

HYDROXYUREA in Sickle Cell Disease

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Learning Objectives

- 1.To explain the possible mechanisms of action of hydroxyurea in sickle cell disease.**
- 2.To evaluate the current evidence base for hydroxyurea in sickle cell disease.**
- 3.To develop an appropriate treatment and monitoring protocol for patients taking hydroxyurea..**

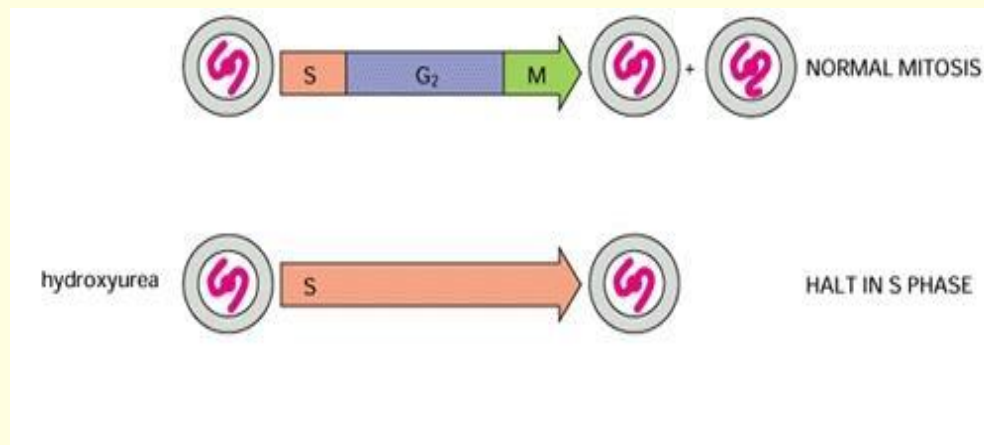
Hydroxyurea – mechanism of action

- Patients with sickle cell anemia with higher Hb F levels 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

Hydroxyurea – mechanism of action

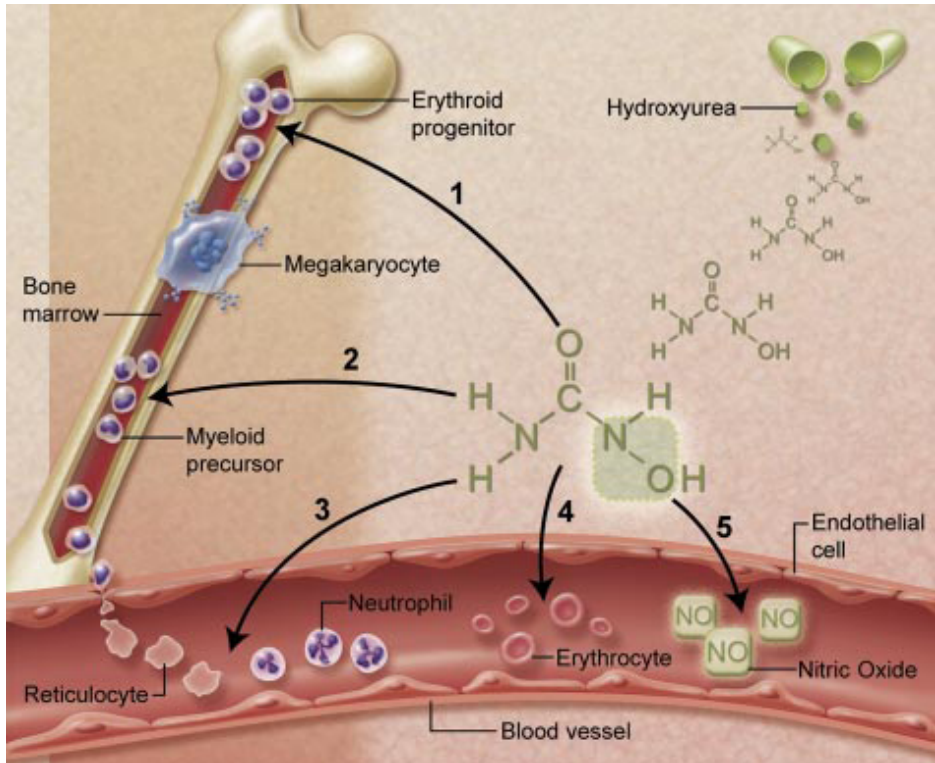
Mechanism is not completely understood

Inhibitor of ribonucleotide reductase (RR), an enzyme involved in transforming ribonucleosides to deoxyribonucleosides



Short case

- 7 year old male, SCA, seen at SCD clinic after 4 years in Canada.
- 2004- 4 VOC admissions
- 2005 4 VOC admissions
- 2006 2 VOC admissions
- 2007 4 VOC admissions
- 2008 Jan to June 30 days missed from school
2 admissions
- Start of Hydroxyurea April 2008



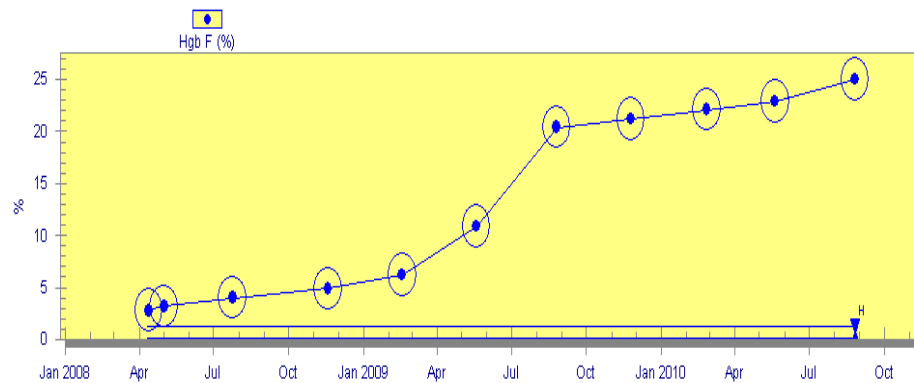
Benefits for SCD

1

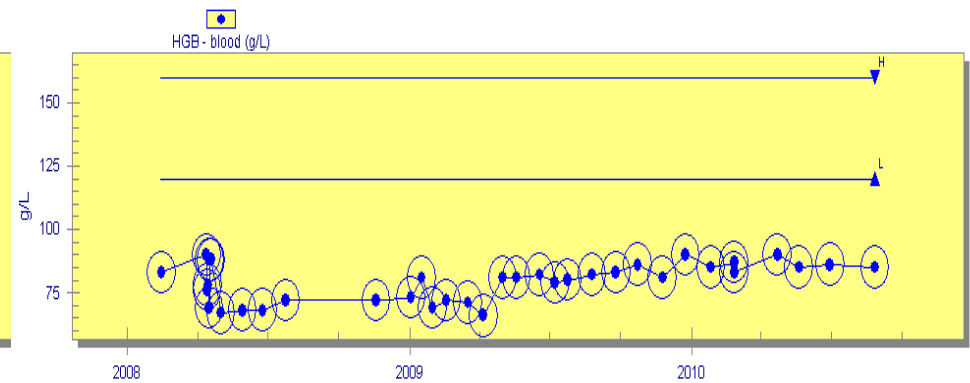
Fetal hemoglobin induction and altered red cell kinetics

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Hgb F



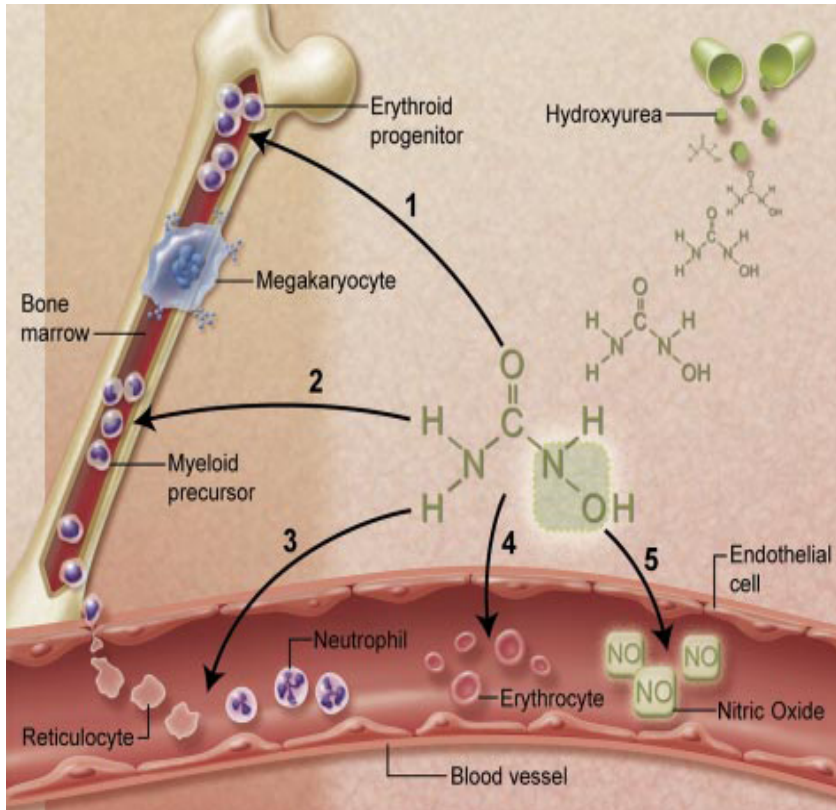
HGB - blood



Benefits for SCD

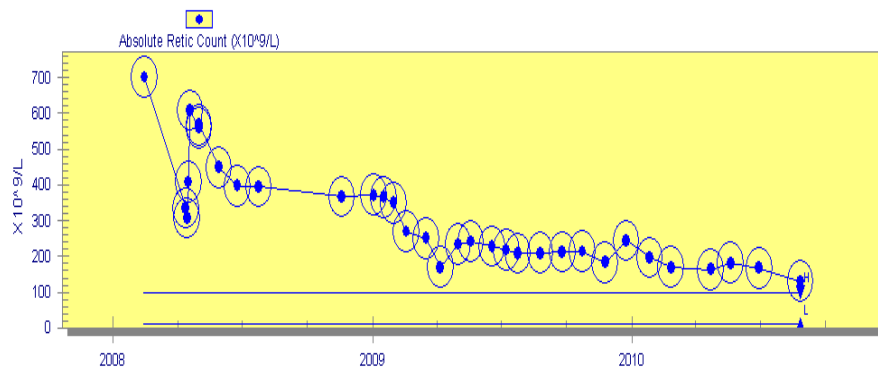
2

Lower neutrophil and reticulocyte counts from ribonuclease reductase inhibition and marrow cytotoxicity

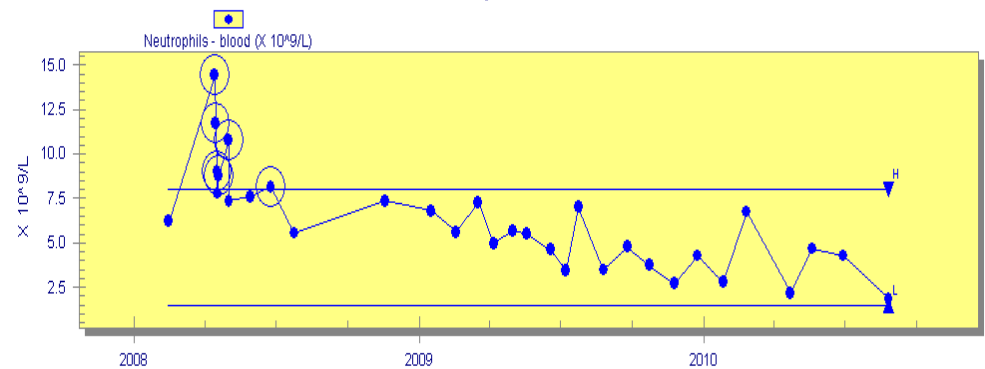


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Absolute Retic Count



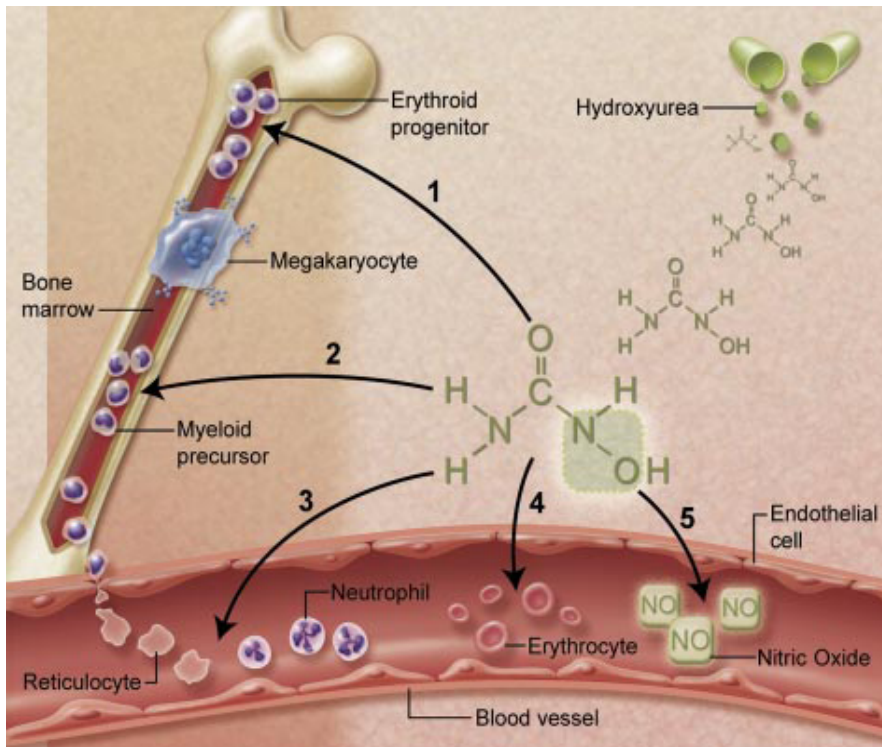
Neutrophils - blood



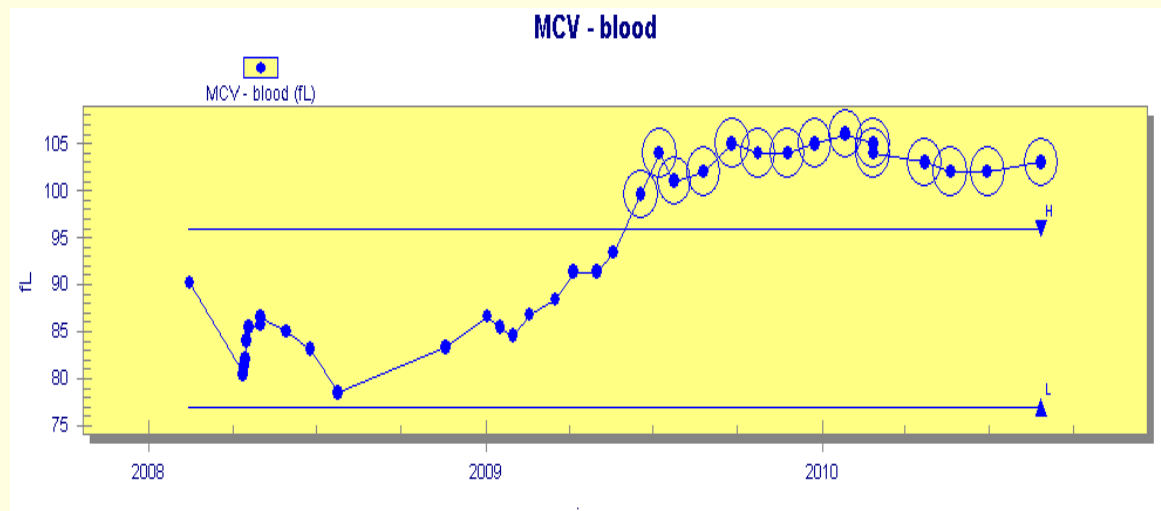
Benefits for SCD

3

Decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes



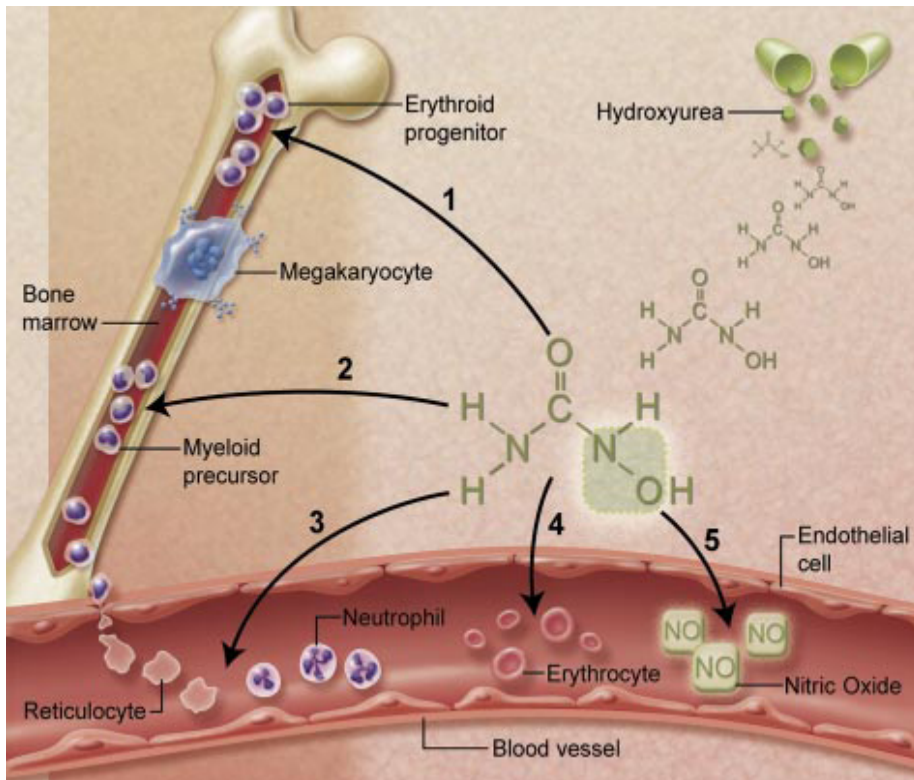
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Benefits for SCD

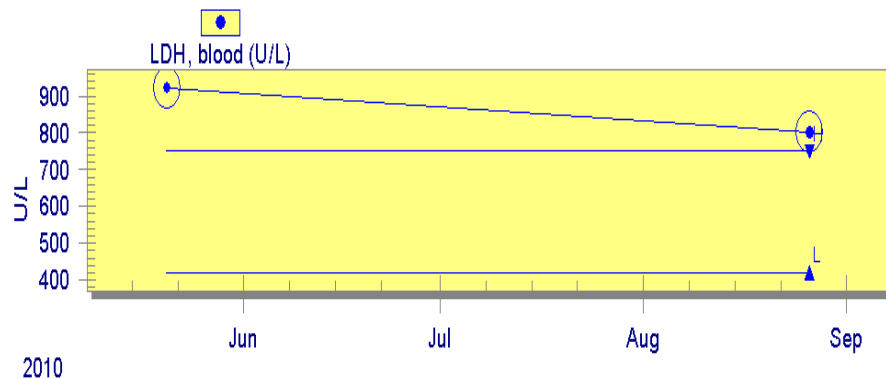
4

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

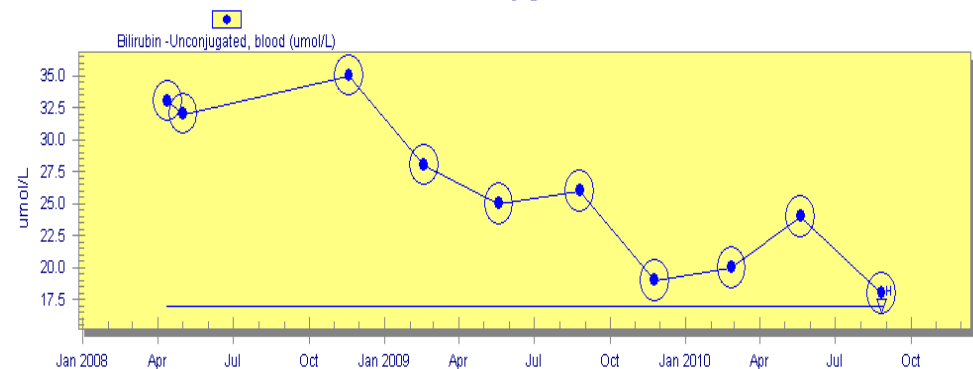


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LDH, blood



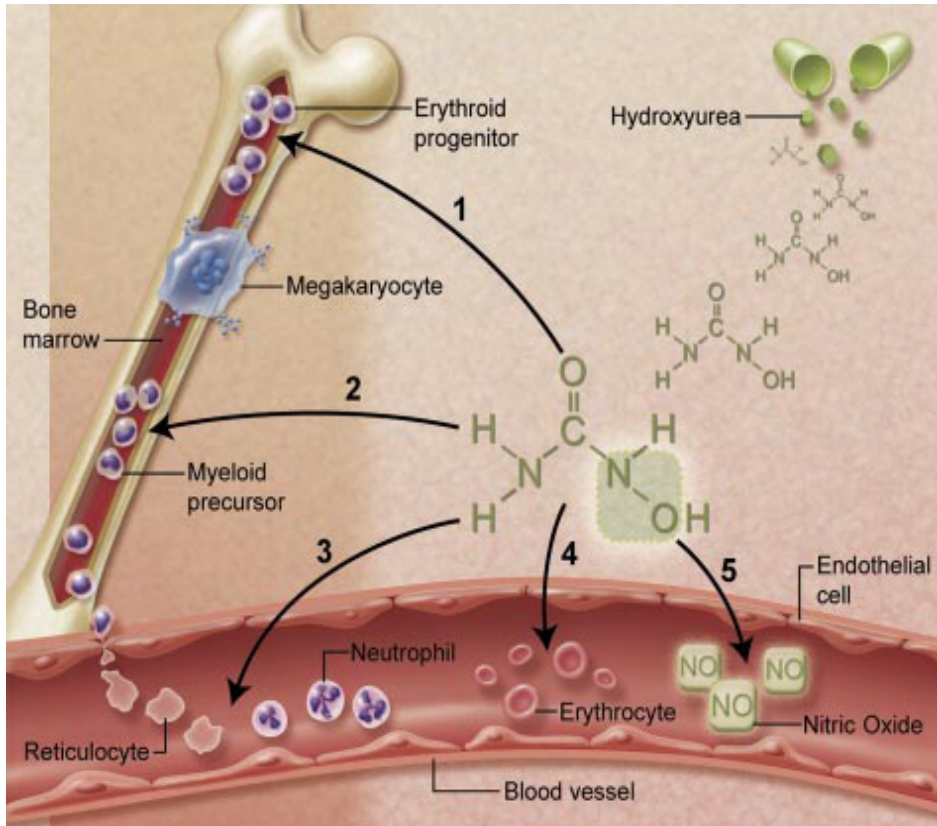
Bilirubin -Unconjugated, blood



Benefits for SCD

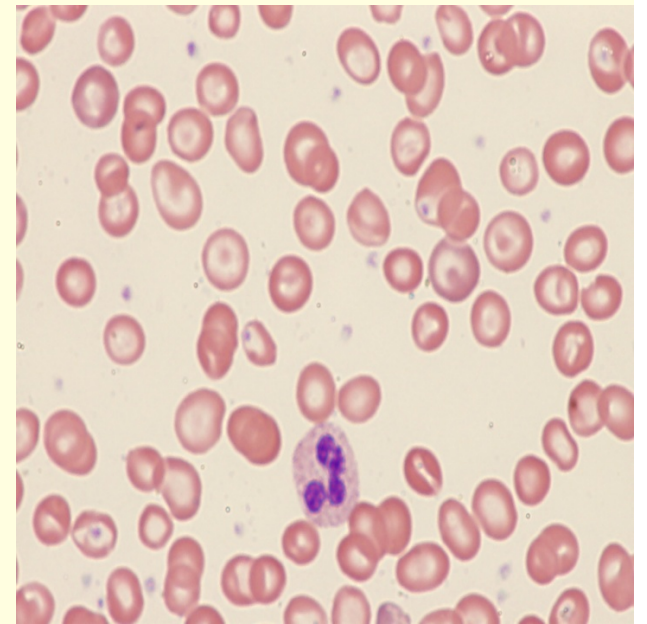
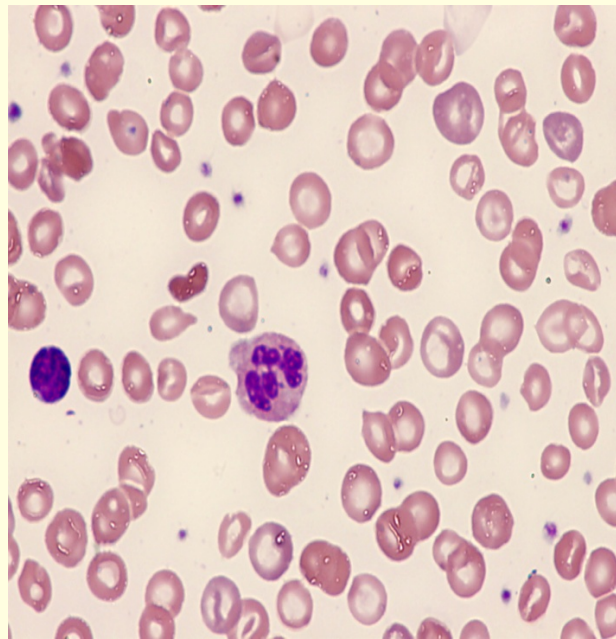
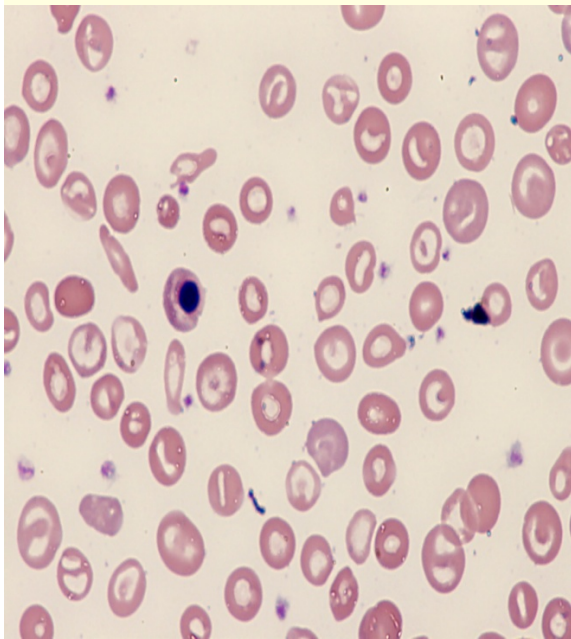
5

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



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Red Cell Response to Hydroxyurea



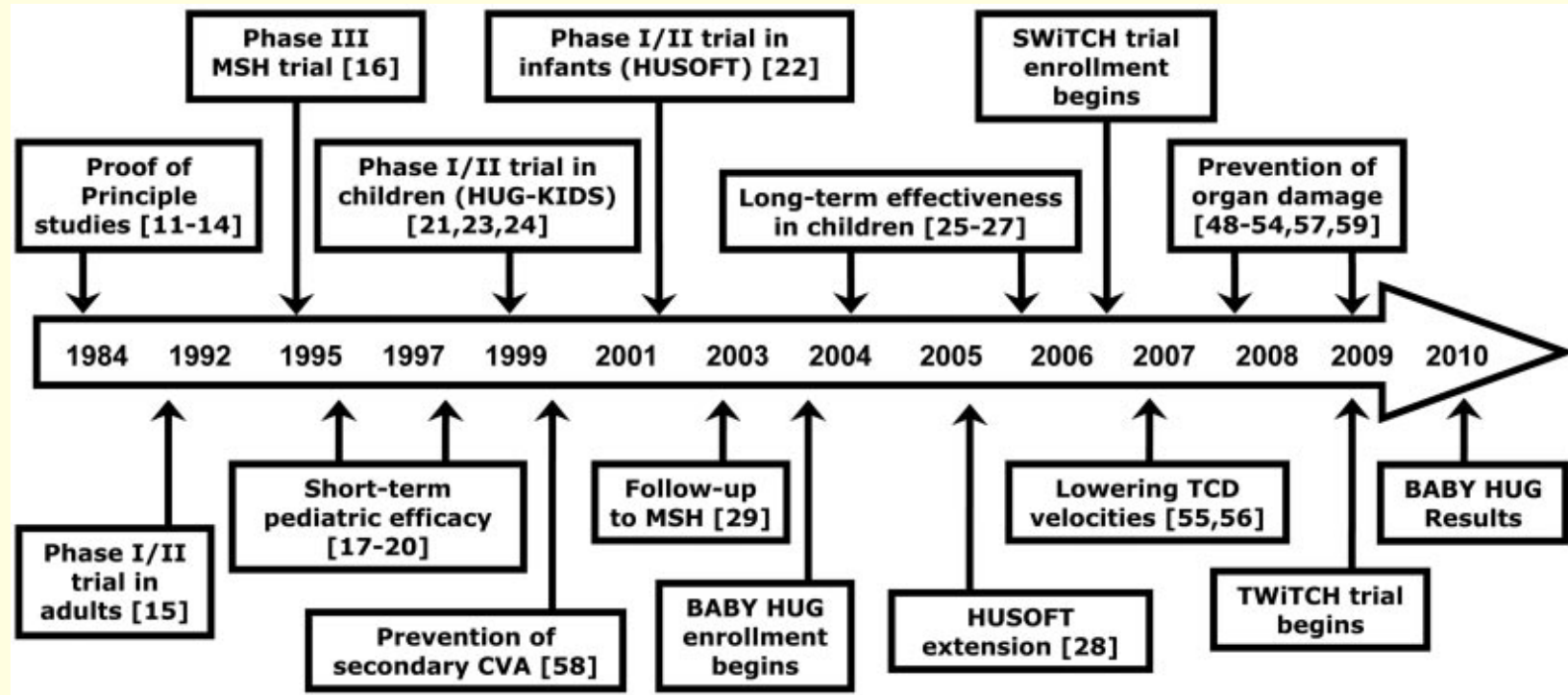
Back to the case

2009 and 2010 number of hospital admissions = 0

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Timeline of studies of hydroxyurea in sickle cell disease



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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 over the age of 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 crises in sickle cell anemia. NEJM vol 332, 1995 1317-1322

Effect of Hydroxyurea on Mortality and Morbidity in Adult Sickle Cell Anemia

Objective To determine whether hydroxyurea attenuates mortality in patients with SCA.

Design Long-term observation follow-up of patients who participated in the MSH study 1992-1995.(MSH study randomized SCA patients to placebo or Hydroxyurea)

Patients Of the 299 MSH study patients, data were complete on 233 patients.

Outcome measures Mortality, Hb F levels, painful episodes, ACS, and blood counts

Results

75 of 299 patients had died

28% pulmonary complications

Higher Hb F levels were associated with lower death rate.

>2 VOC episodes 27%, mortality c/w 17% with fewer VOC episodes.

Taking hydroxyurea was associated with a *40% reduction* in mortality.

Conclusions Adult patients taking Hydroxyurea appear to have reduced mortality after 9 years of follow-up. Survival was related to HbF level and frequency of VOC events.

Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA*. 2003;289(13):1645-1651.

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.

Safety of Hydroxyurea in Children with Sickle Cell Anemia: Results of the HUG-KIDS Study, a Phase 1/11 trial

Methods Children with SCA, age 5 to 15years

Dose 15mg/kg/day as daily dose.

Dose escalated to 30mg/kg/day

Monitoring q2weekly: compliance

toxicity

clinical adverse events

growth parameters

laboratory efficacy

Results Significant hematologic changes included: Increased MCV, Hb F, MCH
Decreased WBC, neutrophils, retics,

No life threatening toxicities

No growth failure

Conclusion Study showed that drug was safe when patients were treated by pediatric hematologist.

Kinney TR, Helms RW, O'Branski EE, et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS- study, a phase I/II trial. Pediatric Hydroxyurea Group. *Blood*. 1999;94(5):1550-1554.

Effect of Hydroxyurea on growth in children with sickle cell anemia; results of the HUG-KIDS Study

Study design

SCA, ages 5 to 16 years treated with hydroxyurea
Serial height, weight and Tanner stage measurements
Comparison made with the CSSCD groups

Results:

Girls- there were no differences in the pretreatment, treatment or CSSCD groups.
Boys- HUG-KIDS boys were heavier than CSSCD groups
Tanner stage transitions took place at appropriate ages.

Conclusion : Hydroxyurea had no adverse impact on height, weight or pubertal development

Wang WC, Helms RW, Lynn HS, et al. Effect of anemia: results of the HUG-KIDS study.
J. Pediatr. 2002;140(2):225-229.

Long term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study

Patients 21

17 patients completed 4 years of hydroxyurea

11 completed 6 years

Results

After 4 years, HU was associated with increased Hb F, increased hemoglobin concentration, increase MCV, decreased white cells, platelets and reticulocytes.

Treated patients had better spleen function, fewer ACS events, better than expected growth rates, sustained hematologic benefits.

Regarding concern of cancer/myelodysplasia

Survey 16, 613 patients in 52 institutions revealed 2 cases of cancer and only 3 of over 16,000 had prior exposure to HU.

Hankins JS, Ware RE, Rogers ZR, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood*. 2005;106(7):2269-2275.

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Indications for Hydroxyurea

Hb SS and S β^0 Thalassemia:

- 3 or more hospitalizations for VOC episodes in a 12 month calendar period
- One or more acute chest crisis requiring transfusion
- Significant number of days missed from school / work due to VOC pain managed at home regardless of # of hospital admissions
- Abnormal TCD in patient refusing transfusion therapy
- Chronic hypoxemia
- Low hemoglobin less than 70g/l

Potential Indications

Decisions for treatment should be made on an individual basis

- HbS/C Disease with clinically severe disease (may need to think about phlebotomy with HU)
- High Conditional TCD velocities
- Presence of Silent infarcts on Screening
- Neurocognitive decline
- Age less than 24 months
- Poor growth and development

Starting a patient on Hydroxyurea

History/physical

Details of VOC episodes- number and severity

Evidence of organ damage - TCD velocities, proteinuria, hypoxemia, academic performance.

Does patient have sleep apnea?

Review psychosocial issues which might impact compliance with treatment regimen such as transportation, and finances for drug coverage

Document growth and development

Thorough physical examination

Starting a patient on Hydroxyurea

Document

the discussion

history

physical including Ht and Wt, Oxygen saturation

laboratory reports

Starting a patient on Hydroxyurea

Discuss fully with patient / parents / supports the following:

- Studies as outlined previously
- Benefits, expected trends in blood parameters and clinical state
- Short term and medium term side effects
- Theoretical long term risks
- Expectations for monitoring and follow-up
- Give literature to take home
<http://www.aboutkidshealth.ca/healthaz/Hydroxyurea-for-Sickle-Cell-Disease>.
- Arrange OHIP lab requisition for monitoring closer to home with fax number and name of receiving RN/MD.

Short and Medium Term Effects

- Nausea and vomiting
- Skin rash
- Hair loss
- Bone marrow suppression
- Liver dysfunction
- Skin and nail hyperpigmentation
- Weight gain

Long term effects

Potential for malignancy theoretical

- Anecdotes exist in individual practices, SCD patients can develop cancer as does the general population.

*Infertility - no relationship between hydroxyurea usage and neonatal abnormalities or teratogenic effects

Contraception is strongly recommended.

- *The effect of prolonged administration of Hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes; results of a 17-year, single center trial (LaSHS) .*Blood*2010;115(12):2354-2363

Proposed treatment plan for hydroxyurea

- Pretreatment blood work:
 - CBC, MCV, diff, retic count
 - Hemoglobin F level
 - ALT, LDH, total/direct bilirubin,
 - BUN,Creat
 - Serum B12, RBC folate, Iron studies
 - Beta-HCG if woman of child bearing age

Proposed treatment plan for hydroxyurea

Initial Dose

10-20mg/kg/day as single dose (rounded to nearest 500mg).

May be taken with food

Time of day should be decided by family as best time to ensure good compliance

Start of oral or other contraception should be arranged.

Dose escalation

Increase dose by 5 -10 mg/kg/day q 2-3 months until MTD or clinical efficacy achieved, or dose is up to 30mg/kg/day

NB In Canada only capsules 500mg are available. May have to teach family to dose and divide using the usual chemotherapy protocol for handling this agent for daily doses under 500mg.

Proposed treatment plan for hydroxyurea

Monitoring

Q2 weekly CBC, diff, retics until stable dose achieved for 6 months, then q monthly thereafter.

At 1month of therapy

CBC, diff, retics

ALT, LDH, Creatinine, BUN,

Q3 monthly

CBC, diff, retics

ALT, LDH, Creatinine, BUN, Bili

Hb analysis (Hb F%)

Proposed treatment plan for hydroxyurea

Threshold for dose reductions

Neutrophil ANC < $2.0 \times 10^9/l$

Retic ct < $80 \times 10^{12}/l$

Platelets < $80 \times 10^3/l$

Hemoglobin < 70G/L

If hematologic toxicity occurs

Discontinue HU until counts recover (usually 5-7 d).

Restart at same dose. If threshold is again reached, reduce to previous dose and that is MTD.

Proposed treatment plan for hydroxyurea

Patient and family involvement.

Clinical effect

Review VOC episodes with family

Side effects

Hematologic toxicity and beneficial effects

Keep patient/family engaged in management. This improves compliance and instills confidence in taking the drug.

Celebrate beneficial effects, and be open when toxicities occur. Show graphs of responses e.g. MCV, Hb F%

**Thank you for your attention.
Stand up and stretch😊**