressin or hydrea or "hydroxy carbamid*" or "hydroxy urea" or hydroxycarbamid* or litalir or "nsc 32065" or oncocarbide or oxycarbamid* or oxyuria
2. ("sickle cell" OR "hemoglobin s" OR drepanocytemia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease") and ((health and policy) OR ethic* OR (delivery and "health care") OR "social support" OR psychology OR bias OR cost OR costs OR "health behavior*" OR communication* OR barrier* OR "patient satisfaction" OR comorbidity OR depression OR "socioeconomic status" OR "social class" OR "social support" OR "family support" OR education OR insurance OR (quality and care) OR "practice pattern" OR "disease severity" OR burden OR "cognitive ability" OR respect OR religion OR religious OR spiritual* OR "internal-external control" OR control)
3. 1 or 2

Scopus

1. "sickle cell" OR "hemoglobin s" OR drepanocytemia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease"
2. thrombocythemia OR thrombocytosis
3. hydroxyurea OR biosupressin OR hydrea OR "hydroxy carbamid*" OR "hydroxy urea" OR hydroxycarbamid* OR litalir OR "nsc 32065" OR oncocarbide OR oxycarbamid* OR oxyuria
4. (1 or 2) and 3
5. toxicity OR harm OR "adverse event*" OR neoplasm* OR malignanc* OR cancer* OR ulcer* OR nausea OR vomit* OR alopecia OR "hair loss" OR (delay* AND (development* OR growth)) OR teratogen* OR safety OR leukemia* OR gangrene OR hyperpigmentation OR erythema OR exanthema OR nail OR nails OR carcinoma* OR macrocytosis OR myelosuppression OR atrophy OR scaling OR rash OR rashes OR melanonychia OR keratosis OR keratoses OR poikilodermat* OR telangiectas* OR polycythemia OR dermatitis OR lesion* OR (lichen W/2 planus) OR diarrhea OR constipation OR anorexia OR vomit* OR mucositis OR stomatitis OR pancreatitis OR leukopenia OR subarachnoid hemorrhage OR fever* OR azotemia OR respiratory failure OR "Myelodysplastic Syndrome*" OR (abnormal* W/2 chromosome*) OR reticulocytopenia OR hepatotoxicity OR hepatitis OR "systemic lupus erythematosus" OR drowsiness OR dizziness OR dizzy OR seizure* OR headache* OR migraine* OR "peripheral neuropathy" OR blepharitis OR flaky OR flakiness OR confusion OR disorient* OR hallucinat* OR cystitis OR dysuria OR kidney OR renal OR "pulmonary fibrosis" OR interstitial lung disease* OR dyspnea OR cough OR fetal OR maternal
6. 3 and 5
7. (health W/2 policy) OR ethic* OR (delivery W/2 "health care") OR "social support" OR psychology OR bias OR cost OR costs OR "health behavior*" OR communication* OR barrier* OR "patient satisfaction" OR comorbidity OR depression OR "socioeconomic status" OR "social class" OR "social support" OR "family support" OR education OR insurance OR (quality W/3 care) OR "practice pattern" OR "disease severity" OR burden OR "cognitive ability" OR respect OR religion OR religious OR spiritual* OR "internal-external control" OR control
8. 1 and 7
9. 4 or 6 or 8
10. Pubyear aft 2006
11. 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*)
12. (9 and 10) and not 11
13. review OR "meta-analy*" OR metaanaly*
14. 12 and not 13
15. Language(English)
16. 14 and 15

CINAHL

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S96	S3 and S94	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	52
S95	S3 and S94	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	490
S94	S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89 or S90 or S91 or S92 or S93	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	689251
S93	(MH "Spirituality")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	5987
S92	(MH "Religion and Religions+") or (MH "Religion and Psychology+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	16213
S91	(MH "Quality of Health Care+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	201066
S90	(MH "Insurance+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	49236
S89	(MH "Education+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	342622
S88	(MH "Patient Education+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	37847
S87	(MH "Social Class+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	3145
S86	(MH "Depression+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	30181
S85	(MH "Comorbidity")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	13671
S84	(MH "Patient Satisfaction")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	17,150

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S83	(MH "Communication+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	82,789
S82	(MH "Health Behavior+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	32,006
S81	(MH "Costs and Cost Analysis+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4,030
S80	(MH "Psychology+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	716
S79	(MH "Support, Psychosocial+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	2,850
S78	(MH "Health Care Delivery+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	15,139
S77	(MH "Ethics+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	5,749
S76	(MH "Health Policy+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4,505
S75	S3 and S73	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	54
S74	S3 and S73	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	54
S73	(health N2 policy) OR ethic* OR (delivery N2 "health care") OR "social support" OR psychology OR bias OR cost OR costs OR "health behavior*" OR communication* OR barrier* OR "patient satisfaction" OR comorbidity OR depression OR "socioeconomic status" OR "social class" OR "social support" OR "family support" OR education OR insurance OR (quality N3 care) OR "practice pattern" OR "disease severity" OR burden OR "cognitive ability" OR respect OR religion OR religious OR spiritual* OR "internal-external control" OR control	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	84,056
S72	S8 and S70	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	1

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S71	S8 and S70	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	8
S70	S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	66,664
S69	S8 and S67	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	0
S68	S8 and S67	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	14
S67	S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	18,128
S66	S8 and S64	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	1
S65	S8 and S64	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	10
S64	S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	12,532
S63	S8 and S61	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	2
S62	S8 and S61	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	65
S61	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	186,749
S60	S8 and S10	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4
S59	S8 and S10	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	116
S58	(s3 or s4 or s5) and s8	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S57	(s3 or s4 or s5) and s8	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	86
S56	(MH "Fetal Diseases+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S55	(MH "Cough")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S54	(MH "Dyspnea+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S53	(MH "Lung Diseases, Interstitial+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S52	(MH "Pulmonary Fibrosis")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S51	(MH "Kidney Diseases+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S50	(MH "Cystitis+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S49	(MH "Hallucinations")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S48	(MH "Confusion+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S47	(MH "Blepharitis")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S46	(MH "Peripheral Nervous System Diseases+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S45	(MH "Headache+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S44	(MH "Seizures+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S43	(MH "Dizziness")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S42	(MH "Lupus Erythematosus, Systemic+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S41	(MH "Hepatitis+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S40	(MH "Chromosome Abnormalities+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S39	(MH "Myelodysplastic Syndromes+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S38	(MH "Respiratory Failure+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S37	(MH "Uremia+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S36	(MH "Fever+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S35	(MH "Subarachnoid Hemorrhage")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S34	(MH "Leukopenia+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S33	(MH "Pancreatitis")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S32	(MH "Stomatitis+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S31	(MH "Mucositis")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S30	(MH "Vomiting+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S29	(MH "Anorexia")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S28	(MH "Constipation")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S27	(MH "Diarrhea")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S26	(MH "Lichen Planus") or (MH "Lichen Planus, Oral")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S25	(MH "Dermatitis+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S24	(MH "Polycythemia")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S23	(MH "Telangiectasis+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S22	(MH "Keratosis+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S21	(MH "Nail Diseases+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S20	(MH "Exanthema")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S19	(MH "Hyperpigmentation+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S18	(MH "Erythema+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S17	(MH "Gangrene")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S16	(MH "Safety+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S15	(MH "Alopecia+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S14	(MH "Nausea")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S13	(MH "Ulcer")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S12	(MH "Neoplasms+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S11	(MH "Drug Toxicity+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S10	toxicity OR harm OR "adverse event*" OR neoplasm* OR malignanc* OR cancer* OR ulcer* OR nausea OR vomit* OR alopecia OR "hair loss" OR (delay* AND (development* OR growth)) OR teratogen* OR safety OR leukemia* OR gangrene OR hyperpigmentation OR erythema OR exanthema OR nail OR nails OR carcinoma* OR macrocytosis OR myelosuppression OR atrophy OR scaling OR rash OR rashes OR melanonychia OR keratosis OR keratoses OR poikilodermat* OR telangiectas* OR polycythemia OR dermatitis OR lesion* OR (lichen N2 planus) OR diarrhea OR constipation OR anorexia OR vomit* OR mucositis OR stomatitis OR pancreatitis OR leukopenia OR subarachnoid hemorrhage OR fever* OR azotemia OR respiratory failure OR "Myelodysplastic Syndrome*" OR (abnormal* N2 chromosome*) OR reticulocytopenia OR hepatotoxicity OR hepatitis OR "systemic lupus erythematosus" OR drowsiness OR dizziness OR dizzy OR seizure* OR headache* OR migraine* OR "peripheral neuropathy" OR blepharitis OR flaky OR flakiness OR confusion OR disorient* OR hallucinat* OR cystitis OR dysuria OR kidney OR renal OR "pulmonary fibrosis" OR interstitial lung disease* OR dyspnea OR cough OR fetal OR maternal	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S9	(s3 or s4 or s5) and s8	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S8	S6 or S7	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S7	hydroxyurea OR biosupressin OR hydrea OR "hydroxy carbamid*" OR "hydroxy urea" OR hydroxycarbamid* OR litalir OR "nsc 32065" OR oncocarbide OR oxycarbamid* OR oxyuria	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

Search ID Number	Search Terms	Search Options	Last Run Via	Results
S6	(MH "Hydroxyurea")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S5	(MH "Thrombocytosis")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S4	thrombocythemia OR thrombocytosis	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S3	S1 or S2	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S2	"sickle cell" OR "hemoglobin s" OR drepanocytemia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease"	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S1	(MH "Anemia, Sickle Cell+")	Search modes: Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

Appendix D. Excluded Studies

List of Excluded Studies

Study Label	Title	Reason For Exclusion
Adewoye, 2007	Effectiveness of a dedicated day hospital for management of acute sickle cell pain	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Akar, 2008	Ten-year review of hospital admissions among children with sickle cell disease in Kuwait	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Alvarez, 2008	Short-term follow-up of patients with sickle cell disease and albuminuria	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Andaloussi, 2007	New complex chromosomal translocation in chronic myeloid leukaemia: T(9;18;22)(q34;p11;q11)	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Asnani, 2008	Quality of life in patients with sickle cell disease in Jamaica: rural-urban differences	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Aygun, 2009	Chronic transfusion practice for children with sickle cell anaemia and stroke	Other: no outcomes
Bachmeyer, 2008	Hydroxyurea for sickle cell anemia	Excluded because it is nonoriginal (i.e., review)
Barakat, 2007	A prospective study of the role of coping and family functioning in health outcomes for adolescents with sickle cell disease	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Barosi, 2007	A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group.[Erratum appears in Leukemia. 2007 May;21(5):1135]	Excluded because it is nonoriginal (i.e., review)
Beitler, 2007	Phase II clinical trial of parenteral hydroxyurea and hyperfractionated, accelerated external beam radiation therapy in patients with advanced squamous cell carcinoma of the head and neck: Toxicity and efficacy with continuous ribonucleoside reductase inhibition	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Boehm, 2009	Evaluation of in vivo antineoplastic effects of rapamycin in patients with chemotherapy-refractory AML	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Carobbio, 2007	Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: Interaction with treatment, standard risk factors, and Jak2 mutation status	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Chakraborty, 2008	Joint pain in AML: Successful pain control with radiotherapy	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Chamberlain, 2008	Interferon-alpha for recurrent world health organization grade 1 intracranial meningiomas	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Chi, 2009	Hit or miss?	Excluded because it is nonoriginal (i.e., review)
Christoforidou, 2008	Hydroxyurea and anagrelide combination therapy in patients with chronic myeloproliferative diseases resistant or intolerant to monotherapy	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Citro, 2007	The role of catastrophizing in sickle cell disease: The PiSCES project	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)

Study Label	Title	Reason For Exclusion
Costa, 2007	Gene expression profiles of erythroid precursors characterize several mechanisms of the action of hydroxycarbamide in sickle cell anaemia	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Cotton, 2009	Religious/Spiritual coping in adolescents with sickle cell disease: a pilot study	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Dahabreh, 2007	Management of hypereosinophilic syndrome: a prospective study in the era of molecular genetics	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Dahdaleh, 2009	A “neurosurgical crisis” of sickle cell disease: Case report	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
DeBaun, 2010	Finally, a consensus statement on sickle cell disease manifestations: a critical step in improving the medical care and research agenda for individuals with sickle cell disease	Excluded because it is nonoriginal (i.e., review)
Dejmek, 2009	DNA-dependent protein kinase (DNA-PK)-dependent cisplatin-induced loss of nucleolar facilitator of chromatin transcription (FACT) and regulation of cisplatin sensitivity by DNA-PK and FACT	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Desjardins, 2007	Phase II study of imatinib mesylate and hydroxyurea for recurrent grade III malignant gliomas	Other: cannot separate toxicity from HU from other drugs
Drotar, 2010	Treatment adherence in patients with sickle cell anemia	Excluded because it is nonoriginal (i.e., review)
Dubowy, 2008	Sequential oral hydroxyurea and intravenous cytosine arabinoside in refractory childhood acute leukemia: a pediatric oncology group phase 1 study	Other: Toxicity reported was due to ara-c—not HU
Erb, 2008	Primary Amenorrhea in a Young Adult with Sickle Cell Disease: A Case Report and Brief Literature Review on Adolescent Reproductive Health and Sickle Cell Disease	Excluded because it is nonoriginal (i.e., review)
Erba, 2009	Prognostic factors in elderly patients with myelodysplastic syndrome or acute myeloid leukemia and the implications for treatment	Excluded because it is nonoriginal (i.e., review)
Farra, 2010	Vascular at-risk genotypes and disease severity in Lebanese sickle cell disease patients	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Fitzhugh, 2010	Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Friedman, 2008	Case 1: An unusual cause of headaches and priapism in a teenager	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Gaudreau, 2009	Treatment with hydroxyurea in a patient compound heterozygote for a high oxygen affinity hemoglobin and beta-thalassemia minor	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Ghatpande, 2008	Pharmaco-proteomic study of hydroxyurea-induced modifications in the sickle red blood cell membrane proteome	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Ghatpande, 2010	In vivo pharmaco-proteomic analysis of hydroxyurea induced changes in the sickle red blood cell membrane proteome	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Girodon, 2008	Frequent reduction or absence of detection of the JAK2-mutated clone in JAK2V617F-positive patients within the first years of hydroxyurea therapy	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Gosavi, 2009	Atrial septal defect closure on cardiopulmonary bypass in a sickle cell anemia: role of hydroxyurea and partial exchange transfusion	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)

Study Label	Title	Reason For Exclusion
Goto, 2009	Chronic neutrophilic leukemia with congenital Robertsonian translocation successfully treated with allogeneic bone marrow transplantation in a young man	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Grace, 2010	Resolution of cerebral artery stenosis in a child with sickle cell anemia treated with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Hall, 2008	Treatment of recalcitrant disseminated granuloma annulare with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Hankins, 2007	Therapy preference and decision-making among patients with severe sickle cell anemia and their families	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Hankins, 2008	Phase I study of magnesium pidolate in combination with hydroxycarbamide for children with sickle cell anaemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Harousseau, 2009	A randomized phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older	Other: no outcomes
Hernigou, 2009	Septic arthritis in adults with sickle cell disease often is associated with osteomyelitis or osteonecrosis	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Hildreth, 2008	Sickle cell vasculopathy	Excluded because it is nonoriginal (i.e., review)
Howard, 2007	Treatment for children with severe aplastic anemia and sickle cell disease in low income countries in Latin America: A report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO): Part III	Excluded because it is nonoriginal (i.e., review)
Irfan, 2009	Clinico-pathological features and outcomes in chronic phase chronic myeloid leukemia patients treated with hydroxyurea	Other: no outcomes
Italia, 2010	Exposure to hydroxyurea during pregnancy in sickle-beta Thalassemia: A report of 2 cases	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Janot, 2008	Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Karimi, 2009	Echocardiographic finding in beta-thalassemia intermedia and major: Absence of pulmonary hypertension following hydroxyurea treatment in beta-thalassemia intermedia	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Karimi, 2010	Effect of combination therapy of hydroxyurea with l-carnitine and magnesium chloride on hematologic parameters and cardiac function of patients with beta-thalassemia intermedia	Other: no outcomes, all 4 groups received HU
Kurabayashi, 2007	Delayed manifestation and slow progression of cerebral infarction caused by polycythemia rubra vera	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Lanaro, 2009	Altered levels of cytokines and inflammatory mediators in plasma and leukocytes of sickle cell anemia patients and effects of hydroxyurea therapy	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Lanzkron, unknown year	Examining the effectiveness of hydroxyurea in people with sickle cell disease	Unobtainable full text
Levenson, 2008	Depression and anxiety in adults with sickle cell disease: the PiSCES project	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Li, 2008	The negative prognostic impact of derivative 9 deletions in patients who received hydroxyurea treatment for chronic myelogenous leukemia in the chronic phase	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects

Study Label	Title	Reason For Exclusion
Liao, 2007	Unnatural amino acid-substituted (hydroxyethyl)urea peptidomimetics inhibit gamma-secretase and promote the neuronal differentiation of neuroblastoma cells	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Linardi, 2008	Diagnosis and treatment of polycythemia vera: Brazilian experience from a single institution	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Lukusa, 2008	Use of hydroxyurea from childhood to adult age in sickle cell disease: semen analysis	Excluded because it is nonoriginal (i.e., review)
Ma, 2007	Fetal hemoglobin in sickle cell anemia: Genetic determinants of response to hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Machtay, 2008	Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: An RTOG analysis	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Masera, 2007	Periodic erythroexchange is an effective strategy for high risk pediatric patients with sickle-cell disease	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Mayor, 2008	UK enquiry shows lack of knowledge about complications in patients with sickle cell disease	Excluded because it is nonoriginal (i.e., review)
Meo, 2008	Effect of hydroxyurea on extramedullary haematopoiesis in thalassaemia intermedia: Case reports and literature review	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Miller, 2010	Urine concentrating ability in infants with sickle cell disease: baseline data from the phase III trial of hydroxyurea (BABY HUG)	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Mizutani, 2010	Emergence of chronic myelogenous leukemia during treatment for essential thrombocythemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
NA, 2008	Sickle cell protocol helps patients' self-management	Excluded because it is nonoriginal (i.e., review)
NA, 2008	Summaries for patients: Pain and health care visits in patients with sickle cell disease	Excluded because it is nonoriginal (i.e., review)
Naina, 2008	Hydroxyurea for sickle cell anemia	Excluded because it is nonoriginal (i.e., review)
Nand, 2008	Hydroxyurea, azacitidine and gemtuzumab ozogamicin therapy in patients with previously untreated non-M3 acute myeloid leukemia and high-risk myelodysplastic syndromes in the elderly: results from a pilot trial	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Nozaki, 2010	Hydroxyurea as an inhibitor of hepatitis C virus RNA replication	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
O'Brien 2009	Decision analysis of treatment strategies in children with severe sickle cell disease	Excluded because it is nonoriginal (i.e., review)
O'Keefe, 2009	A patient with a previous diagnosis of hemoglobin S/C disease with an unusually severe disease course	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Olnes, 2009	Improvement in hemolysis and pulmonary arterial systolic pressure in adult patients with sickle cell disease during treatment with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Patra, 2010	Chronic idiopathic myelofibrosis with myeloid metaplasia presenting as refractory ascites	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Platt, 2008	Hydroxyurea for the treatment of sickle cell anemia	Excluded because it is nonoriginal (i.e., review)
Rahim, 2008	Diagnosis and treatment of cord compression secondary to extramedullary hematopoiesis in patients with beta-thalassemia intermedia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)

Study Label	Title	Reason For Exclusion
Reardon, 2009	Multicentre phase II studies evaluating imatinib plus hydroxyurea in patients with progressive glioblastoma	Other: adverse effects were not clearly related to HU
Reardon, 2009	Phase I pharmacokinetic study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor vatalanib (PTK787) plus imatinib and hydroxyurea for malignant glioma	Other: both groups received HU and adverse effects are not attributable to HU
Rodzaj, 2009	A diagnostically difficult case of chronic myeloid neoplasm with eosinophilia and abnormalities of PDGFRA effectively treated with imatinib in accelerated phase	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Rose, 2007	Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: A Gynecologic Oncology Group study	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Schwalenstocker, 2009	Appropriate use of quality measures: Response to "Risk factors for hospital readmission within 30 days: A new quality measure for children with sickle cell disease"	Excluded because it is nonoriginal (i.e., review)
Schwarz, 2009	A 62-year-old woman with bilateral pleural effusions and pulmonary infiltrates caused by extramedullary hematopoiesis	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Scott, 2010	Hydroxyurea and sickle cell disease: It's been a long, long time coming	Excluded because it is nonoriginal (i.e., review)
Sedrak, 2009	A prospective appraisal of pulmonary hypertension in children with sickle cell disease	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Seiwert, 2007	A phase I trial of docetaxel based induction and concomitant chemotherapy in patients with locally advanced head and neck cancer	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Seiwert, 2008	Phase I study of bevacizumab added to fluorouracil- and hydroxyurea-based concomitant chemoradiotherapy for poor-prognosis head and neck cancer	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Seth, 2009	Successful use of terbutaline in persistent priapism in a 12-year-old boy with chronic myeloid leukemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Setty, 2009	Prolonged chronic phase of greater than 10 years of chronic myelogenous leukemia in a patient with congenital human immunodeficiency virus infection	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Shah, 2007	Myelosuppression in patients benefiting from imatinib with hydroxyurea for recurrent malignant gliomas	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Singer, 2008	Hydroxycarbamide-induced changes in E/beta thalassemia red blood cells	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Singh, 2008	Resolution of chronic hypoxemia in pediatric sickle cell patients after treatment with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Smith, 2008	Daily assessment of pain in adults with sickle cell disease	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Smith, 2009	Climatic and geographic temporal patterns of pain in the Multicenter Study of Hydroxyurea	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Snyder, 2009	Therapeutic doses of hydroxyurea cause telomere dysfunction and reduce TRF2 binding to telomeres	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects

Study Label	Title	Reason For Exclusion
Sodani, 2010	Purified T-depleted, CD34+ peripheral blood and bone marrow cell transplantation from haploidentical mother to child with thalassemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Solomon, 2008	Treatment and prevention of pain due to vaso-occlusive crises in adults with sickle cell disease: an educational void	Excluded because it is nonoriginal (i.e., review)
Soutou, 2009	Myeloproliferative disorder therapy: Assessment and management of adverse events: A dermatologist's perspective	Excluded because it is nonoriginal (i.e., review)
Spencer, 2008	Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck	Other: cannot attribute toxicity to HU
Stagno, 2009	Uncommon long-term survival in a patient with chronic myeloid leukemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Sugino, 2009	Miliary tuberculosis associated with chronic neutrophilic leukemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Suliman, 2009	Hydroxyurea or chronic exchange transfusions in patients with sickle cell disease: role of transcranial Doppler ultrasound in stroke prophylaxis	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Takahashi, 2007	Epstein-Barr virus-associated post-transplant lymphoproliferative disorder presenting with skin involvement after CD34-selected autologous peripheral blood stem cell transplantation	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Thompson, 2010	The pediatric hydroxyurea phase III clinical trial (BABY HUG): Challenges of study design	Excluded because it is nonoriginal (i.e., review)
Tomson, 2007	Hydroxycarbamide: A treatment for lichen sclerosus?	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Trelinski, 2009	The influence of low-dose aspirin and hydroxyurea on platelet-leukocyte interactions in patients with essential thrombocythemia	Other: cannot separate HU effect from ASA
Tsikrikas, 2008	Acute splenic sequestration crisis (ASSC) in an adult patient with beta-thalassemia sickle cell disease: A life-threatening complication	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Tufan, 2007	Spinal epidural extramedullary hematopoiesis during the complicated course of polycythemia vera	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Tutaeva, 2007	Application of PRV-1 mRNA expression level and JAK2V617F mutation for the differentiating between polycythemia vera and secondary erythrocytosis and assessment of treatment by interferon or hydroxyurea	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Tybura, 2009	The influence of low-dose aspirin and hydroxyurea on platelet-leukocyte interactions in patients with essential thrombocythemia	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
van den Tweel, 2008	Quality of life of female caregivers of children with sickle cell disease: A survey	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
van Tuijn, 2010	Acute chest syndrome in sickle cell disease due to the new influenza A (H1N1) virus infection	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Varma, 2008	Thrombotic complications of polycythemia vera	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Voskaridou, 2007	Pulmonary hypertension in patients with sickle cell/beta thalassemia: Incidence and correlation with serum N-terminal pro-brain natriuretic peptide concentrations	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)

Study Label	Title	Reason For Exclusion
Wang, 2010	Summary of 615 patients of chronic myeloid leukemia in Shanghai from 2001 to 2006	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Ware, 2010	renal function in infants with sickle cell anemia: Baseline data from the BABY HUG Trial	Excluded because it does not describe patients who used HU or describes non-SCD patients who used HU but no reported side effects
Yates, 2009	Simultaneous acute splenic sequestration and transient aplastic crisis in children with sickle cell disease	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Zhang, 2007	Modified conditioning regimen busulfan-cyclophosphamide followed by allogeneic stem cell transplantation in patients with multiple myeloma	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)

Appendix E: Acronyms and Abbreviations

Numbered		AUC	area under the curve
3TC	lamivudine	avL	automated volt left, EKG lead
32P	radioactive phosphorous	B	
51Cr-EDTA	chromium-51 labeled ethylenediaminetetraacetic acid; see Cr-EDTA	β	beta, second letter of the Greek alphabet
6MWD	6-minute walk distance	β -thal	See β -thalassemia
A		β -thalassemia	beta thalassemia
α	alpha, first letter of the Greek alphabet	β^0 -thal	beta zero-thalassemia
α -thal	See α -thalassemia	BABY HUG	Pediatric Hydroxyurea Phase III Clinical Trial
α -thalassemia	alpha-thalassemia	B cell	type of lymphocyte or immune mediator cell
AA	African American	beta	See β
AB	blood group AB	b.i.d.	<i>bis in die</i> , twice a day
Ab	antibody	BM	Black male; bone marrow; bowel movement [see context]
ABC	abacavir	BMI	Body Mass Index
ABG	arterial blood gas	BMT	bone marrow transplant
A/C	albumin to creatinine ratio	BP	blood pressure
ACE	angiotensin converting enzyme	B-TI	beta thalassemia intermedia
ACEI	angiotensin-converting enzyme inhibitor	B-TM	beta thalassemia major
ACS	acute chest syndrome	C	
AE	adverse event	C	Celsius
Æ	per each	Ca	calcium
AER	albumin excretion rate	CAD	coronary artery disease
AHR	airway hyperresponsiveness	CAR	Central African Republic haplotype
AI	augmentation index	CBD	cortical bone density
ALT	alanine aminotransferase	CBFv	cerebral blood flow velocity
ANC	absolute neutrophil count	CBT	cognitive behavioral therapy
ara-c	arabinosylcytosine (cytarabine)	CCNU	1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine)
ARV	antiretroviral	CCT	clinically controlled trial
ASA	acetylsalicylic acid (aspirin)	CH	chronic hepatomegaly
ASPEN	Association of Sickle Cell Disease, Priapism, Exchange Transfusion and Neurological Events	CI	confidence interval
ASSC	acute splenic sequestration crisis	cm	centimeter
AST	aspartate aminotransferase	cm ²	square centimeter
atm	atmospheric	cm ³	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; <i>see</i> 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
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 ²
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 α^+ -thal	hemoglobin S alpha plus-thalassemia
HbS β -thal	hemoglobin S beta-thalassemia
HbS β^0 -thal	sickle hemoglobin beta zero-thalassemia
HbS β^+ -thal	sickle hemoglobin beta positive-thalassemia
HbSC	hemoglobin SC disease; sickle hemoglobin C disease
HbSD	hemoglobin SD disease
HbSD ^{LA}	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
M	
μ	Greek letter mu; micro-
m	milli-; moles per liter [see context]
m	meter
m ²	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 ³	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
N	
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 NOx	nitric oxide
NR	not reported
NR/NC	not reported/not clear
NS	not significant; normal saline [see context]
ns	nanosecond
O	
Obs	observational
OCP	oral contraceptive pill
Od or o.d.	<i>omni die</i> , every day
Op	Operation; opioid [see context]
OR	odds ratio
P	
<i>p</i>	probability
P, Obs	prospective observational
PAH	pulmonary arterial hypertension
PaO ₂	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 ₂ or PO ₂	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	

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-α	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
µg	microgram
µl	microliter
ULN	upper limit of normal
µm	micrometer
µmol	micromole
UNTH Enugu	University of Nigeria Teaching Hospital at Enugu
US	ultrasound; ultrasonography
UTI	urinary tract infection

V

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

VAS	visual analogue scale
VC	Vital capacity
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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