What's NEW is what's OLD in Sickle cell disease

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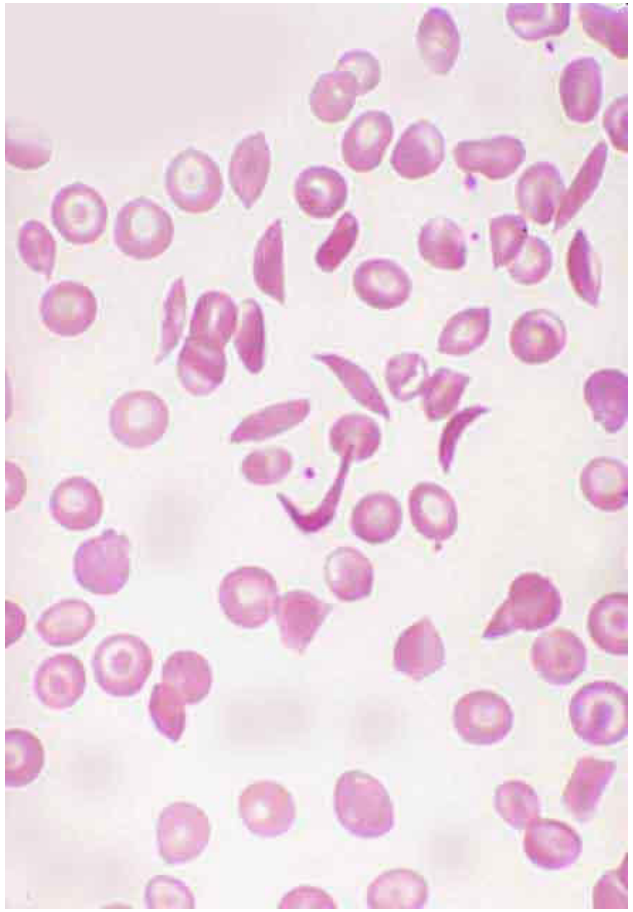


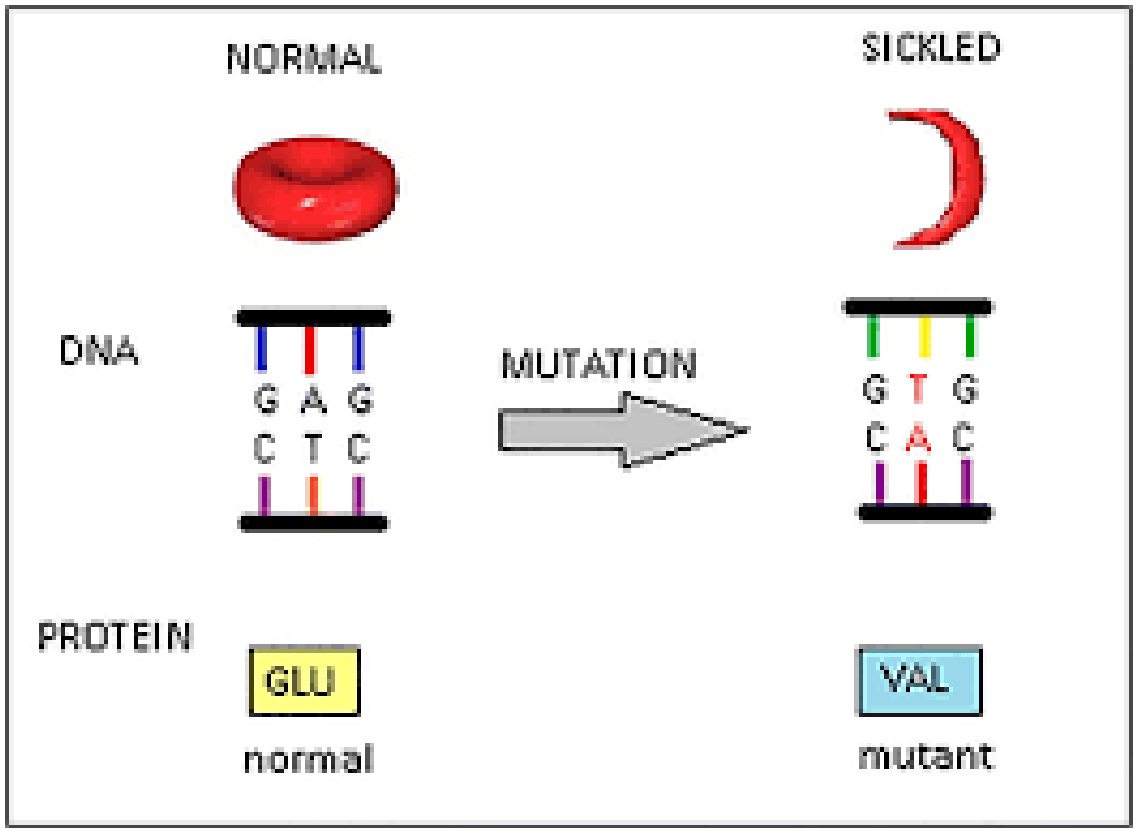
- Today I am going to remind you what is sickle cell in its main genotypes and manifestations of the disease.
- Then:
- PAIN: what exactly causes it? and how to treat?
- HYDROXYUREA: why it is more important than ever in 2026
- HEALTH CARE MAINTENANCE for SCD

- I will mention pitfalls that I myself fell into…

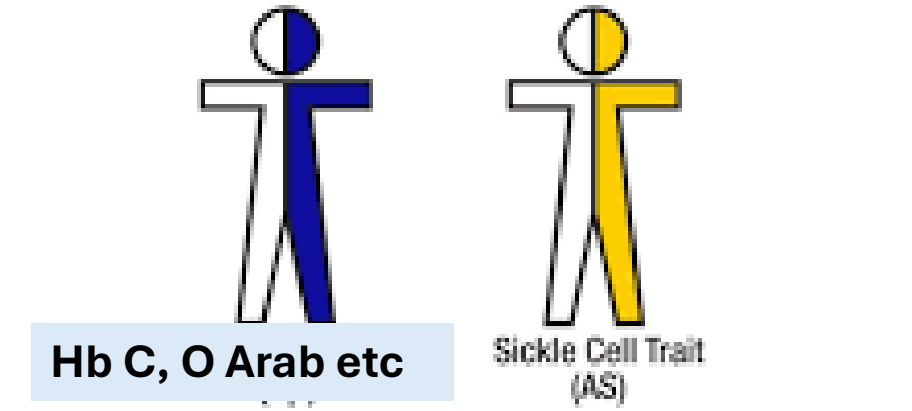
Sickle cell disease

- Most common single gene disease in the world, **1.9% of the world's population carries HbS.**
- **It was the first molecular disease! Genetic structure learned on globin genes.**
- Millions of carriers and hundreds of thousands of homozygotes
- Point mutation in codon 6 glutamic acid to valine
- Conformational change: polymerization under low oxygen conditions
- In Israel there are patients with HbS homoygosity and also S/beta thal etc. HOW MANY? No one knows!

Sickle Cell Anemia is Caused by a Missense Mutation in Codon 6 (GAG->GTG)



Sickle cell disease has different genotypes



There are additional hemoglobins that sickle!

Most common one is HbC which is a different mutation in same codon as Hb S
Glutamic Acid to LYSINE (not valine)

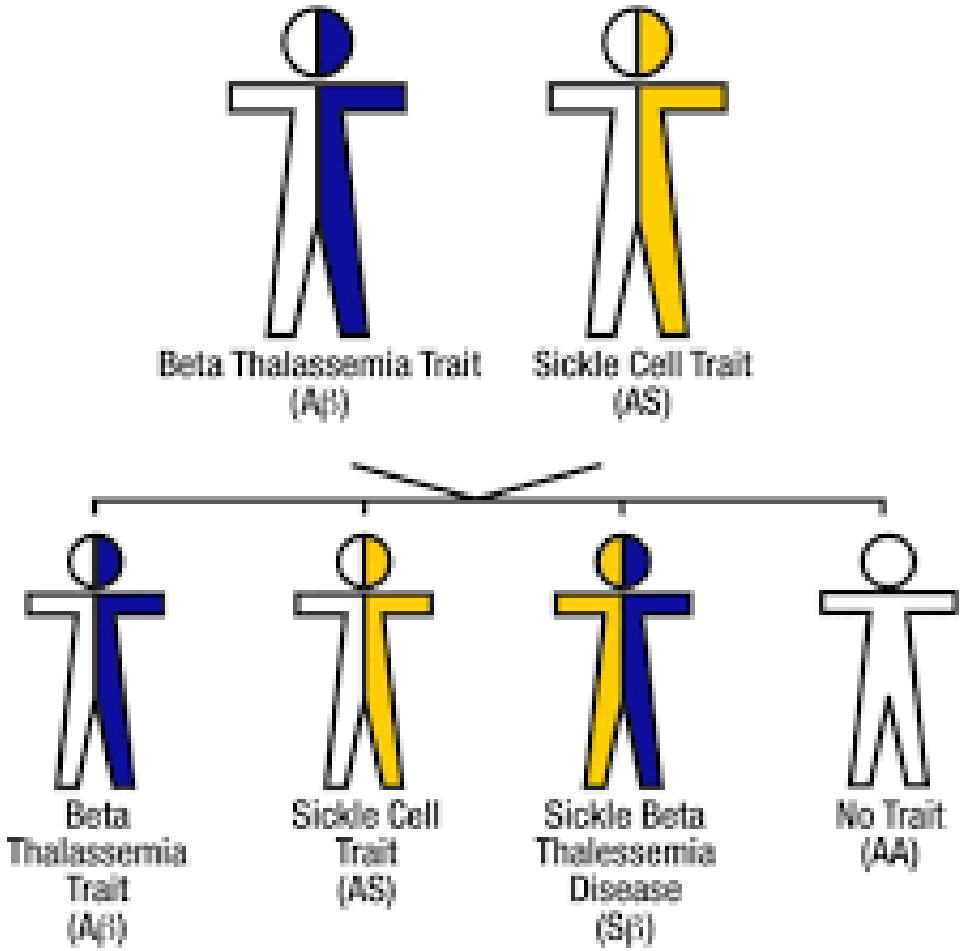
Hb O Arab is a different mutation, also sickles But milder disease, mutation is in codon 121.
Hb D Punjab is also in codon 121 and sickles.

There are patients in Israel with Hb C and also Hb O Arab (mostly in Jisser A Zarka) but also in Emek Jezreel.

Each genotype has different clinical presentation.

Sickle Beta Thalassemia:

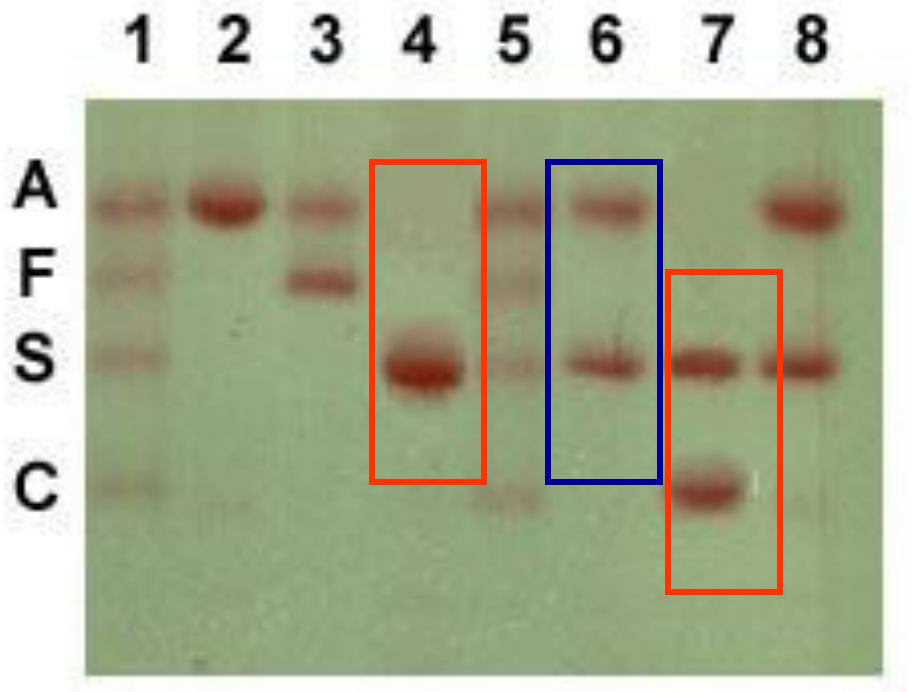
Coinheritance of Two Mutant Beta Globin Genes, one from each parent: COMMON IN ISRAEL!



The clinical picture of S/beta thal patient depends on what amount of HbS and what amount of Hb A he/she has (and HbF).
Patient can be S/beta PLUS or Beta ZERO thal among others.

If patient has S/beta ZERO thal, he/she has NO HbA, but if he has S/beta PLUS thal, there is some HbA, amount depends on severity of thalassemia mutation.

Hemoglobin Electrophoresis

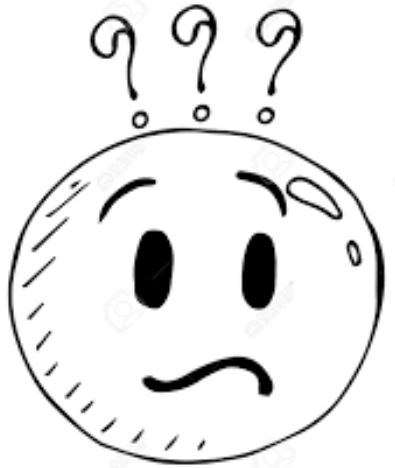


F= Fetal Hb

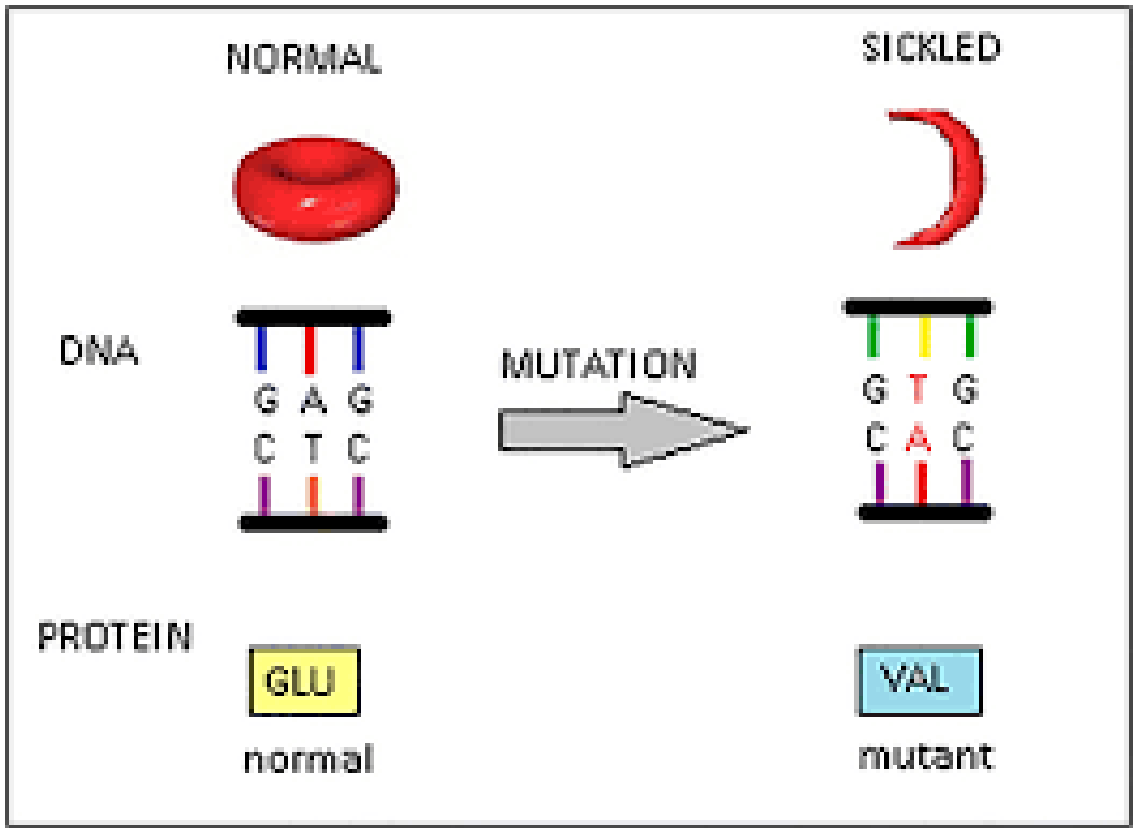
4=homozygous sickle, 6=sickle trait, 7=SC disease

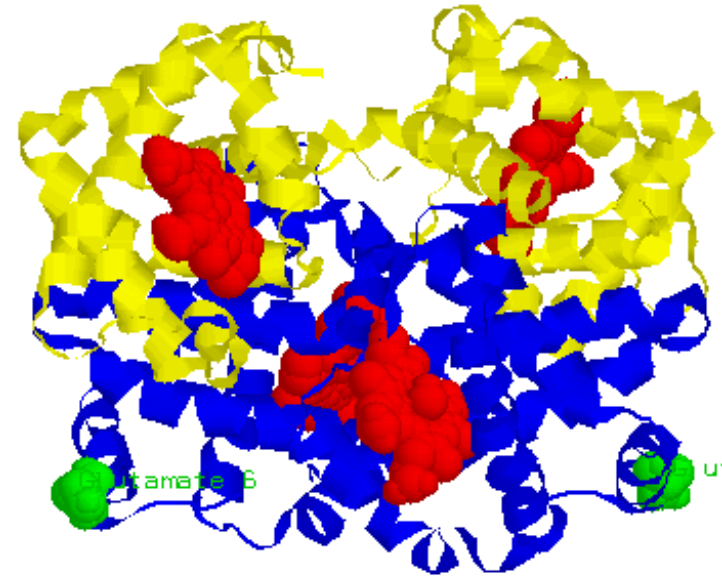
Sickle thalassemia, the worst of both diseases

- Anemia, which is worse since only ONE beta globin gene is making a normal amount of beta chains but they are HbS. The other gene is supposed to make HbA but only partial production or NO production due to thalassemia mutation.
- Most sickle cell patients have very high retics, 10-15% which partly compensates for short RBC lifespan (even 2 weeks!)
- Sickle thal patients have LOWER retics, worse anemia.
- Besides worse anemia… ALSO sickling crises!
- Splenomegaly like thalassemia…

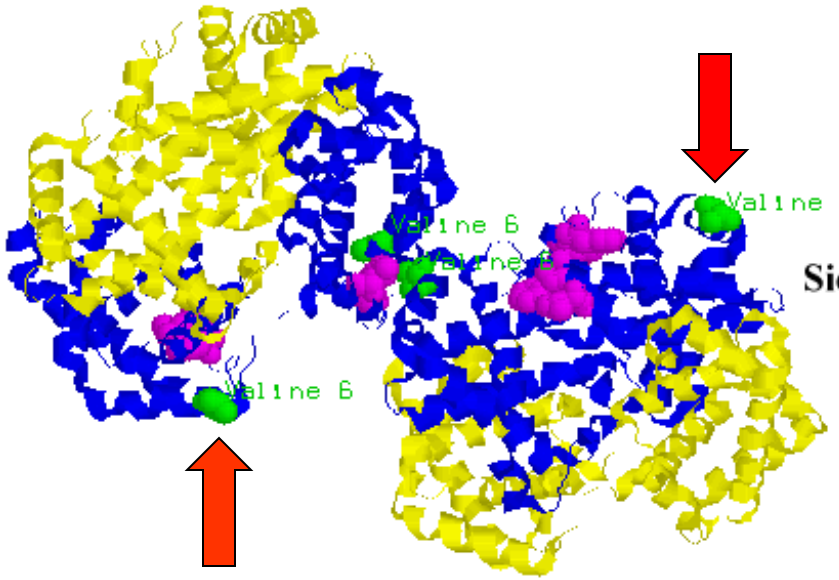


Sickle Cell Anemia is Caused by a Missense Mutation in Codon 6 (GAG->GTG)





Normal Hemoglobin



Sickle Hemoglobin

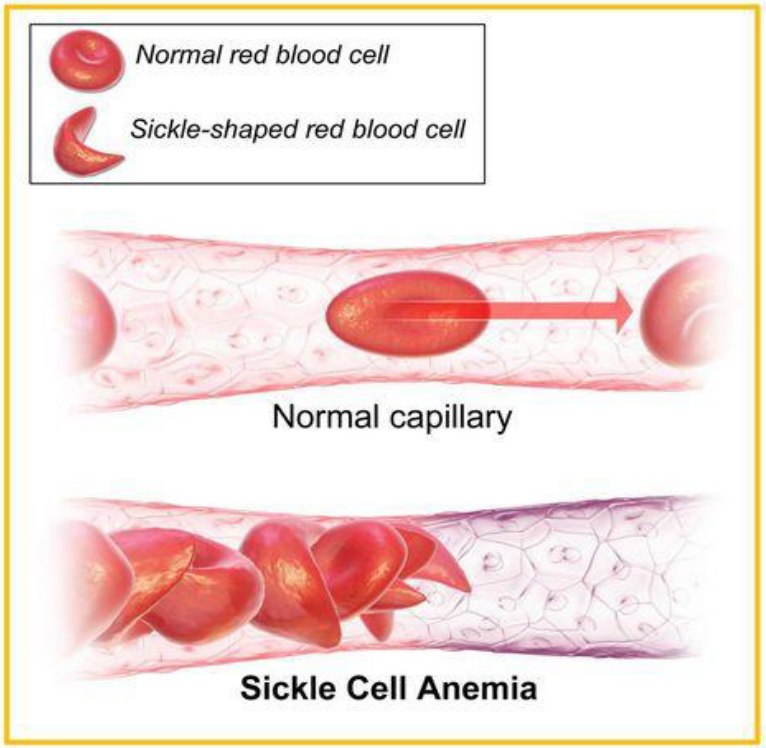
Note: The Sickle hemoglobin image is drawn at 50% of the size of the Normal hemoglobin

Symptoms

Vaso-occlusive crises

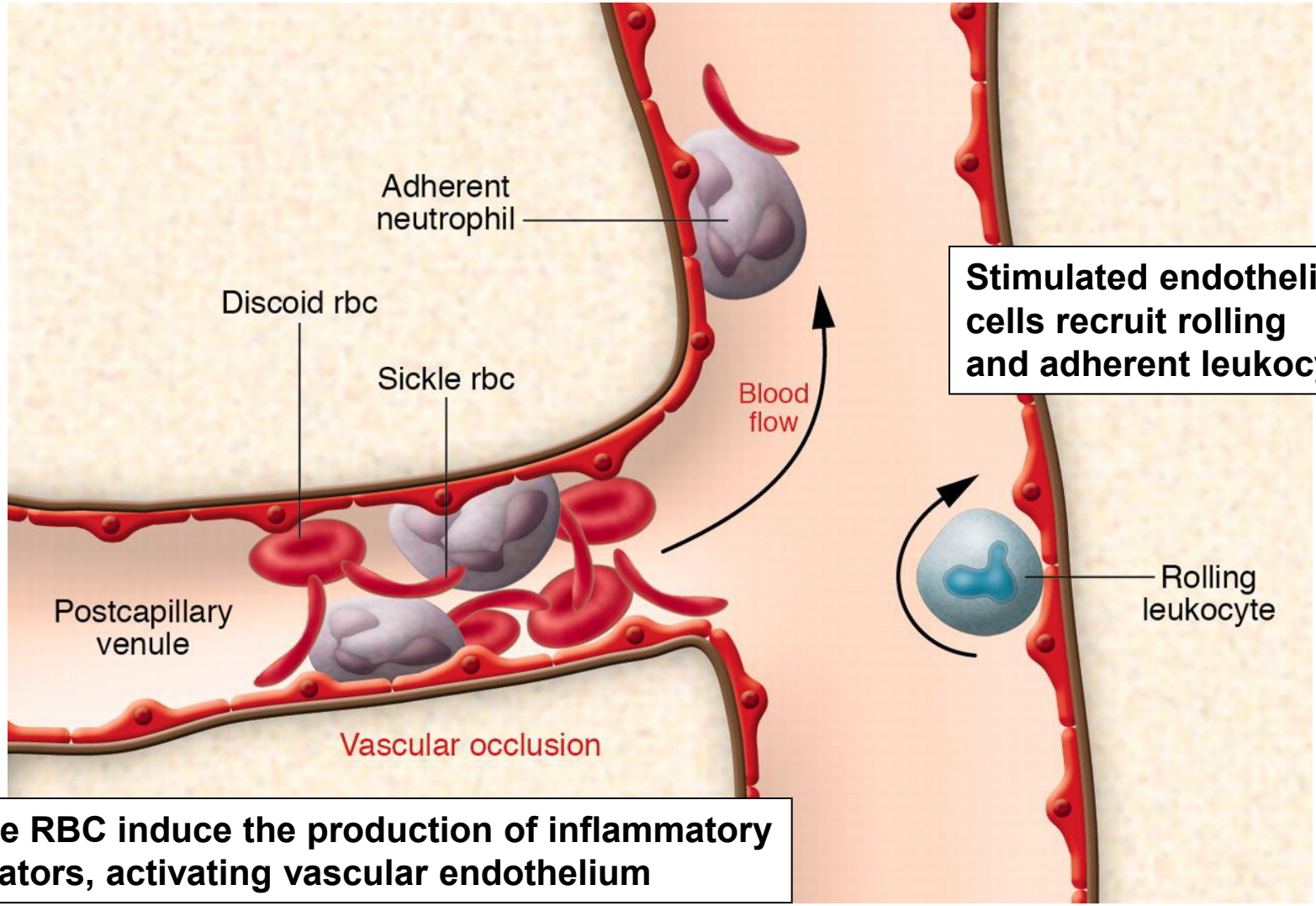
(microcirculation obstructed by sickled red blood cells, causing ischemia):

- Small vessels occlusion by sickled erythrocytes causes **pain** from mild to severe.
- It may be precipitated by:
  - Cold
  - Infection
  - Dehydration
  - Exertion or ischemia.
  - Often no cause can be found.



This sounds nice but is a gross oversimplification, the obstruction is not mechanical by sickled cells but involves adhesion to endothelium mostly by reticulocytes and bridged by PMNs.

Vascular pathophysiology of sickle cell disease:
Leukocyte adhesion and inflammatory response are critical for vaso-occlusion

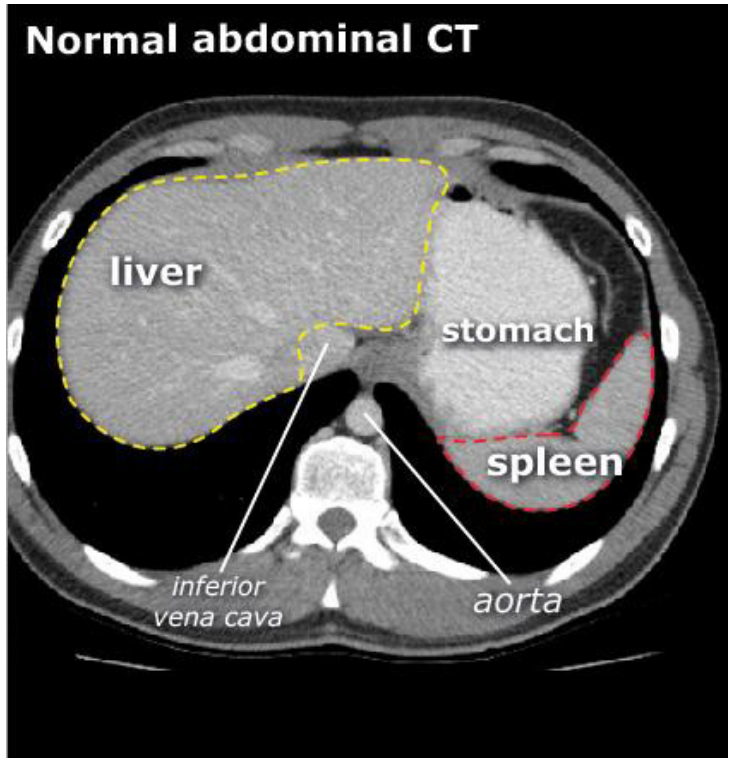


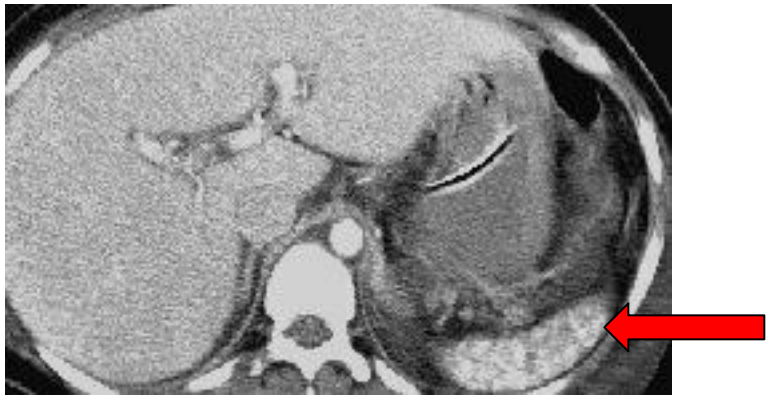
Stimulated endothelial cells recruit rolling and adherent leukocytes

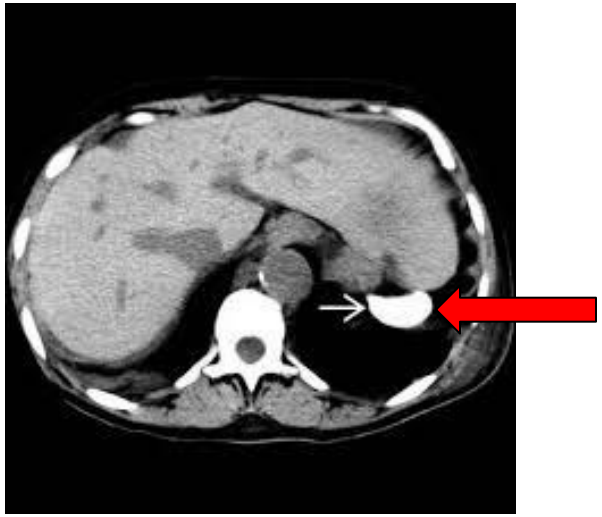
Sickle RBC induce the production of inflammatory Mediators, activating vascular endothelium

“Autosplenectomy” in Sickle Cell

Occurs early in life due to ischemia, infarction, leads to **infection**!



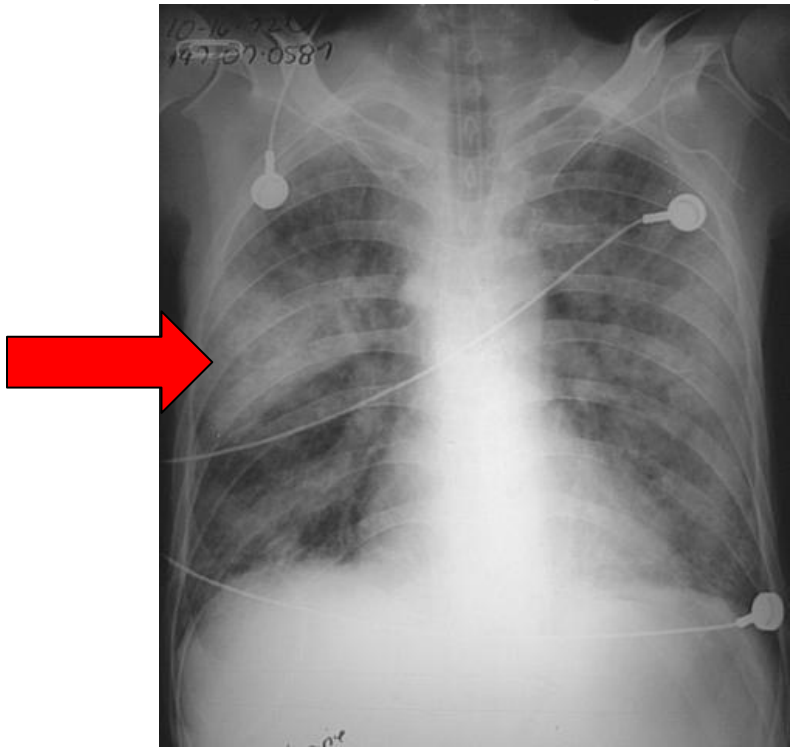


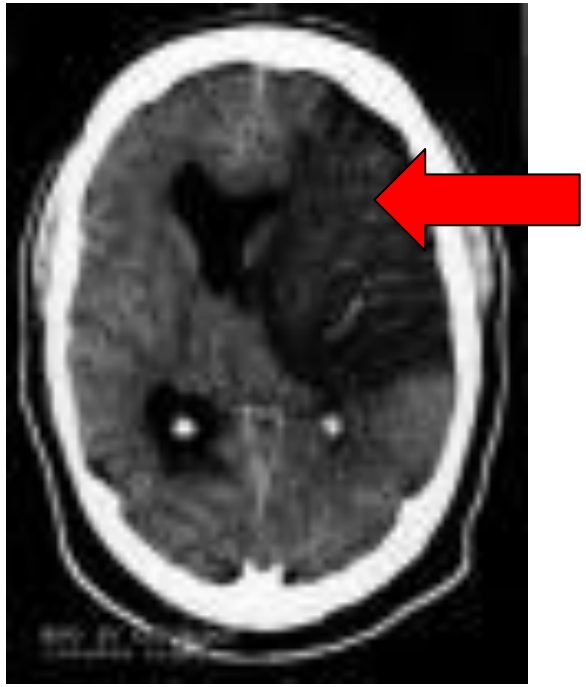


Red arrows show small calcified spleen from repeated infarctions

Two Types of Severe Vasooclusive Crises in Sickle Cell Disease

- Disabling stroke (11% before age 20!), also silent strokes
- Acute chest syndrome can be FATAL!





Many more types of crises...every organ can be affected!

Multicenter Study of Acute Chest Syndrome June, 2000

- 671 episodes of the acute chest syndrome in 538 patients, did bronchoscopy
- Found mostly FAT EMBOLI and infections (38% had a pathogen identified, 27 different pathogens)
- 13% mechanical ventilation, 3% died, over age 20 were more severe.
- 11% also developed a stroke in same admission!
- **Over half initially admitted for pain**!

- Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, Nickerson B, Orringer E, McKie V, Bellevue R, Daeschner C, Manci EA. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000 Jun 22;342(25):1855-65.

Sickle Cell Clinical Manifestations: Acute and Chronic

ACUTE:

- A “simple” crisis can become a severe one
- Crises! (remember: exchange transfusion for severe crises)
- One severe crisis can bring along with it another severe one

- Hypercoagulability-thromboses, severe infections, gallstones.

- Every organ can develop an acute sickle crisis event: renal papillary necrosis, etc.

What starts as painful crisis may become something more…..

- Prediction is impossible as to whether something worse will occur such as **chest crisis**…
- Recent article JAMA Open: prediction score for chest crisis was only 27% predictive..
- BE AWARE!! Must be vigilant on patients admitted for pain! **I was not….!**

Sickle Cell Clinical Manifestations

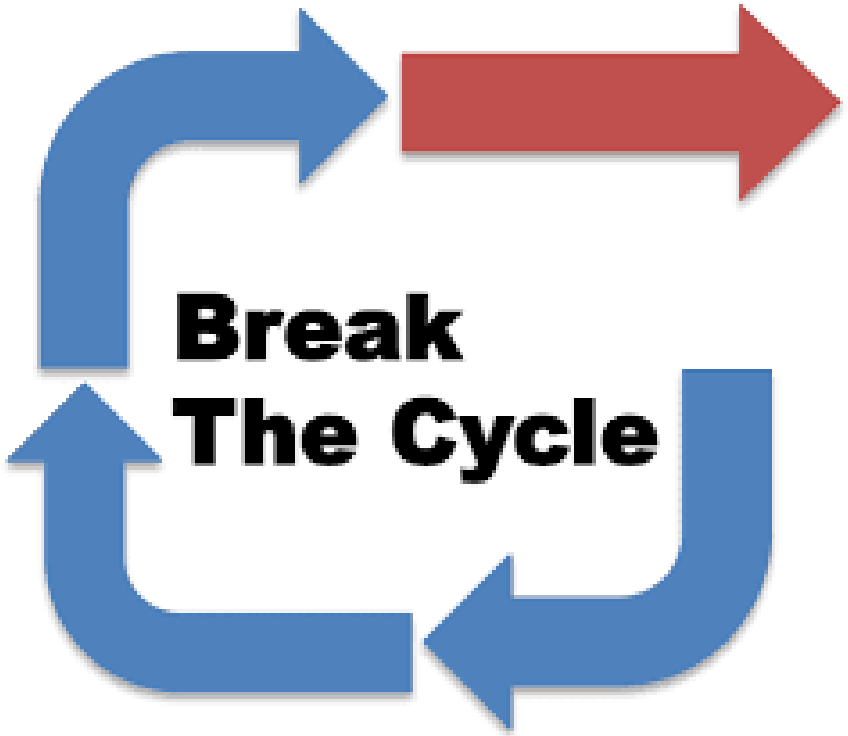
- CHRONIC:
- Organ damage: renal insufficiency, pulmonary hypertension, etc.

BUT: Main chronic problem is **PAIN**

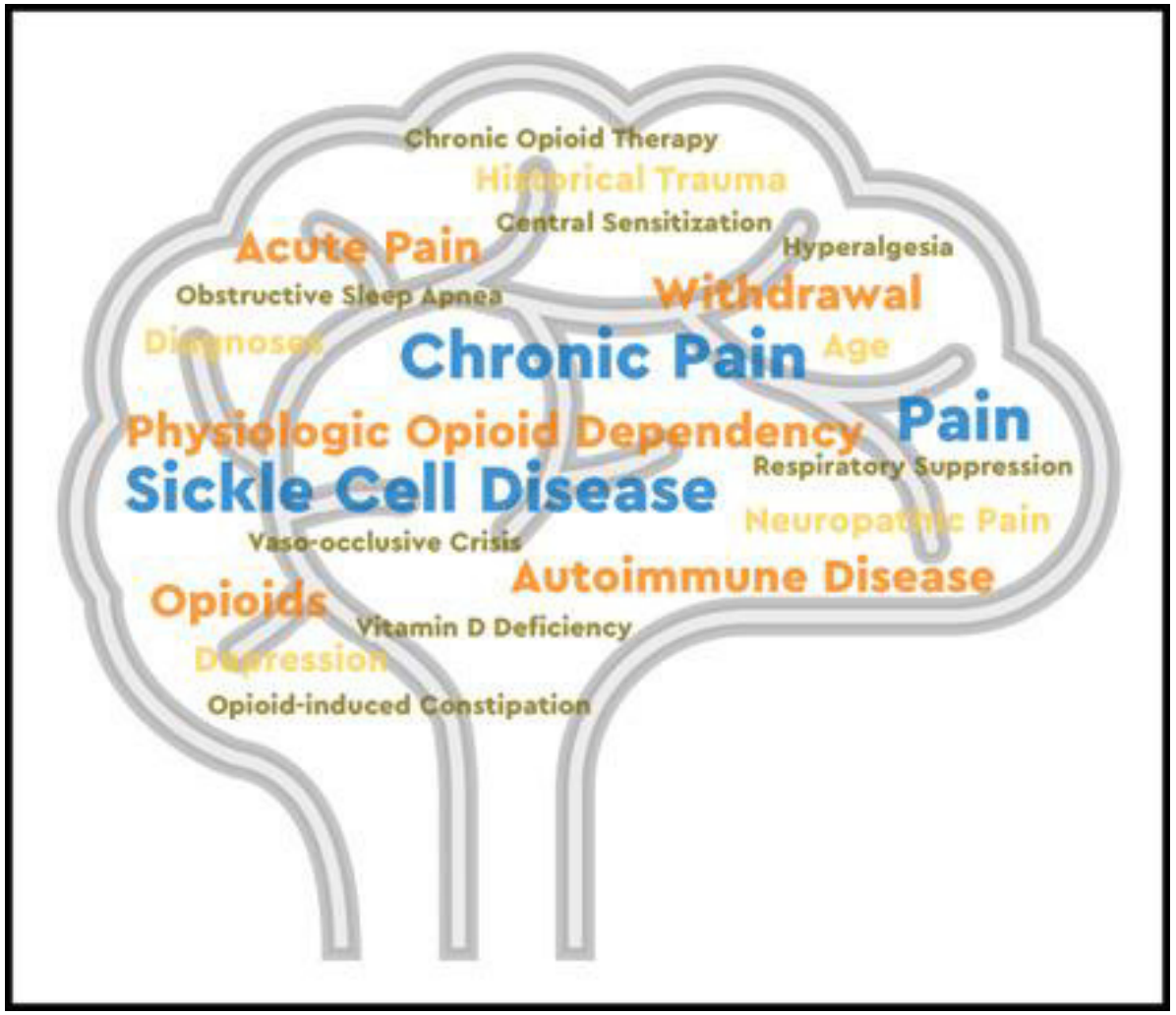
Unfortunately the causes of pain in SCD are poorly understood and treatment is VERY suboptimal for most patients.

Sickle cell treatments:
SYMPTOM RELIEF and DISEASE MODIFYING THERAPY

- Two separate issues but obviously interrelated
- If disease manifestations are reduced, then need less symptom relief!
- Back to PAIN…



Etiologies of Sickle cell pain: ACUTE and CHRONIC



I am not a pain physiologist but many pain specialists have studied Sickle cell pain

Nociceptive pain: from tissue injury

Neuropathic pain: from nerve stimulation, not direct tissue injury.

Easy to understand ACUTE pain is from **tissue ischemia** but what causes CHRONIC pain?

Chronic Pain is Very Common, increases with age

- Do not be misled: I was mistaken!
- By adulthood, 55% have pain on >50% of days, 30% on 95% of days
- Repeated tissue ischemia from sickling leads to chronic damage that causes chronic pain, such as
- Bone infarction (pain like in myeloma), microfractures…compression fractures… osteomyelitis? Autoimmunity: arthritis.
- Even after alloBMT, chronic pain may persist for a year!

- Osunkwo I, O'Connor HF, Saah E. Optimizing the management of chronic pain in sickle cell disease. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):562-569.
- Carroll CP, Brandow AM. Chronic Pain: Prevalence and Management. Hematol Oncol Clin North Am. 2022 Dec;36(6):1151-1165.

What makes sickle cell pain so severe and refractory to therapy?

Vaso-Occlusive Pain

Recurrent episodes of hypoxic-ischemic reperfusion injury to bones and tissues due vaso-occlusion. This results in inflammation and tissue damage leading to repetitive nociceptive injury.

Central Sensitization

Increased responsiveness of nociceptors to normal painful and non-painful stimuli. Hypersensitivity to pain: both allodynia and hyperalgesia.

Hyperalgesia
Increased pain perception incongruent to degree of noxious stimuli.

Allodynia
Pain from a stimulus that does not normally cause pain such a light touch, pressure, heat, or cold.

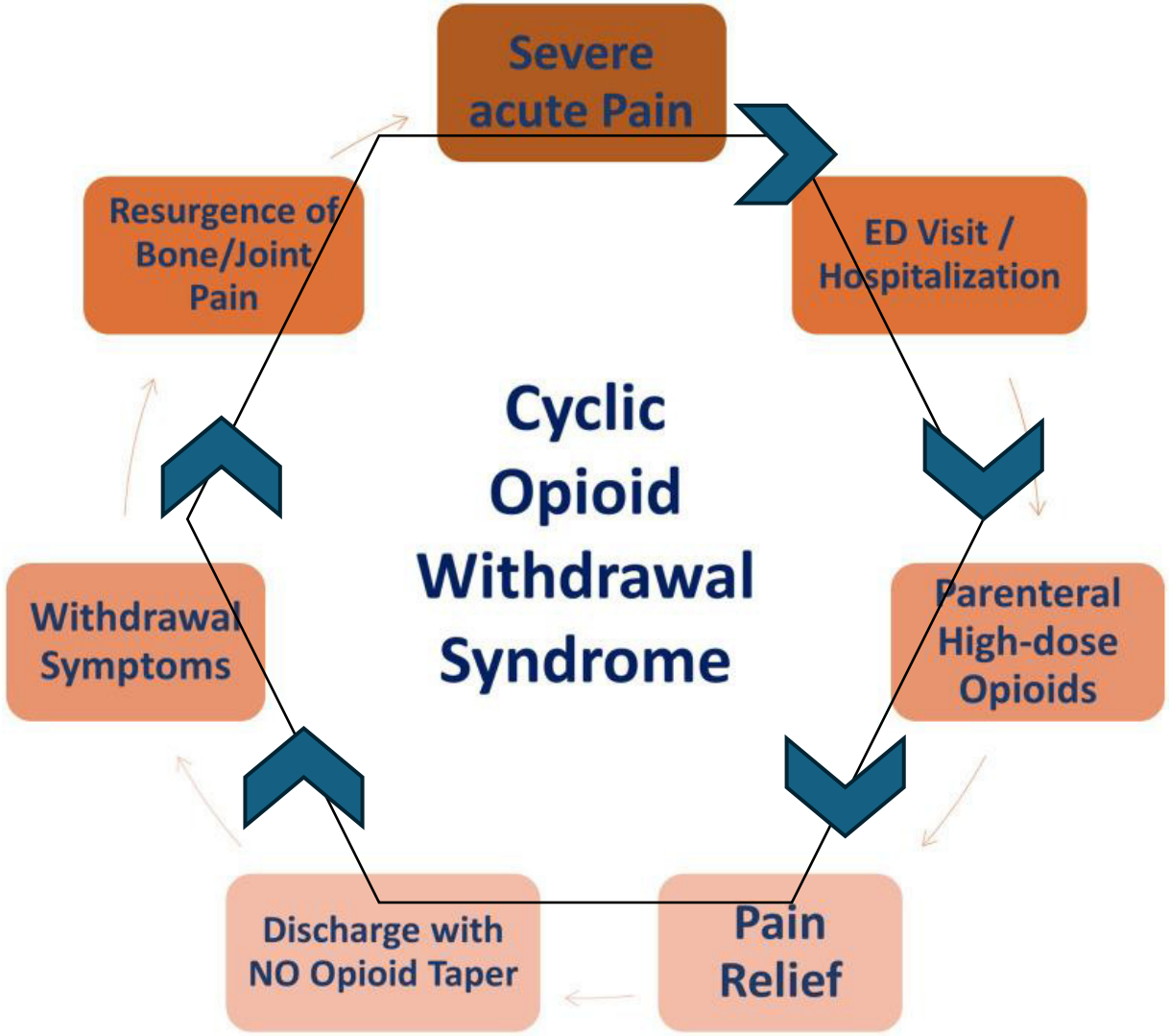
Opioid–Induced Hyperalgesia
Abnormally enhanced pain sensitivity to a familiar painful trigger that is associated with long-term opioid use. It causes generalized pain "all over".

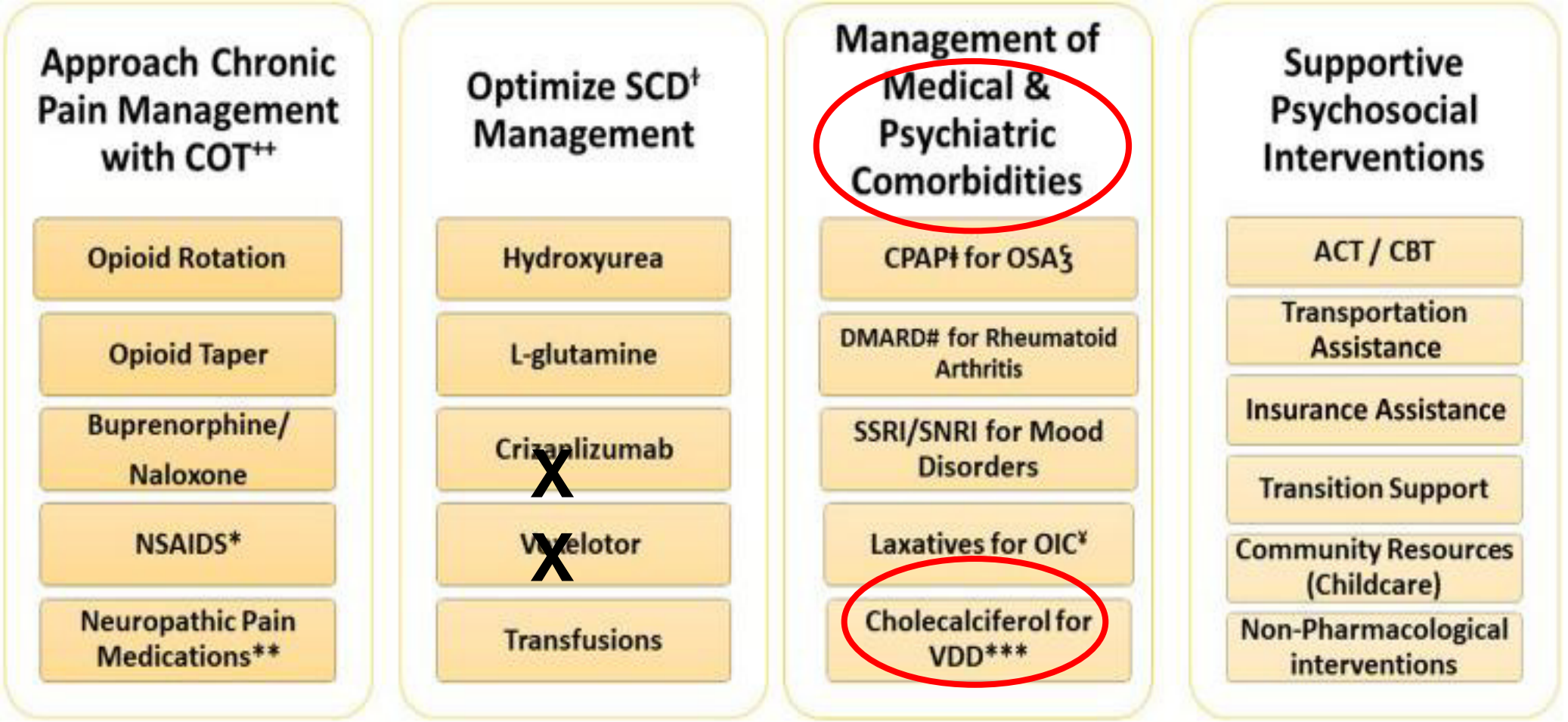
Neuropathic Pain
Pain caused by damage or disease to the somatosensory nervous system. Heightened response to both painful and non-painful stimuli.

Cyclic Opioid Withdrawal

Self-perpetuating cycle of pain exacerbation & opioid withdrawal triggered by abrupt discontinuation or tapering of opioids after prolonged use or high doses. Often under-recognized by providers and patients.

Opiates are necessary but cause issues if not used correctly



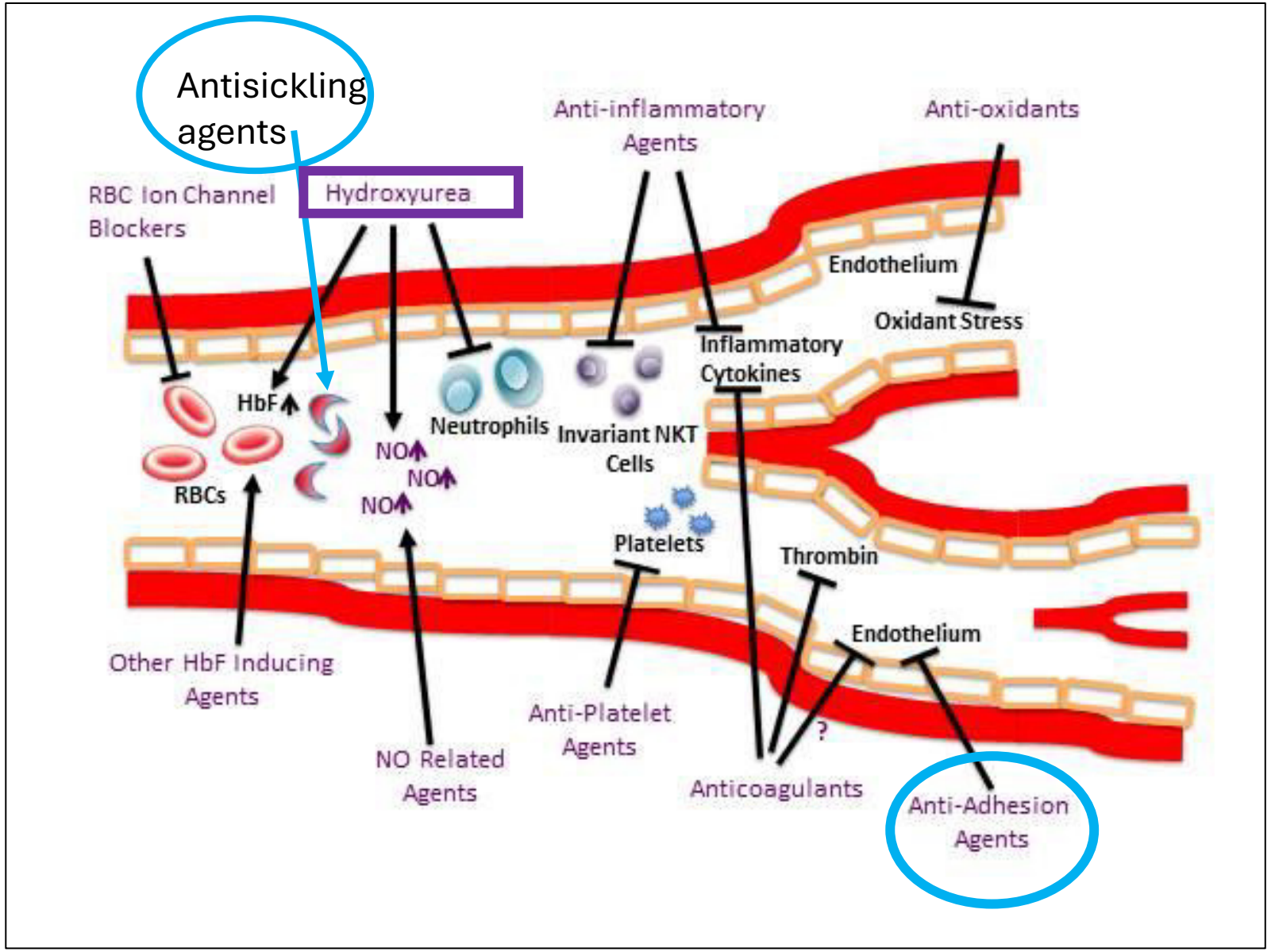


++ Chronic Opioid Therapy; * Nonsteroidal anti-inflammatory drugs; ** Neuropathic Pain Medication e.g. Gabapentinoids, Tricyclic antidepressants, SSRIs and SNRIs; ǂ sickle cell disease, ł continuous positive airway pressure; ʒ obstructive sleep apnea; # disease modifying autoimmune drug; ¥ opioid induced constipation; *** *Vitamin D deficiency

Note I am not giving you specific names of drugs. Each patient is different. In USA they have different drugs which we don't have here such as buprenorphine/nalaxone. Or buprenorphine alone.

Could this ever happen in Israel??

Sickle cell: Treatment Possibilities



Chronic Therapies for Sickle Cell Disease

- Can simply transfuse but that alone is not a good solution, get iron overload. Also alloimmunization is big problem in some parts of world.
- Need to give enough blood transfusion to bring HbA+F to about 50% so that the patient “clinically behaves” like sickle trait!
- Using logical reasoning we can imagine that we don’t want to raise the patient’s Hb too high (increases viscosity).

Chronic Therapies for Sickle Cell Disease

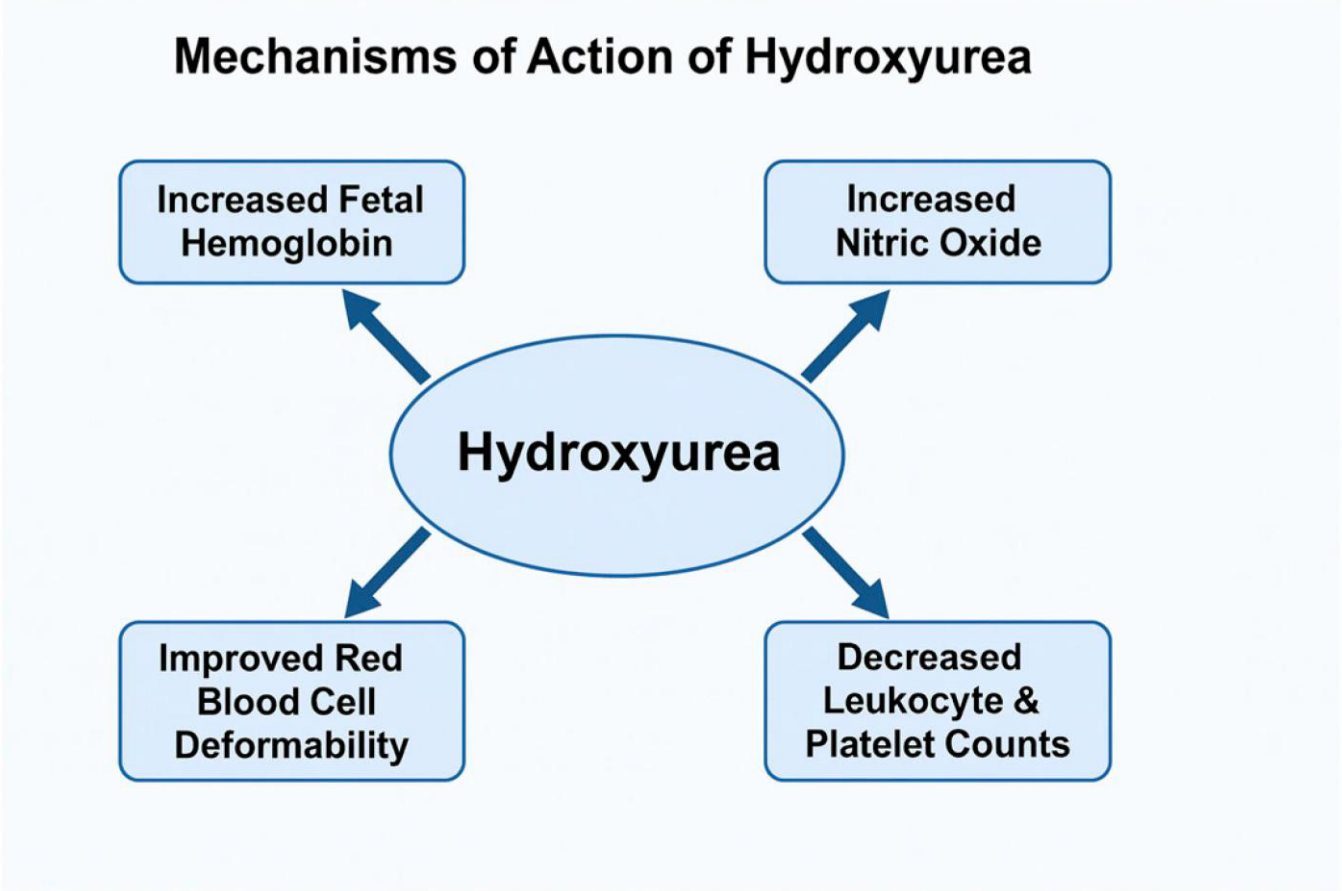
- A fair amount of patients have elevated HbF but most don’t have enough.
- **HbF inhibits polymerization of HbS.**

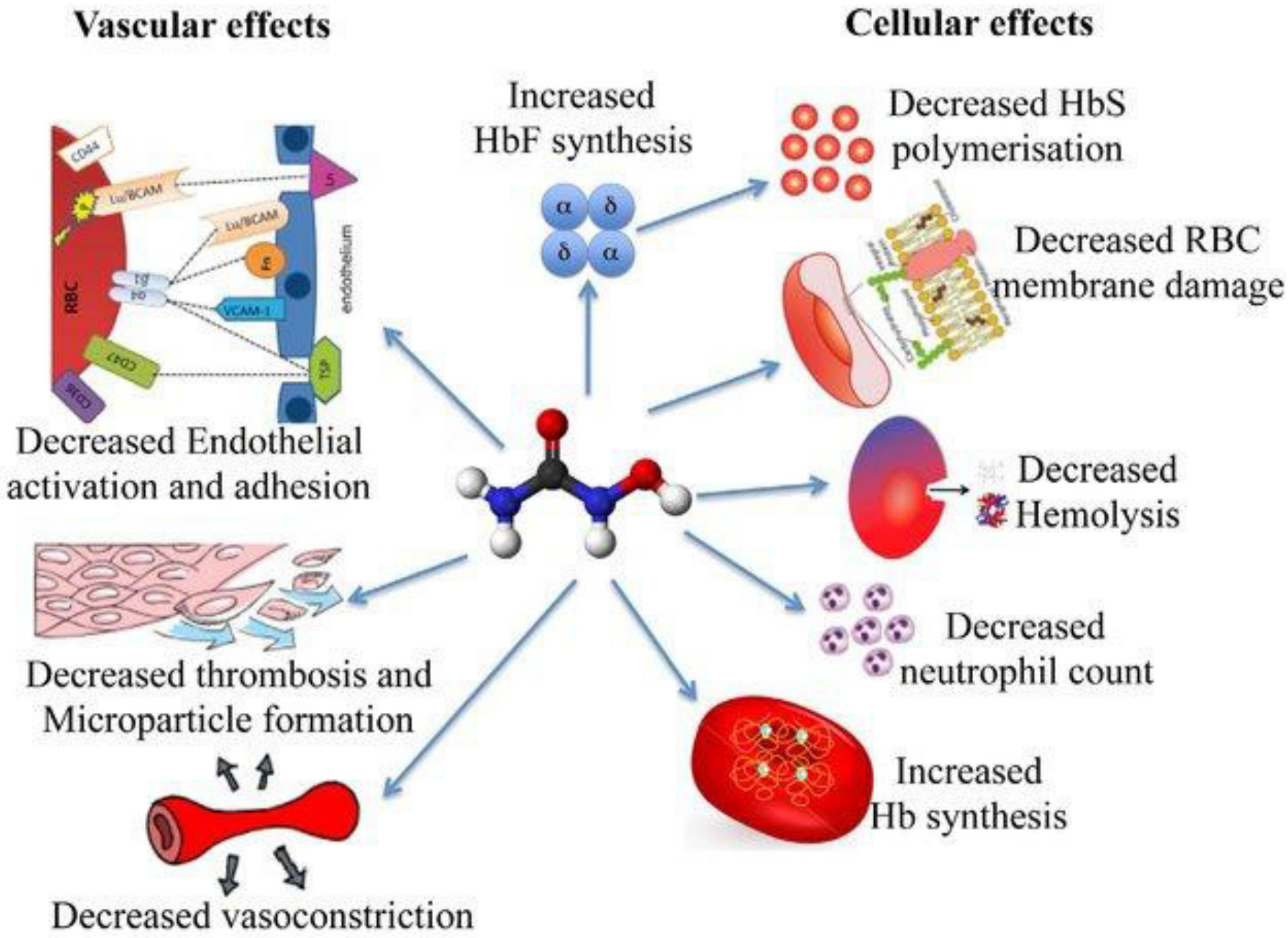
Chronic Therapies for Sickle Cell Disease

- Goal is to PREVENT SICKLING!!
- First FDA approved agent was HYDROXYUREA.
- WHY HYDREA?
- First agent was 5-Azacytidine (1983) to demethylate gamma globin and raise HbF
- Because of toxicity and fear of adverse effects, tried hydroxyurea… and it worked

- Ley TJ, DeSimone J, Noguchi CT, Turner PH, Schechter AN, Heller P, Nienhuis AW. 5-Azacytidine increases gamma-globin synthesis and reduces the proportion of dense cells in patients with sickle cell anemia. **Blood**. 1983 Aug;62(2):370-80.
- Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. **N Engl J Med**. 1995 May 18;332(20):1317-22.
- Costa E, Ware R, Tshilolo L, Luzzatto L. Thirty Years of Hydroxyurea for Sickle Cell Anemia - Scientific Progress, Global Health Gaps. **N Engl J Med**. 2025 Oct 23;393(16):1556-1559.

Hydroxyurea: first used about 30 years ago




Vascular effects
Cellular effects
Increased
HbF synthesis
Decreased HbS
polymerisation
Decreased RBC
membrane damage
Decreased Endothelial
activation and adhesion
Decreased
Hemolysis
Decreased
neutrophil count
Decreased thrombosis and
Microparticle formation
Increased
Hb synthesis
Decreased vasoconstriction
RBC
endothelium
CD44
Lu/BCAM
VCAM-1
CD47
CD36
TSP
α
δ

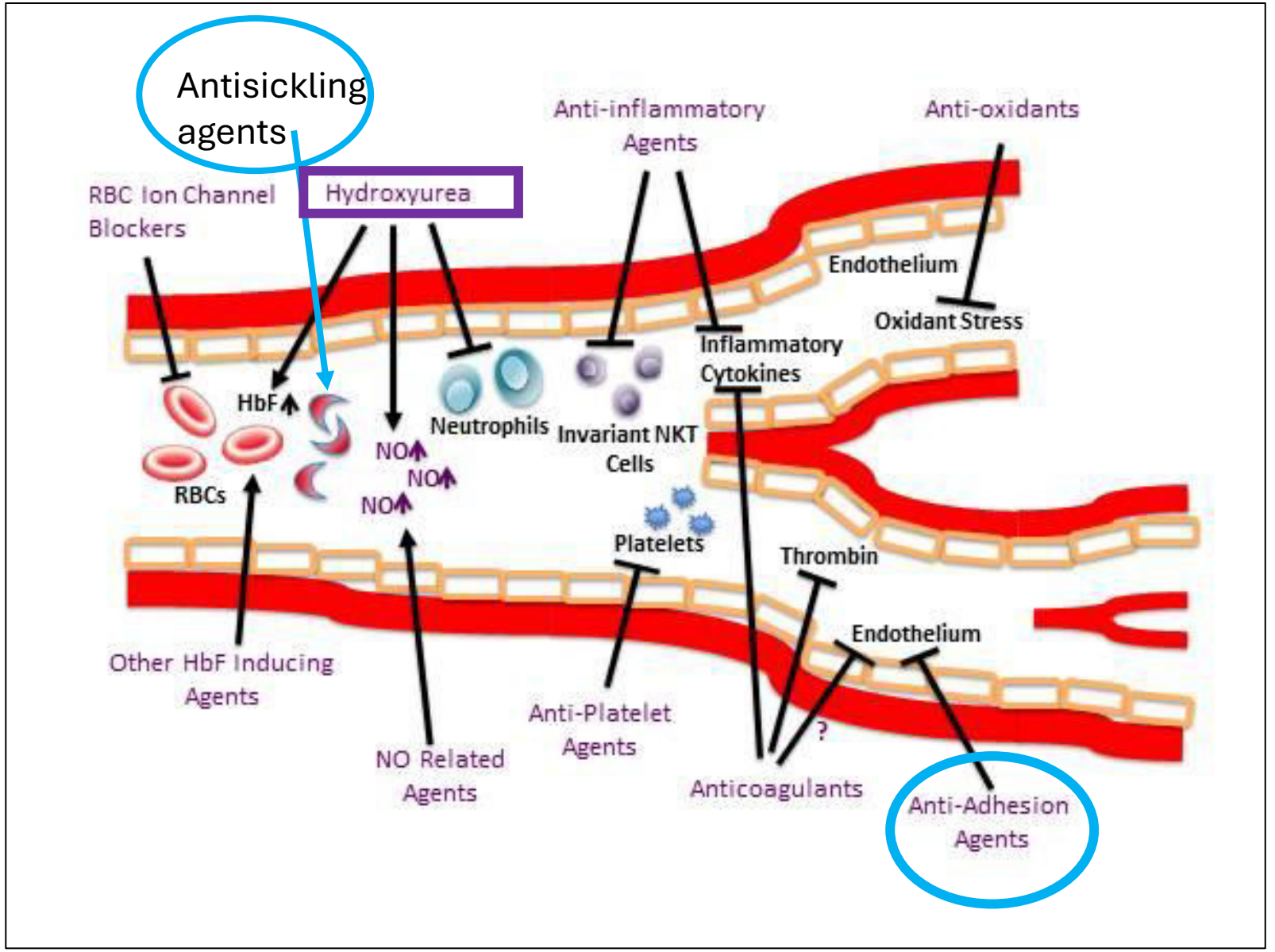
Hydroxyurea: Mechanisms of action

- Multiple mechanisms:
- 1. raises HbF which inhibits sickling (not all patients respond).
- 2. Reduces WBC and plts.
- 3. Increases nitric oxide.

AND MORE….reduces inflammatory markers, reduces hospitalizations, reduces vasooclusive events, reduces transfusions

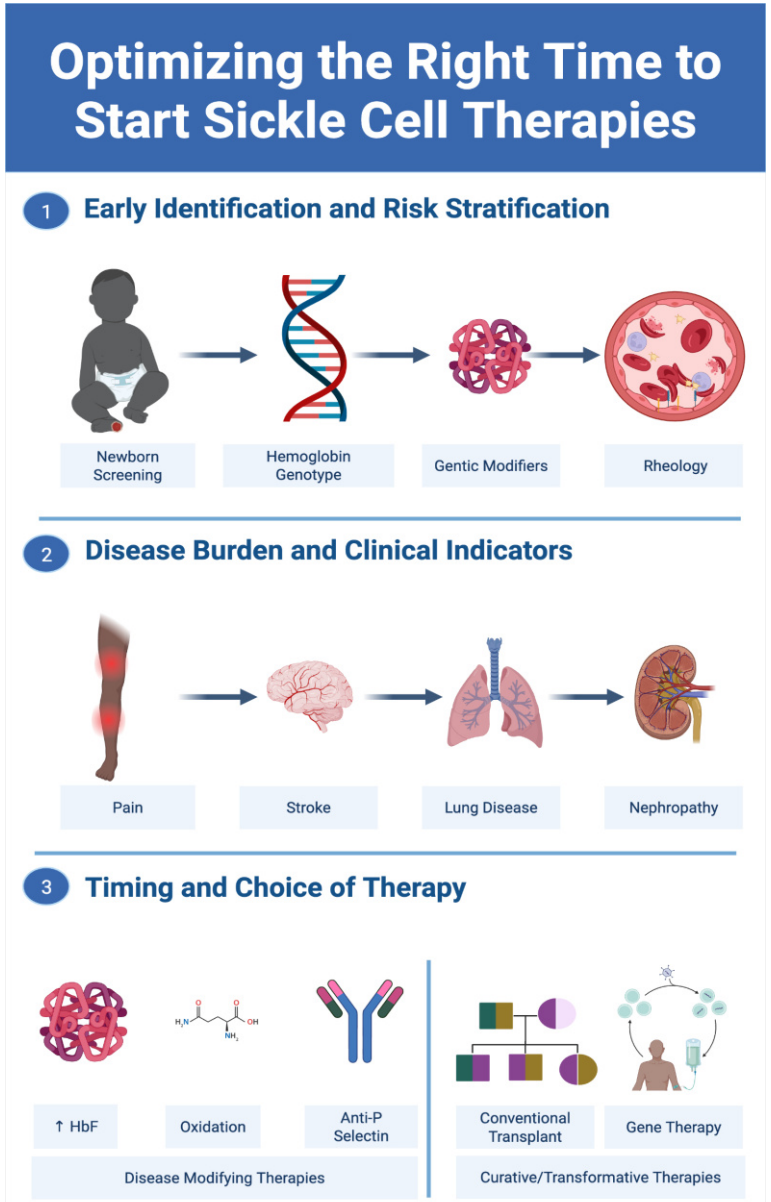
- Not ideal BUT it prolongs life, reduces crisis!!
- Over 100 interventional studies have been done which prove its benefits AND safety at doses 500 mg-1 gram a day (titrate dose according to WBC, Hb F level and also genotype, SC or S/beta thal get cytopenias more easily).
- FDA approved for adults in 1998 and children in 2005

Sickle cell: Treatment Possibilities



Advanced Therapies for Sickle Cell Disease

- Novel **pharmacological** therapies: now there are **none**…
- Two novel agents: Crizanlizumab (antiadhesion), Voxelotor (antisickling)
- Very frustrating chain of events….both fast tracked in 2019 and both either removed by pharma company or lost approval in 2025.
- Voxelotor… probably harmful
- Crizanlizumab… probably ineffective
- **Bone marrow transplantation**: need donor, costly! Impairs fertility.
- **Gene Therapy** with gene addition or gene editing: no donor needed but still need myeloablative chemo COSTLY! Impairs fertility. But it works!
- What is left?? Back to hydroxyurea.



Olufunke Y. Martin,Seethal A. Jacob, Optimizing the right time to start sickle cell therapies, Hematology Am Soc Hematol Educ Program, 2025,

Routine Care of Sickle Cell Patients: An ounce of prevention is worth a pound of cure

- I strongly suggest reading this if you have any sickle cell patients
- Recommendations are different in different locations (countries) and at different ages
- A lot will be different in Israel
- First recommendation is newborn screening which we don't have!
- **Genetic counseling** for parents: prenatal diagnosis??

- Jacob SA, Frei-Jones M, Saif-Ur-Rehman S, Hulbert ML, O'Brien ARW, Strunk C, Villella A, Talati R, Owusu-Ansah A, Coyne F, McGann PT, Rai P, Miller R, Rampersad A, Sakhalkar V, Bhasin N, Manwani D, Lanzkron S, Kanter J. National Alliance of Sickle Cell Centers Consensus Recommendations on Sickle Cell Disease Health Maintenance: A Consensus Statement. JAMA Netw Open. 2025 Nov 3;8(11):e2543421.

Routine Health Maintenance Sickle Cell

- It is vital that the patient see a specialist hematologist not just family doctor!
- Penicillin prophylaxis: starting at 2 months till age…? Not so sure when to stop
- Immunizations: obviously for encapsulated organisms also viral hepatitis, and usual childhood diseases. Some need extra doses.
- How often to see babies with Sickle cell, at what ages
- What lab tests to do in early childhood? Frequent CBC and retics to see baseline in first 2 years of life as HbF declines.
- Hb electrophoresis to see HbF levels.
- RBC phenotyping prior to first transfusion!

Routine Health Maintenance Sickle Cell

- Unfortunately children may already have painful crises and need to consider analgesia and even hydroxyurea (at 6 or 9 months of age)
- Follow CBC and HbF level to tailor dose (cytopenias? Adequate rise in HbF?
- Even for children who do not have frequent pain:
- Need to be aware of cerebrovascular disease! (high incidence of stroke before age 20!) Silent cerebral ischemia at earlier ages!
- This is assessed by TCD transcranial doppler. Can define risk!
- Very important to do developmental and cognitive assessment!
- Fall in IQ correlates with cerebral events, must try to prevent.
- Many studies show sickle cell children have significantly lower IQ which persists into adulthood.
- Neurocognitive studies show the deficits. Not just social deprivation.

Routine Health Maintenance Sickle Cell

- A lot of what I said sounds simple and obvious BUT

1. if you read the article there is a lot more detail, such as: what does the annual visit for patient with sickle cell comprise?

2. Even if it sounds obvious, auditing has been done and found great gaps in actual implementation of these standards

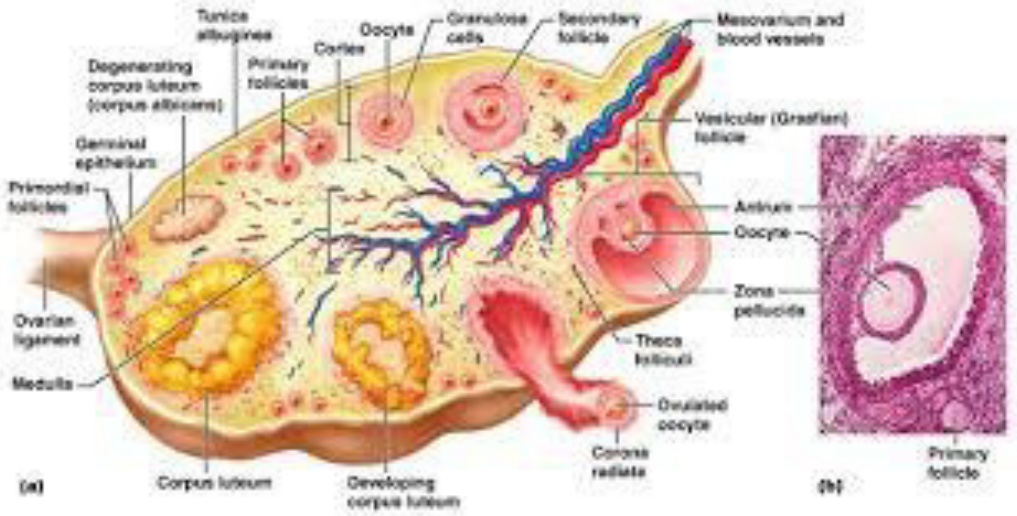
- These patients are difficult to take care of, they can be adversarial, manipulative…not easy! Sometimes the doctor wants to get the visit over with as fast as possible….Need social workers, etc.

Thank you for listening!

Does Hydroxyurea reduce fertility in MEN?

- The answer is unfortunately YES.
- See my lecture from last year for full discussion of this

Fertility: Male and Female
Sickle Cell Patients



Male fertility Sickle cell disease: Case of Sa. Am.

19 year old man from the north had been treated since age 10 with hydroxyurea. Moved to Jerusalem for studies and had a complicated course.

Occasional painful crises, he took his hydroxyurea irregularly

He was genetically sickle/thalassemia. Splenectomy in childhood. When off hydrea he had nearly 100% Hb S, no HbA and low HbF.

He had a severe painful crisis with acute chest syndrome and was admitted to the ICU in Hadassah.

He was treated with exchange transfusion….which is the right thing to do.

Sa. Am. (continued)

- Unfortunately the ICU staff did not understand that RBC exchange is not the same as plasma exchange and they thought he needed to continue this daily (like plasmapheresis for TTP), so he had a second RBC exchange the following day.
- The first RBC exchange went smoothly but during the second one he developed an acute hemolytic transfusion reaction with massive hemolysis, multiorgan failure with acute renal failure with LDH of 10,000 and acidosis required intubation and dialysis.
- He was in the ICU for 3 months….and survived with some neurological damage (apparently had a stroke) with mild aphasia and right sided weakness.

Sa. Am. (continued)

- He was discharged and returned to see me in clinic a few months later…with his fiancée!
- He was not able to continue school but he had previously been engaged to a young woman before this medical catastrophe and she was willing to marry him.
- And they married.
- He resumed hydroxyurea and took it with good compliance. HbF level went to 15%, no pain.
- Note this is not recommended after stroke but putting him on chronic exchange transfusion seemed risky. No alloantibody was identified…Maybe it was not a hemolytic transfusion reaction?

Sa. Am. continued

- They did not actually talk to me about getting pregnant…BUT:
- After a year of marriage his wife worried about not getting pregnant. They came to see me. (I would have told them to stop the hydroxyurea).
- Sperm testing showed severely reduced sperm count (nearly none).
- What is the cause of this and what can be done?
- I will present third case before I talk about what I tried to do and what is evidence regarding hydroxyurea.

Sm. Az. Case Presentation

- 22 year old male patient came to ER known homozygous sickle, on hydrea intermittently. Not followed regularly.
- Generalized pain but eventually the pain localized to scrotum
- Ultrasound showed what they thought was torsion of the testis
- Operating room: Partially infarcted testis! Which was removed (urologists said that otherwise it could cause immune reaction and infertility in contralateral testis?)
- Recovered, he was sent to cryopreserve sperm. No recurrence of gonadal sickling.
- He later married, had two children with IVF (due to problem his wife had), no fertility issues were known to me despite the fact that he had been on hydrea (intermittently) for years. (Not sure what age he started)

- Gofrit ON, Rund D, Shapiro A, Pappo O, Landau EH, Pode D. Segmental testicular infarction due to sickle cell disease. J Urol. 1998 Sep;160(3 Pt 1):835-6. This was cited many times!

Possible contributions of SCD itself to male infertility: not just therapy

Injury to testes due to local sickling with reduced spermatogenesis

Sexual dysfunction due to repeated priapism

Endocrinopathy due to iron overload?

Therapy : Hydroxyurea?

Difficult to sort out if boys get HU at early age prepubertal.

What did I do with my male patient who was on HU and wanted to get his wife pregnant?

- It was obviously too late for sperm cryopreservation.
- Perhaps I should have thought of it when I first met him?? Not much time really before he nearly died.
- To see if stopping hydrea would help, I sent him for exchange transfusion to keep his HbA over 40%
- Fortunately no hemolytic transfusion reactions
- After a YEAR his wife did get pregnant
- My main problem was: The kupah refused to pay for it!!!! Because there is no literature on restoration of fertility.
- In fact the scanty literature says fertility will not return BUT only reported on followup for 3 months. Maybe longer is needed??

Sa Am (continued)

- I had followed his sperm counts and there was some evidence that the sperm count was improving.
- Unfortunately the story has a very sad ending: before his wife gave birth, the patient died of acute postsplenectomy sepsis!
- He had a fever and died within hours of coming to HaEmek Hospital
- I don't have followup with his wife.

"Take home message:"

- If you ever decide to do this with a patient, please be careful what you write about the decision to do exchange transfusion in terms of getting hitchayvut. Probably I should have written that he needed it for prevention of recurrent stroke. Otherwise it is not "in the sal habriut"

For male patients after puberty: cryopreservation of sperm?

- Before starting hydroxyurea in a male patient YES! I would say this is MANDATORY for medicolegal reasons.
- Ample evidence in males that hydroxyurea can reduce sperm count.
- I don’t know what to suggest for pediatric patients
- Excellent summary of the scant literature:
- Sewaralthahab S et al, PLOSOne 2024. Effects of hydroxyurea on fertility in male and female sickle cell disease patients. A systemic review and meta-analysis. PLoS One. 2024 Jun 7;19(6):e0304241.

Fertility for women with sickle cell disease

- Do sickle cell women have trouble getting pregnant?
- Do they need fertility preservation if they are on hydroxyurea?
- Does the disease impair fertility like it does for male patients?

- The answers for women are less clear than for men.

“Ovarian Reserve” can be measured (also for patients with malignancy)

- Different ways of measuring ovarian reserve:

  indirect (AntiMullerian Hormone) (+/- FSH elevation) for patients post puberty (noninvasive)

OR

  directly (follicle count of ovarian tissue) for prepubertal also but this is invasive (done during preparation for BMT)

- **All ways of measuring ovarian reserve are imprecise** (see excellent summary table in Pecker LH, Cameron K. Sickle cell disease and infertility risks: implications for counseling and care of affected girls and women. Expert Rev Hematol. 2024 Aug;17(8):493-504)

Excellent recent articles on female or both M/F

- Pecker LH, Hussain S, Mahesh J, Varadhan R, Christianson MS, Lanzkron S. Diminished ovarian reserve in young women with sickle cell anemia. Blood. 2022 Feb 17;139(7):1111-1115.
- Sewaralthahab S, Alsubki LA, Alhrabi MS, Alsultan A. Effects of hydroxyurea on fertility in male and female sickle cell disease patients. A systemic review and meta-analysis. PLoS One. 2024 Jun 7;19(6):e0304241.
- Pecker LH, Oteng-Ntim E, Nero A, Lanzkron S, Christianson MS, Woolford T, Meacham LR, Mishkin AD. Expecting more: the case for incorporating fertility services into comprehensive sickle cell disease care. Lancet Haematol. 2023 Mar;10(3):e225-e234.
- Pecker LH, Cameron K. Sickle cell disease and infertility risks: implications for counseling and care of affected girls and women. Expert Rev Hematol. 2024 Aug;17(8):493-504.

Female Infertility in SCD: is it a problem?

- The results of the literature are not consistent and reflect different populations studied. Prepubertal girls: Follicle count is good whether or not got hydroxyurea. (VERY low amount of data).
- It is not so clear that hydroxyurea is nontoxic, Pecker's results suggest that hydroxyurea can contribute to infertility (1st article on previous slide).
- It is also less clear that sickle crises contribute to *female* infertility
- The results vary depending on the age of the patients studied. Older women showed no difference with or without HU therapy. All Sickle cell women have decline in fertility with age. But they seem to have faster decline for their ages.

Female fertility preservation: how?

- Not standard to preserve eggs or ovary slices before hydroxyurea
- One publication on girls under 14 did not suggest that HU caused low follicle count… study done before BMT.
- However nearly all studies show that women with SCD have lower ovarian reserve than women without SCD..have kids earlier?
- Warning: low intensity conditioning (RIC) prior to BMT does NOT protect against loss of fertility for Sickle cell

- Nickel RS, Maher JY. RIC does not do the trick to prevent the high infertility risk in females with sickle cell disease after hematopoietic cell transplantation. Transplant Cell Ther. 2023 Sep;29(9):537-538.

Summary: These issues are important

- Important to take into consideration and have open discussions with patients
- Reluctance to use hydroxyurea because of impaired fertility is a consideration
- Desire to have children is now considered normal because sickle cell patients live longer!
- Individual discussion…..