

Hydroxyurea therapy for sickle cell anemia

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References

Works for all Ages

Charache et al., Blood 1992; 79:2555
Kinney et al., Blood 1999; 94:1550

	Adults	Children
MTD (mg/kg/day)	21.3	25.6
Δ Hb (gm/dL)	+ 1.2	+ 1.2
Δ MCV (fL)	+ 23	+ 14
Δ Hb F (%)	+ 11.2	+ 9.6
Δ Retics (10 ⁹ /L)	- 158	- 146
Δ WBC (10 ⁹ /L)	- 5.0	- 4.2
Δ ANC (10 ⁹ /L)	- 2.8	- 2.2
Δ Bilirubin (mg/dL)	- 2.0	- 1.0

Both Infants and Adults Improve

NEJM 1995; 332:1317-1322

Lancet 2011;377:1663-1672

	BABY HUG			MSH		
	HU	PL	p-value	HU	PL	p-value
Patients	96	97		152	147	
Pain	177	372	0.002	2.5/y	4.5/y	<0.001
Acute Chest	8	27	0.017	25	51	<0.001
Dactylitis	24	123	<0.001	—	—	—
Hospitalization	232	321	0.050	1.0/y	2.4/y	<0.05
Transfusion	35	60	0.033	48	73	0.001

Benefits also observed for asymptomatic infants in BABY HUG

Lower Mortality

Steinberg et al., JAMA 2003

9 years of follow-up, 40% reduction in mortality

Voskaridou et al., Blood 2009

17-year single center trial, 131 patients (34 HbSS)

Significant reduction in mortality, HbSS > S/β-thalassemia

Steinberg et al., Am J Hematol 2010

17.5 years of follow-up, significant decrease in mortality

Lobo et al, Br J Haematol 2013

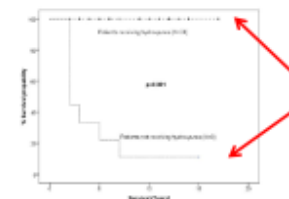
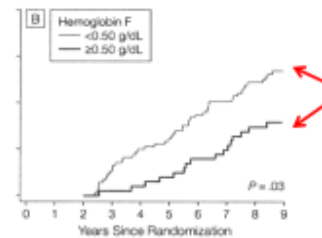
Fewer deaths among pediatric patients on treatment

Le et al, Pediatr Blood Cancer 2015

Less mortality compared to transplant or observation

Karacaoglu et al, Ann Hematol 2016

735 Turkish patients, significant decrease in mortality



Hydroxyurea: Reproductive Effects

Infertility

Men and women – theoretical versus actual

WHO Reference (fertile men): $73 \times 10^6/\text{mL}$ [15-213]

Teratogenicity

More than 100 healthy offspring reported

Safety in pregnancy/lactation

Toxicity is defined in animals

Safety is determined in humans

HELPS study is completed

HELPFUL will soon be open



Resources

Hydroxyurea is a Well-Known Drug

Hydroxylated analog of urea

Originally synthesized in 1869

First studied in animals in 1928

Used clinically in humans

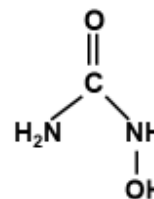
Anti-leukemia activity in 1960's

Treatment for cancers and later HIV

Inhibition of DNA synthesis (RR inhibitor)

Cytotoxic to cell growth

Boosts HbF levels in sickle cell anemia



Hydroxyurea is FDA- and EMA-approved for the treatment of SCA

NHLBI Sickle Cell Guidelines



[http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/\[nhlbi.nih.gov\]](http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/[nhlbi.nih.gov]).

JAMA 2014;312(10):1033-1048



Recommendations (Adults)

- **Educate** all patients with SCA and family members
- **Treat** with hydroxyurea (strong recommendations)
 - 3 or more sickle-related pain crises
 - Sickle-associated pain that interferes with daily living
 - History of severe acute chest syndrome
 - Severe symptomatic chronic anemia
 - Use an established prescribing and monitoring protocol
- **Consult** a specialist (non-response, non-HbSS)

Recommendations (Children)

- Educate all patients with SCA and family members
- In infants 9 months of age and older, children, and adolescents with SCA, **offer** treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, anemia)
 - Strong recommendation, high-quality evidence, ages 9-42 months
 - Moderate recommendation, moderate-quality evidence, ages >42 months
- Use an established prescribing and monitoring protocol

Consensus Treatment Protocol

- Labs before initiating hydroxyurea
- Initiating and Monitoring Therapy
 - Daily dosing
 - Monitoring labs and frequency
 - Targets and treatment goals
- Hold/change the dose for cytopenias
- Escalate the dose if warranted based on clinical and laboratory findings
- Continue hydroxyurea during hospitalization or illness

Hydroxyurea Formulations

Capsules: 200mg, 300mg
400mg, 500mg

Generic capsules: 500mg

Liquid formulation is used for children
who cannot swallow standard
(large) hydroxyurea capsules



Siklos® 100 mg
film-coated tablets
hydroxycarbamide

Siklos® 1000 mg
3-scored
film-coated tablets
hydroxycarbamide