HU: Myths and Facts

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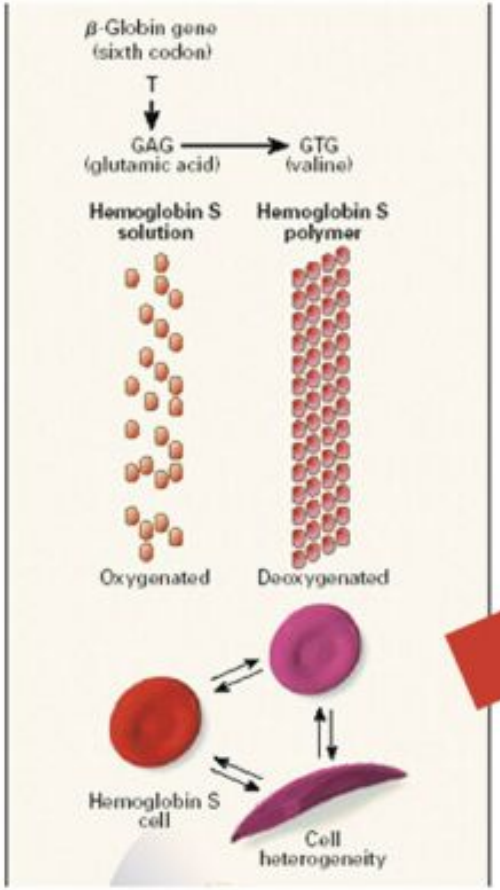
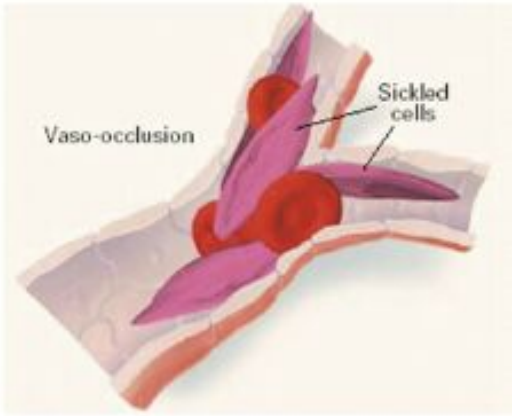
SACGO Hamilton, Ontario
March 5, 2016

Declaration of Disclosure

- I have no actual or potential conflict of interest in relation to this program.
- I also assume responsibility for ensuring the scientific validity, objectivity, and completeness of the content of my presentation.
- Melanie Kirby

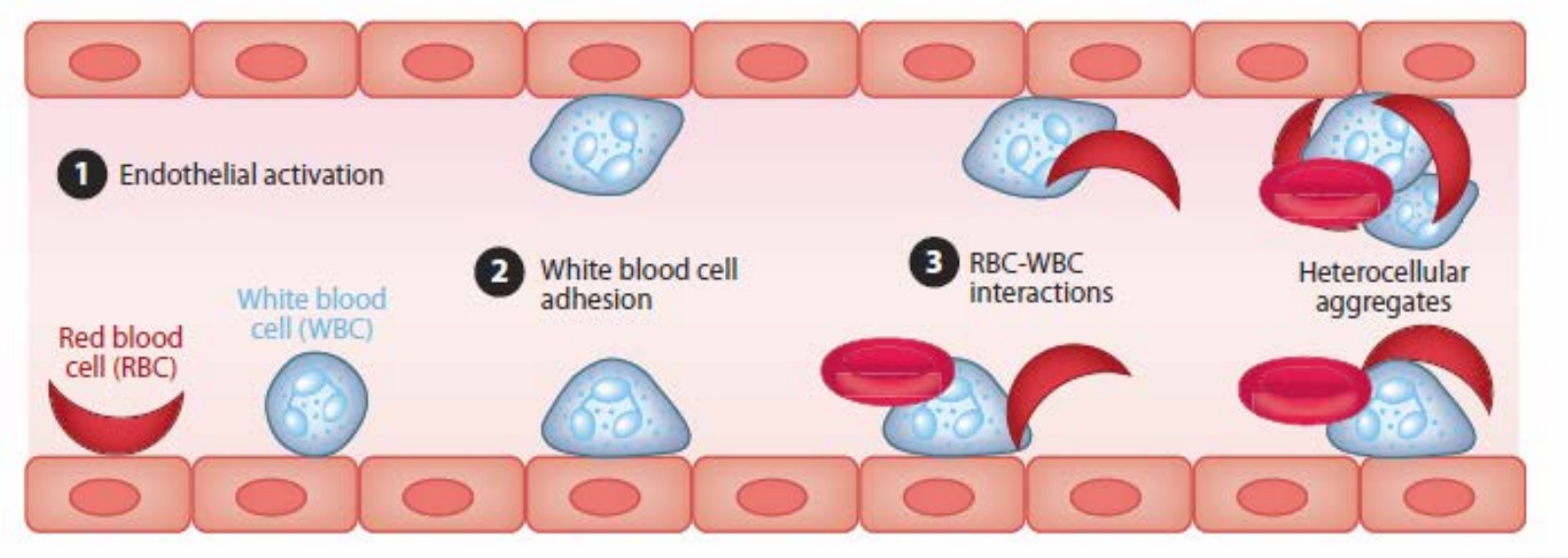
HYDROXYUREA, but first Pathophysiology of SCD





Martin H. Steinberg, M.D.
N Engl J Med 1999; 340:1021-1030April 1, 1999

Multistep model for vascular occlusion in Sickle Cell Disease.



Annu. Rev. Med. 2013. 64:451–66

Hydroxyurea – mechanism of action

- Patients with sickle cell anemia with higher Hb F levels and have less clinically severe disease.
- 1982 - 5 azacytidine recognized to stimulate fetal

hemoglobin synthesis in animal model.

- Several other studies showed that cytotoxic agents

could stimulate HB F production.

Hydroxyurea suitable

- oral
- safe

THE EFFECT OF HYDROXYUREA ON FREQUENCY OF PAINFUL CRISES IN SICKLE CELL ANEMIA

Method

Double-blind, randomized trial of hydroxyurea.
Efficacy of hydroxyurea in reducing the frequency of VOC events in adults with 3 or more VOC events in a 12 month period.
Trial stopped after 21 months.
Patients 299 >18 years with SCA randomized

Results

	hydroxyurea	placebo
Crises per year	2.5	4.5
ACS	25	51
Transfusions	48	73

Conclusions

Hydroxyurea can ameliorate the clinical course of some adult patients with SCA.
Benefits do not manifest for several months and its use must be carefully monitored

Charache S, Terrin ML, Moore RD et al: Effect of hydroxyurea on the frequency of painful crisesn sickle cell anemia. NEJM vol 332, 1995 1317-1322

Hydroxycarbamide in very young children with sickle-cell anemia: a multicentre, randomised, controlled trial (BABY HUG).

Hydroxycarbamide

- ✓ significantly decreased pain
- ✓ some evidence for decreased acute chest syndrome, hospitalisation rates, and transfusion.
- ✓ increased haemoglobin and fetal haemoglobin, and decreased white blood-cell count.
- ✓ Toxicity was limited to mild-to-moderate neutropenia.
- ✓ Did not influence GFR in young children with SCA associated with better urine concentrating ability and less renal enlargement, suggesting some benefit to renal function.

Effect of hydroxyurea treatment on renal function parameters: results from the multi-center placebo-controlled BABY HUG clinical trial for infants with sickle cell anemia Pediatr Blood Cancer. 2012 Oct;59(4):668-74. doi: 10.1002/pbc.24100. Epub 2012 Jan 31

Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG).
Lancet. 2011 May 14;377(9778):1663-72

The risks and benefits of long term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up

Purpose: To search for adverse outcomes and estimate mortality

Patients: Further follow-up of patients in the MSH study. Most patients from the original cohort chose to remain on HU or if they were randomized to placebo, chose to go on HU.

Results

43.1% of the 299 patients had died.

- **Higher Hb F levels were associated with reduced mortality**
- **Mortality was reduced in individuals with long term exposure to hydroxyurea.**
- **Stroke, organ dysfunction, infection, malignancy were similar in patients exposed and**
- **unexposed to HU.**
- **No teratogenic effects in offspring**

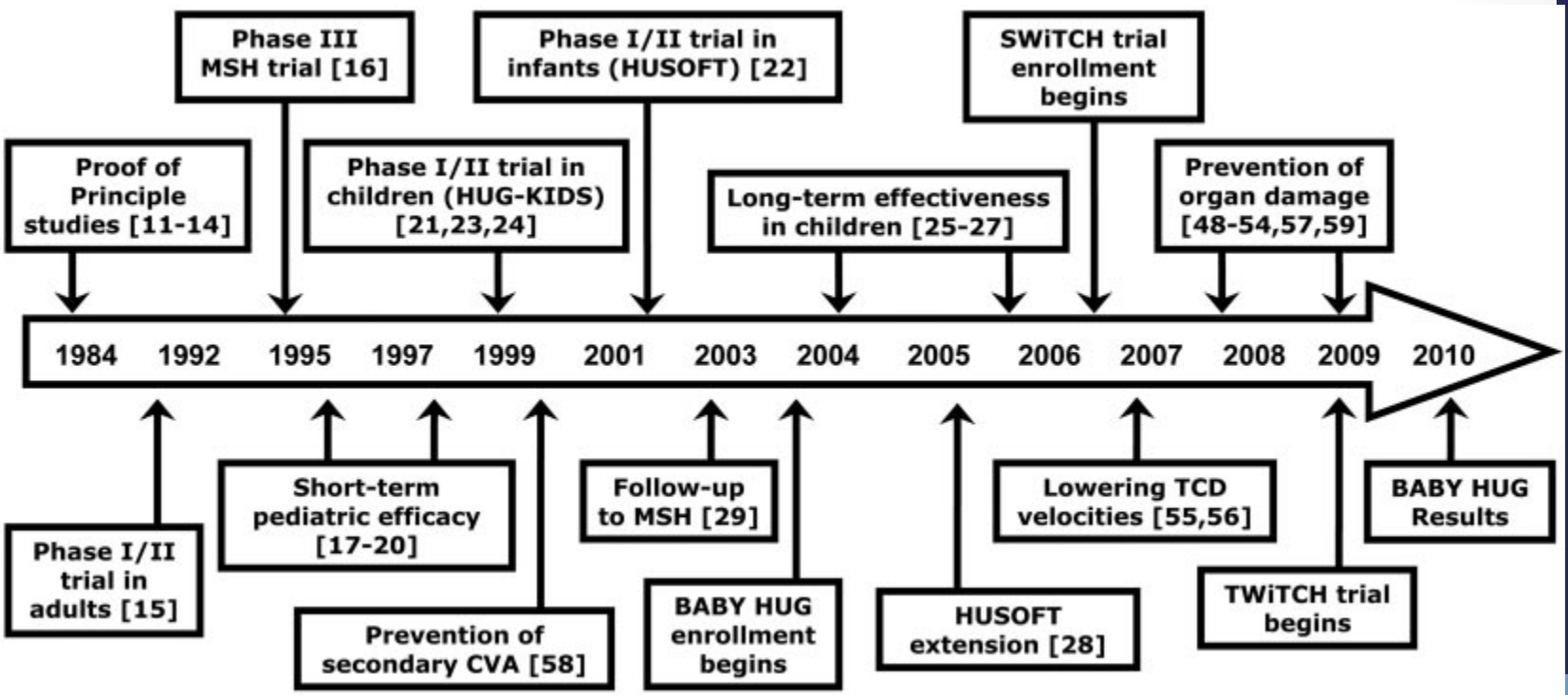
Conclusion

- **Long term use of hydroxyurea is safe and might decrease mortality.**

SteinbergMH, McCarthy W.F, Castro o et al: Am J. Hematol 85: 403-408,2010

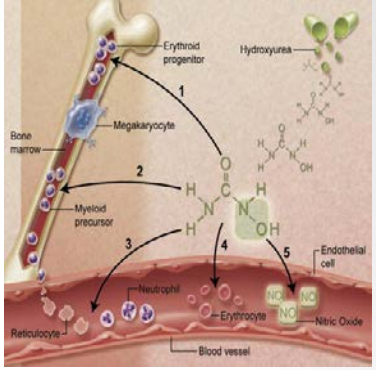
The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up.

Timeline of studies of hydroxyurea in sickle cell disease



Ware, RE, How I use hydroxyurea to treat sickle cell disease. Blood 1 July 2010.Vol 115, number 26

Benefits of Hydroxyurea for SCD



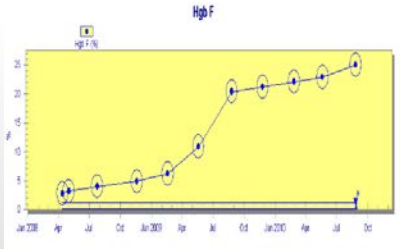
1. Increases fetal hemoglobin

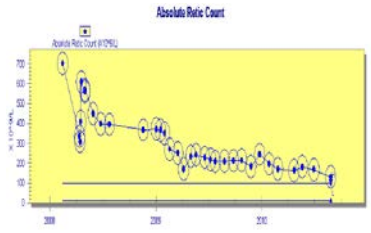
2.Lower neutrophil and reticulocyte counts by affecting the bone marrow

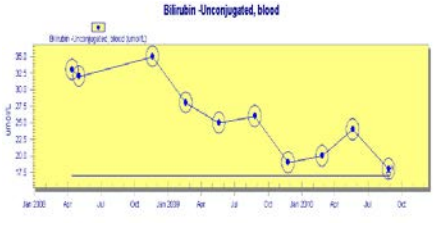
3 .Reduced RBC breakdown through improved RBC hydration, macrocytosis and reduced sickling of cells

4.Decreased stickiness of RBCs and WBCs

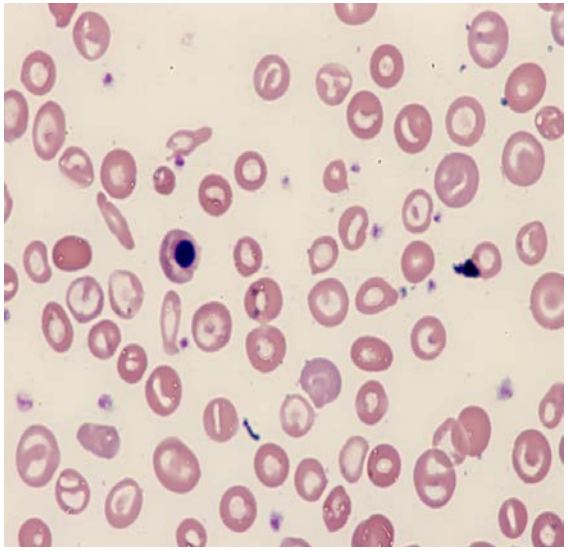
5. Nitric oxide release with potential local vasodilatation and improved vascular response.

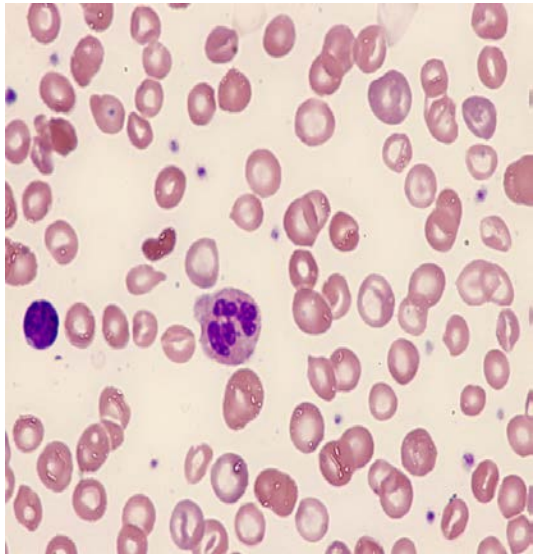


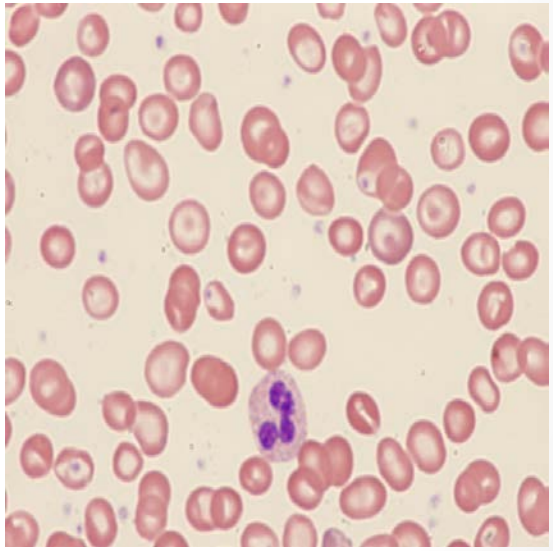




Red Cell Response to Hydroxyurea







What is happening when HU "is not working"

Common explanation

- **Doses are being missed**
- **Children have outgrown their dose as they gain weight**

Why?

- **HU works on red cells as they are being formed.**
- **The effect of the HU will be lost if there is none available to affect new red cells as they are made.**
- **If HU is taken some of the time there is less effect. The response of fetal Hb is less, the cells are more fragile**

How are patients doing when taking HU: my observation

- Energy is increased and life becomes ”normal”
- Some patients gain weight
- Many patients stop coming into hospital for VOC painful episodes
- At camp, the kids swim, hike, and are fully participating in activities of their choice
- Children are able to try out for teams and make the teams
- Parents report great satisfaction with response and encourage others to do the same.
- Adult patients can live a normal life with less or no admissions to hospital- increased energy.

What do we need for optimal adherence?

Clinical setting to optimize treatment adherence

Recognition that chronic diseases pose special challenges which require targeted resources

Rapid access to free care

Staff with expert knowledge and experience

Continuity of care (especially staff)

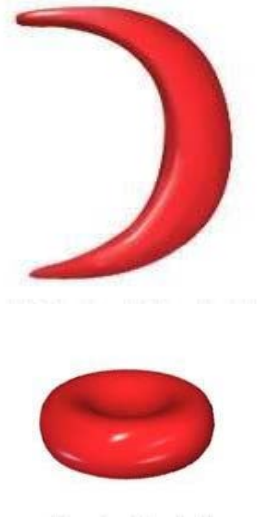
Systems organized to allow best care with minimum disruption to ordinary life

Identity (a "unit") for patients allowing a focus for care but not isolated from hospital

Multidisciplinary team with integrated clinics and investigations

Resources - people with time

Evangeli M, et al. Hemoglobin. 2010;34:305-21.
Porter JB, et al. Int J Hematol. 2011;94:453-60.



Thank you for your attention