SICKLE CELL UPDATES, GUIDELINES, AND MORE 2021

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DISCLOSURES

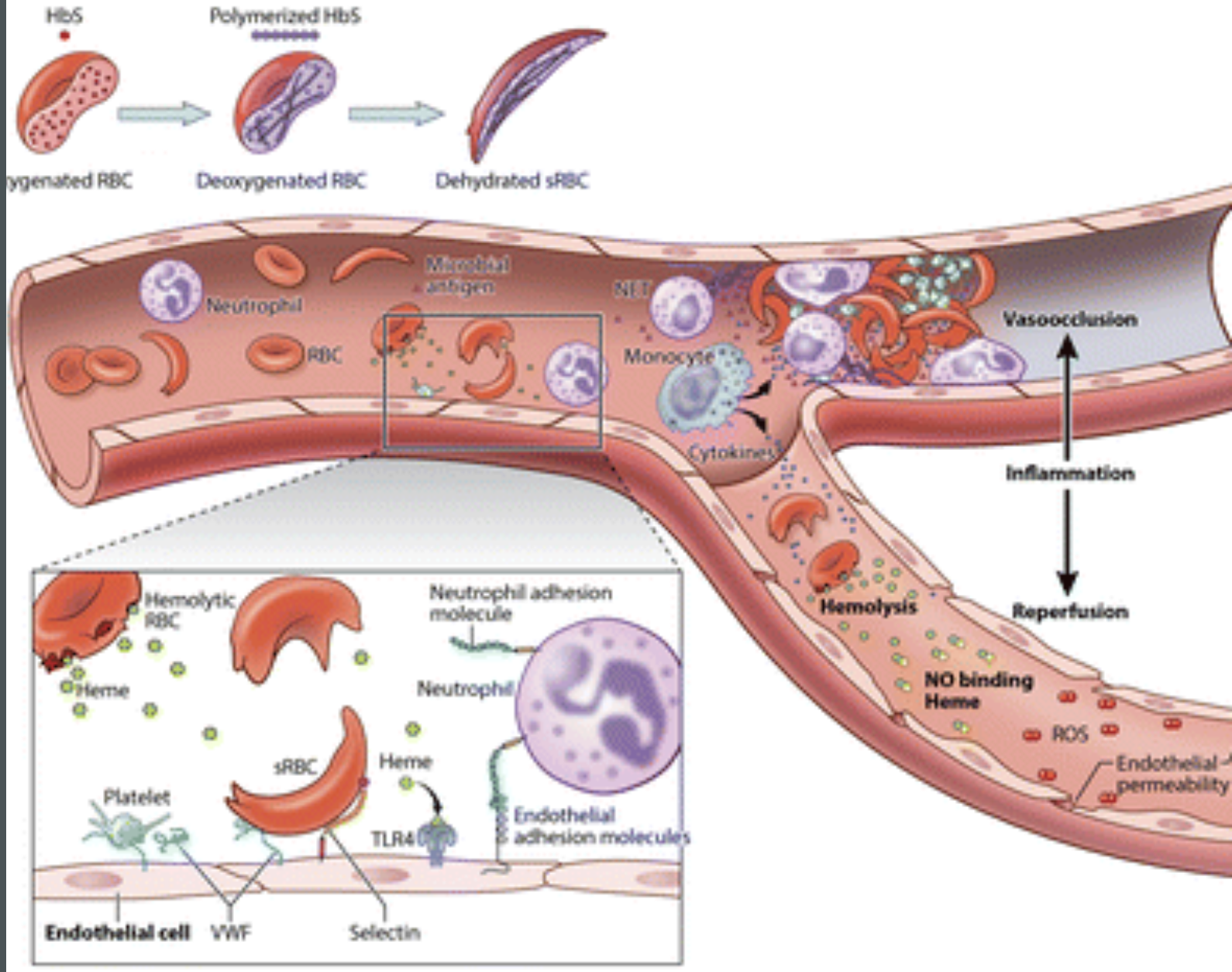
- No Relevant Disclosures

OUTLINE

- Pathophysiology
- Therapeutic Interventions
- ASH Guidelines 2020
- COVID-19

PATHOPHYSIOLOGY

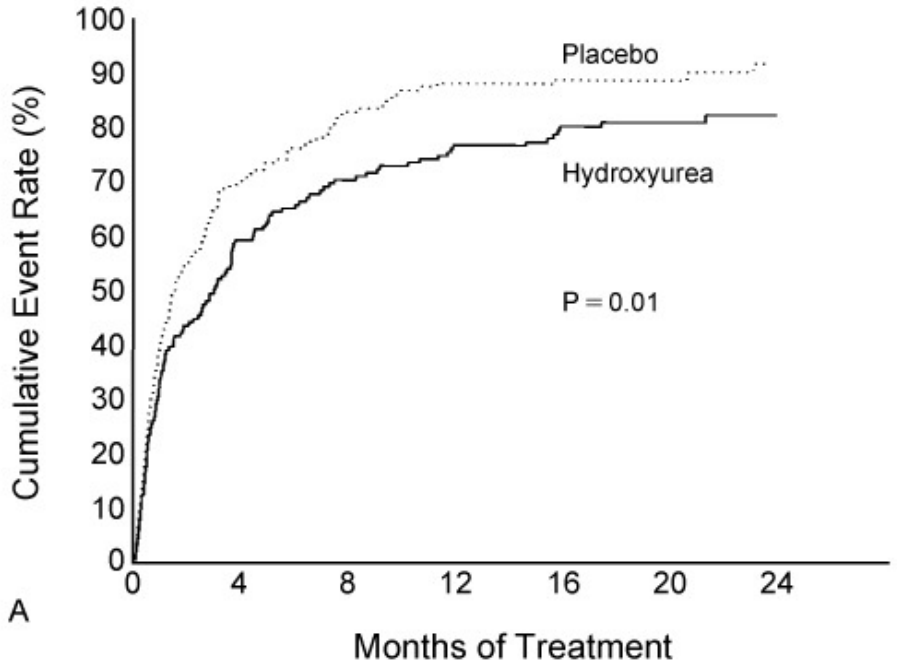
- RED CELLS POLYMERIZE AND FORM SICKLED SHAPE WHEN DEOXYGENATED
- SLUDGE IN VASCULATURE, RBCS A DHERE TO EACH OTHER, CAUSE INFLAMMATION, OXIDATIV E INJURY AND MEMBRANE DAMAGE
- DECREASE NITRIC OXIDE PRODUCTION
- ISCHEMIA AND NECROSIS IN VITAL ORGANS-LUNGS, SPLEEN, CEREBRAL ARTERIES, CORONARY ARTERIES, BONES

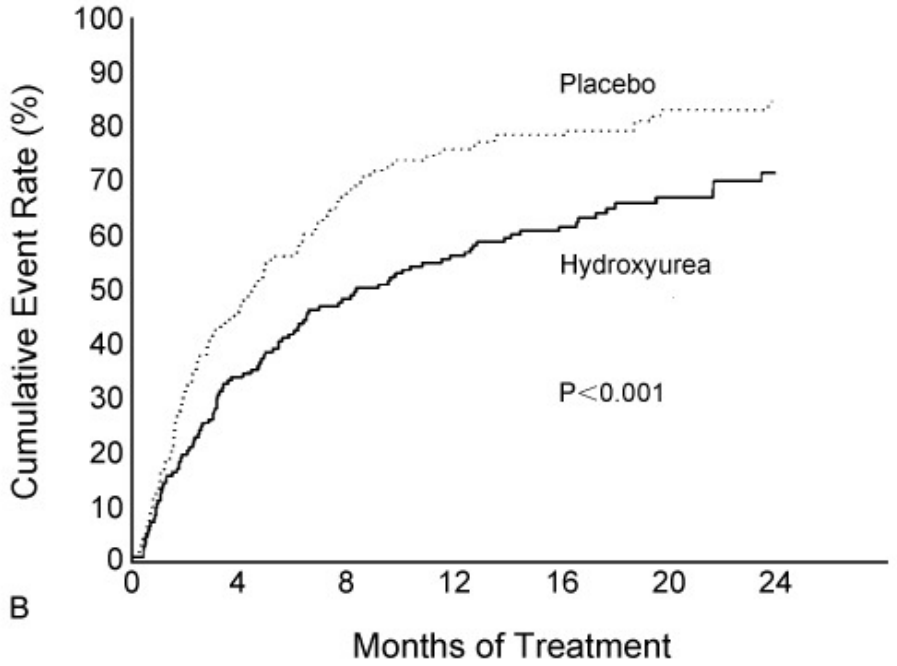


Williams TN, Thein SL. 2018.
Annu. Rev. Genom. Hum. Genet. 19:113–47

THERAPEUTIC INTERVENTIONS

- **Hydroxyurea**
- L-glutamine
- Voxelotor
- Crizanlizumab
- Transplant
- Gene Therapy





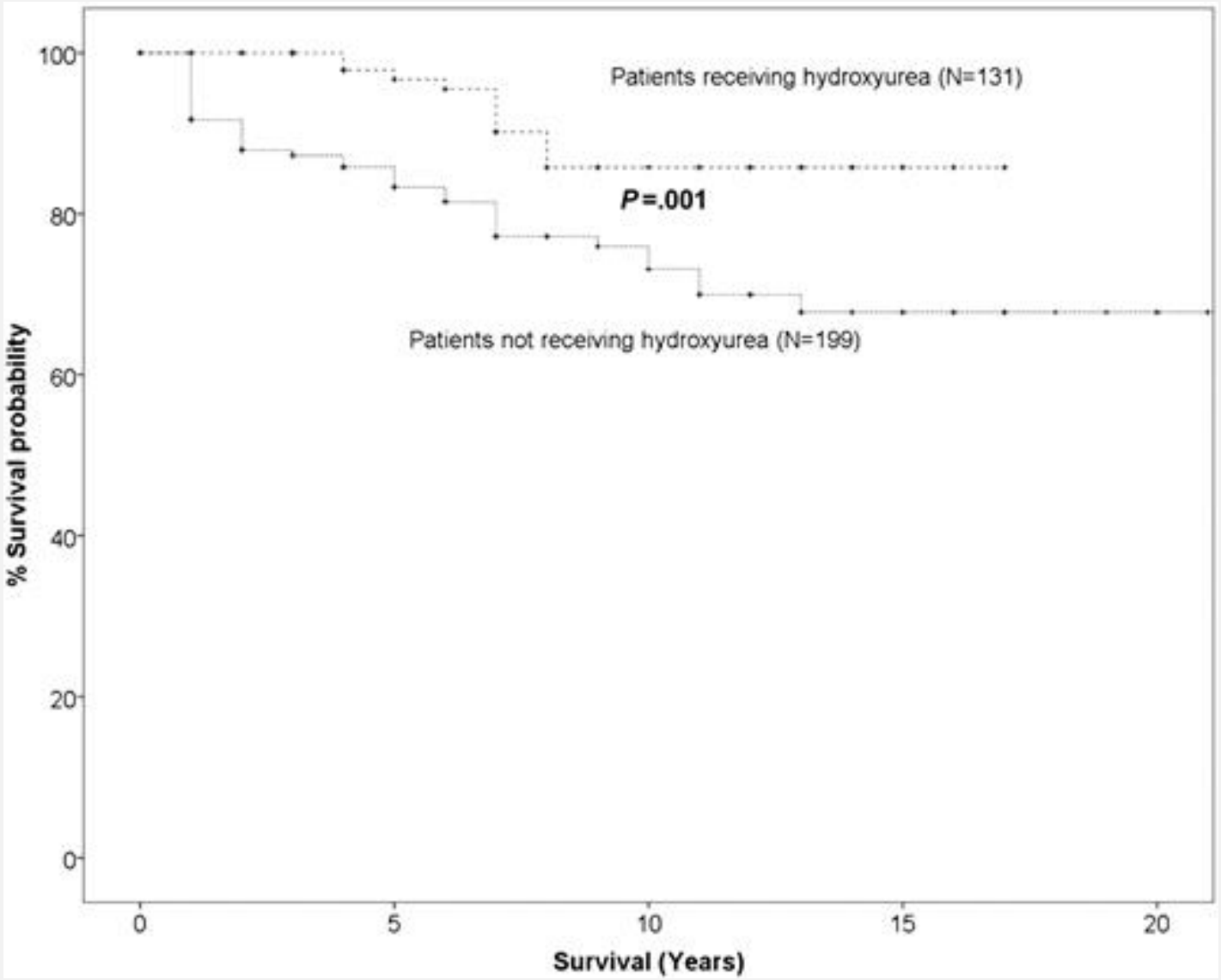
HYDROXYUREA

- Primary outcome: Pain-visit to medical facility lasting longer than 4 hours requiring parenterally administered narcotics
- Pain crisis: median rate 2.5 crises per year in hydroxyurea arm compared to 4.5 crises per year in placebo
- Increase in MCV correlated with HgbF
- Secondary outcomes
  - Acute chest syndrome: 25 hydrea vs 51 placebo arm
  - Transfusions: 48 h

http://www.nejm.org/doi/full/10.1056/NEJM199505183322001#t=article

HYDROXYUREA AND SURVIVAL

- ONLY MEDICATION TO IMPROVE SURVIVAL IN SICKLE CELL PATIENTS
- MULTICENTER STUDY OF HYDROXYUREA(MSH) IMPROVED SURVIVAL OVER 10 YEARS
- PATIENTS >16 YEARS OLD WITH 3+ PAIN CRISES PER YEAR
- 330 PATIENTS WITH SS AND SBETA THAL
- 10 YEAR SURVIVAL FOR HU PATIENTS WAS 86% AND NON HU PATIENTS WAS 65%



Voskaridou, Ersi et al "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* 115.12 (2010): 2354-2363. Web. 11 Dec. 2018.

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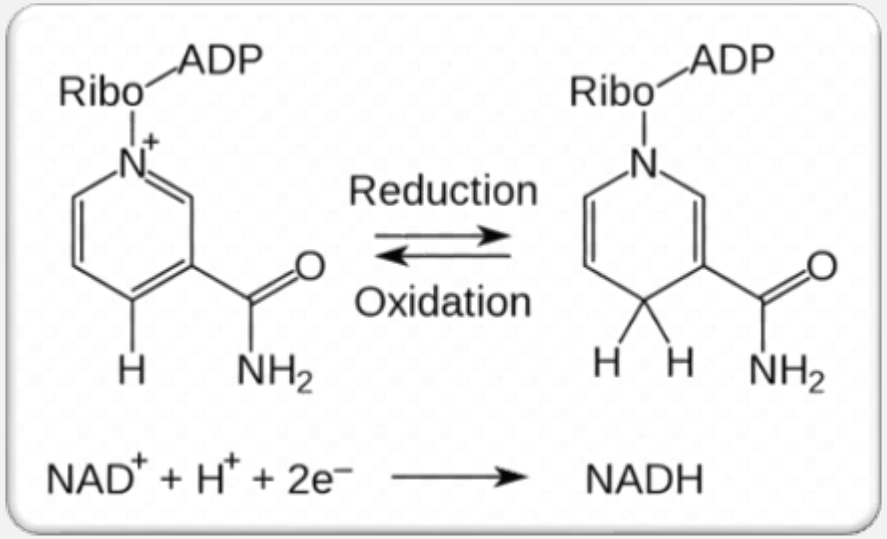
L GLUTAMINE

- FDA APPROVED FOR SICKLE CELL DISEASE JULY 2017
- L GLUTAMINE PRECURSOR TO NAD AND NADH, A NATURAL ANTIOXIDANT
- L GLUTAMINE REDUCES
- OXIDATIVE STRESS
- RBC ADHESION
- VASO-OCCLUSION
- PAIN CRISES



L GLUTAMINE

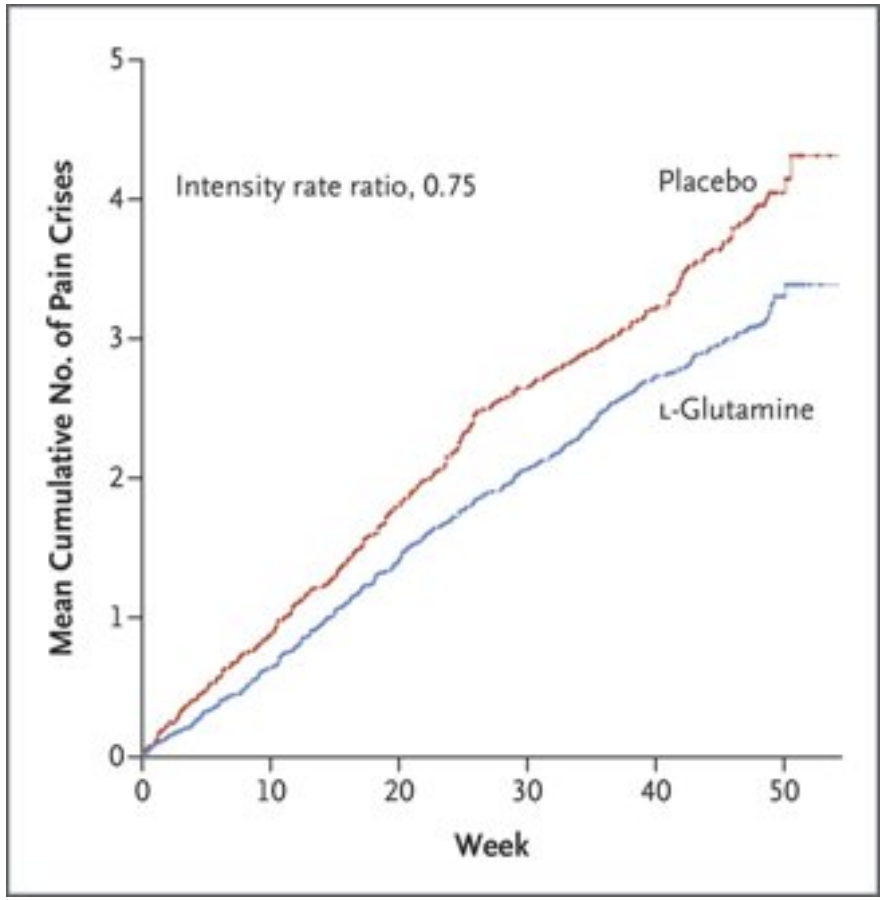
PRIMARY ENDPOINT WAS REACHED - REDUCTION IN MEDIAN SICKLE CELL CRISIS PER YEAR OF 4 TO 3

REDUCE MEDIAN NUMBER OF HOSPITAL FROM 11 TO 6 DAYS

REDUCE BLOOD TRANSFUSIONS PERCENTAGE OF PATIENTS WITH 3+ SIMPLE TRANSFUSIONS FROM 24 TO 12%

EXCHANGE TRANSFUSIONS REDUCED FROM 6.4 TO 2%

Oral L-glutamine Emmaus Medical, Inc. Oncologic Drugs Advisory Committee Briefing Document 24 May 2017



Y Niihara et al. N Engl J Med 2018;379:226-235.

THERAPEUTIC INTERVENTIONS

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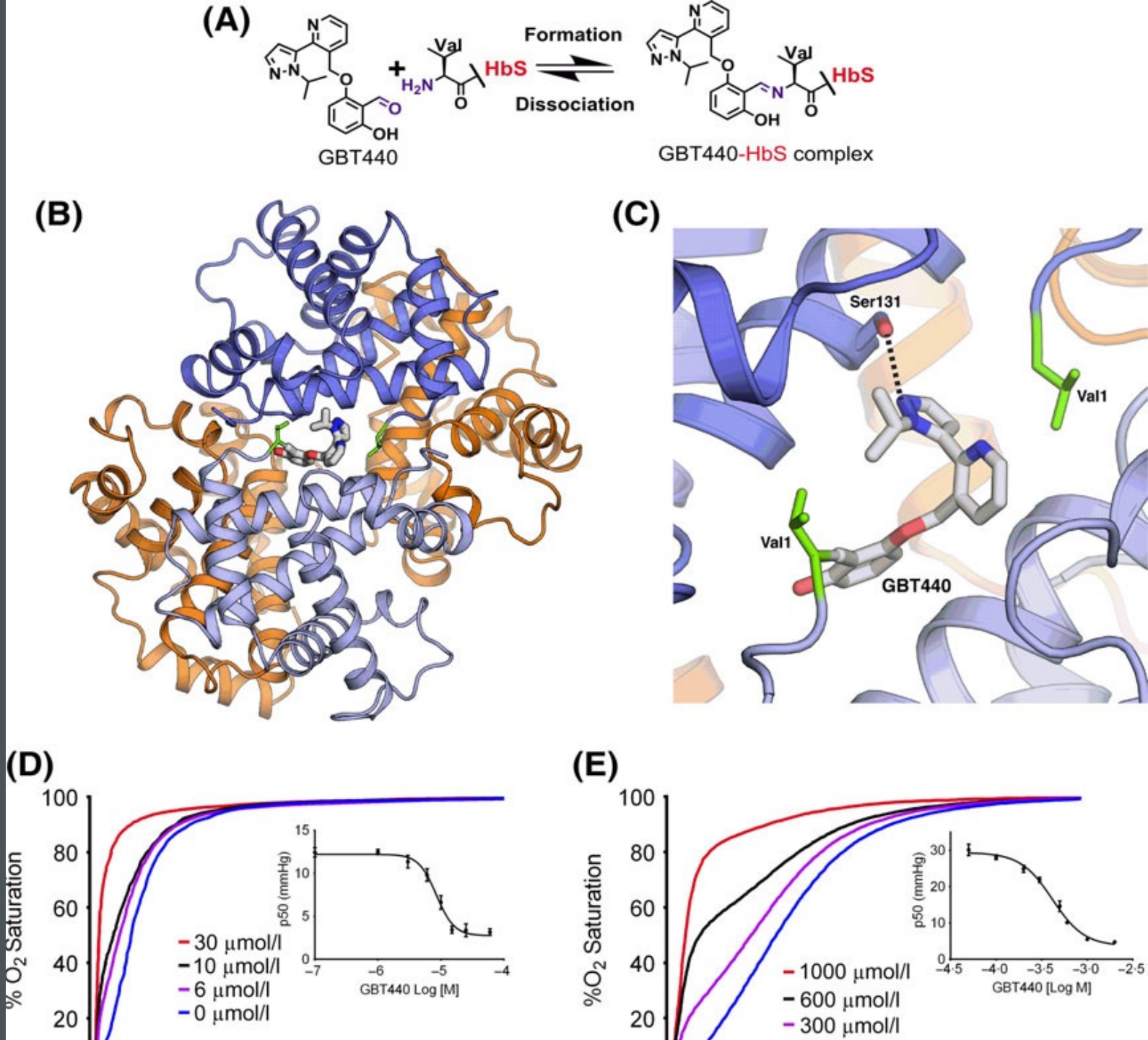
VOXELOTOR

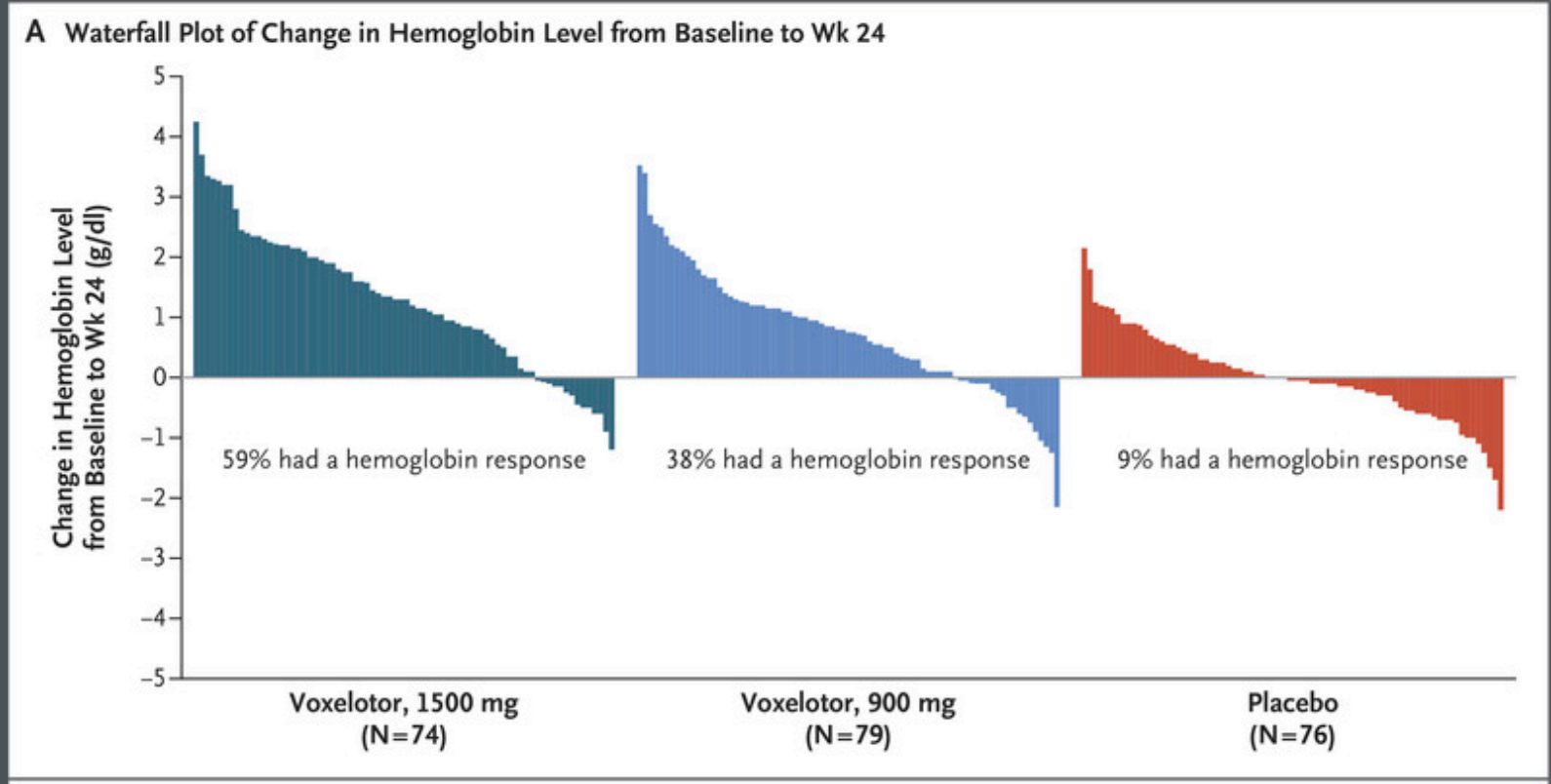
- Hemoglobin modifier
- Binds to the N terminus of the alpha chain-->modifies Hgb structure-->increases oxygen affinity
- Known mechanism: Hgb S in hypoxic conditions, polymerizes, sickled red blood cells
- By increasing HgbS affinity for oxygen--->more oxygenated HgbS, delay polymerization and sickling

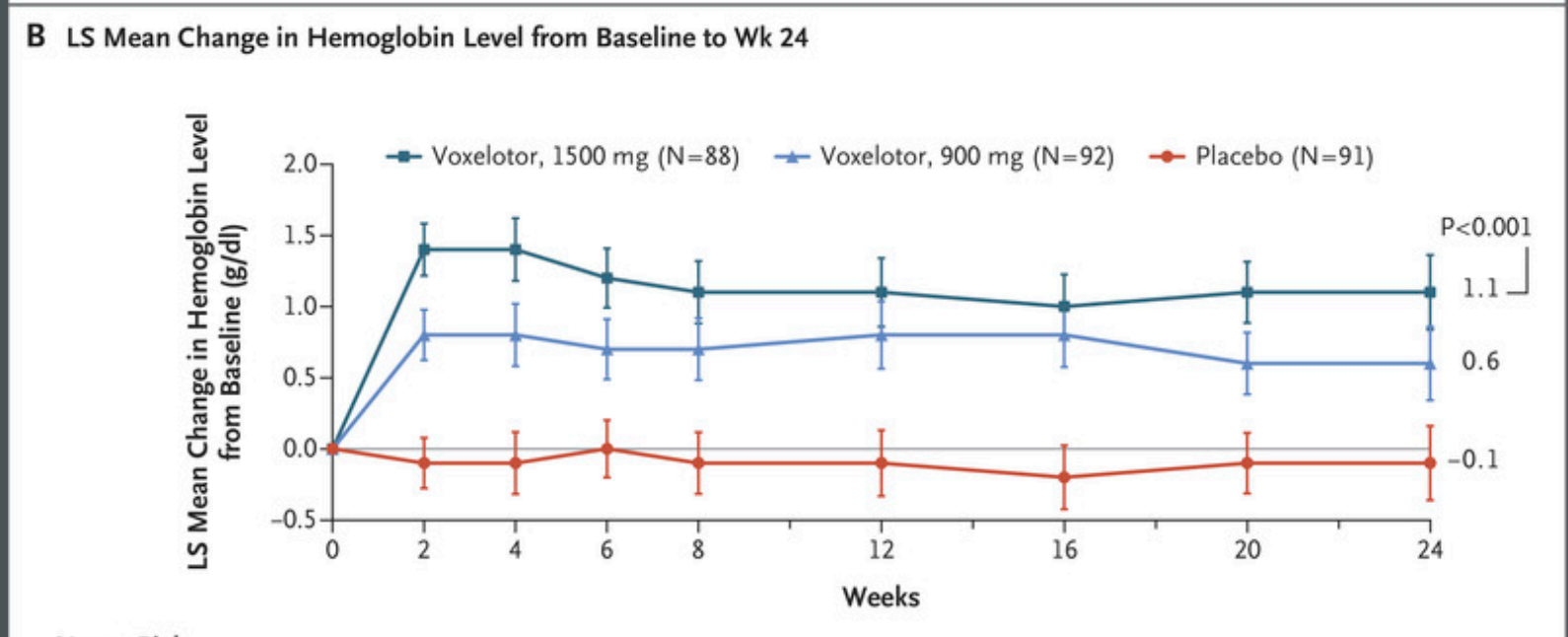
Oksenberg, D., Dufu, K., Patel, M.P., Chuang, C., Li, Z., Xu, Q., Silva-Garcia, A., Zhou, C., Hutchaleelaha, A., Patskovska, L., Patskovsky, Y., Almo, S.C., Sinha, U., Metcalf, B.W. and Archer, D.R. (2016), GBT440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. Br J Haematol, 175: 141-153. doi:10.1111/bjh.14214



VOXELOTOR

- Nov 2019, FDA approved based on HOPE trial
- Patients 12-65 years old
- 1500mg, 900mg, and placebo
- Primary endpoint was increase in hemoglobin by 1 gram or more after 24 weeks
- 51% of patients who received 1500mg dose achieved endpoint





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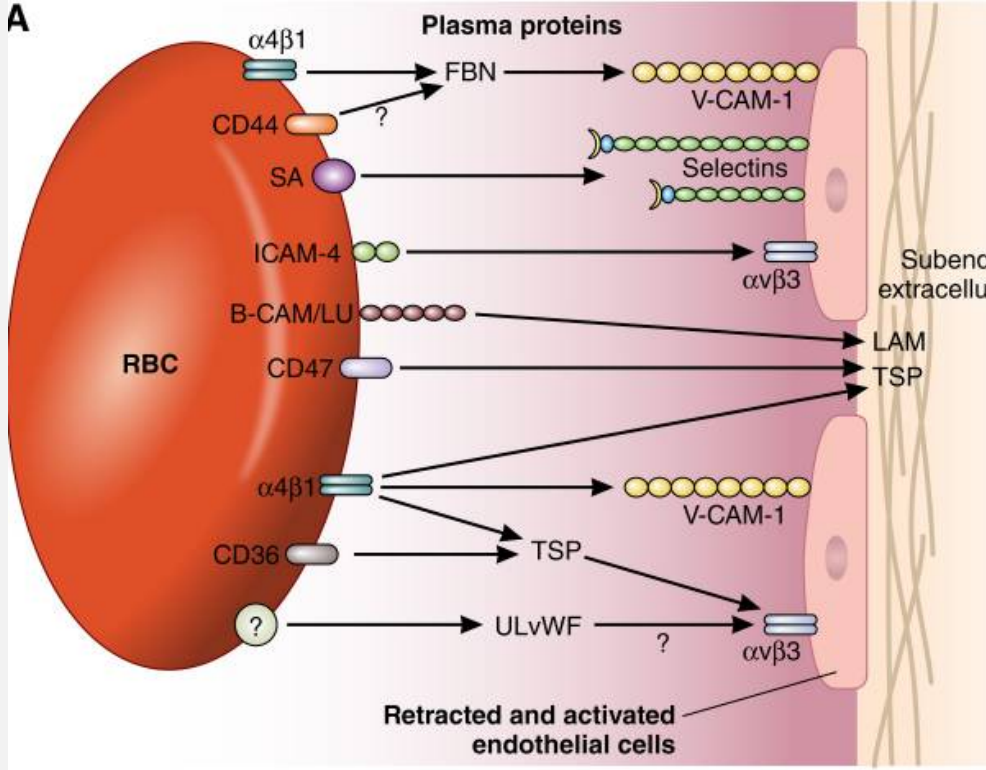
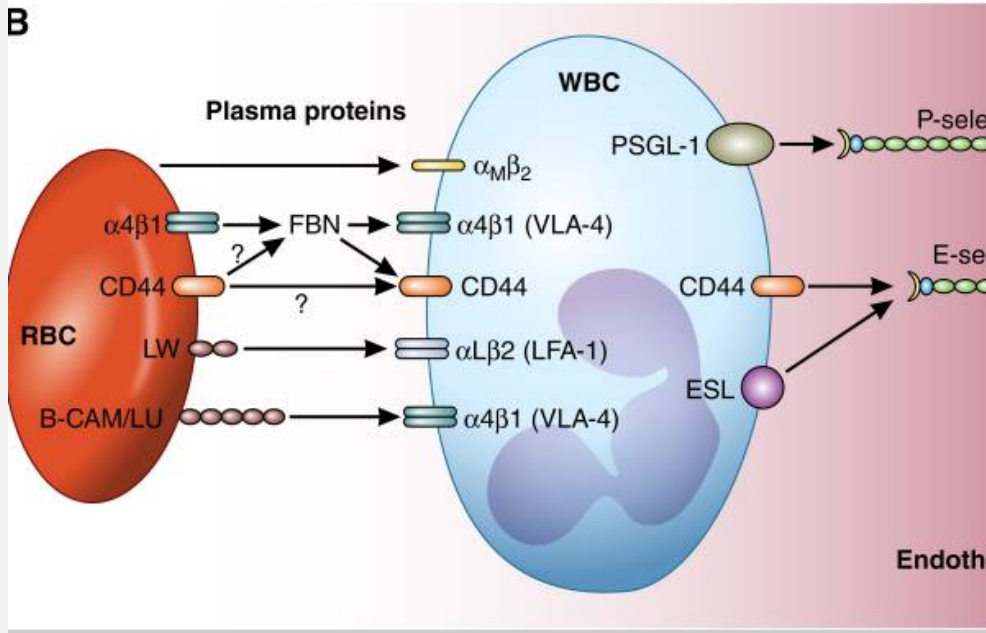
CRIZANLIZUMAB

- SELECTINS: GROUP OF ADHESION MOLECULES AFFECT CELL MIGRATION AND ACTIVATION
- P SELECTIN(PLATELET AND ENDOTHELIAL CELLS)
- E SELECTIN(ENDOTHELIAL CELLS)
- P AND E SELECTIN AFFECT THE INITIAL STEP IN VASO-OCCLUSION: BINDING SICKLE CELLS AND LEUKOCYTES TO ENDOTHELIUM
- P SELECTIN FOUND IN STORAGE GRANULES IN PLATELETS AND ENDOTHELIAL CELLS-->DURING INFLAMMATION-->TRANSFERS TO THE CELL SURFACE





CRIZANLIZUMAB

- Phase 2 multicenter, randomized, placebo controlled double blind study
- Sickle cell disease patients with or without hydroxyurea and 2-10 pain crises in the last year
- Crizanlizumab given 14 times in 52 weeks in high dose 5mg/kg, low dose 2.5mg/kg, or placebo

Table 1. Characteristics and Baseline Values of the Patients in the Intention-to-Treat Population.*

Characteristic	High-Dose Crizanlizumab (N = 67)	Low-Dose Crizanlizumab (N = 66)	Placebo (N = 65)
Age — yr			
Median	29	29	26
Range	16–63	17–57	16–56
Sex — no. (%)			
Male	32 (48)	30 (45)	27 (42)
Female	35 (52)	36 (55)	38 (58)
Race — no. (%)†			
Black	60 (90)	62 (94)	60 (92)
White	4 (6)	2 (3)	3 (5)
Other	3 (4)	2 (3)	2 (3)
Sickle cell disease genotype — no. (%)			
HbSS	47 (70)	47 (71)	47 (72)
Other‡	20 (30)	19 (29)	18 (28)
Concomitant hydroxyurea use — no. (%)			
Yes	42 (63)	41 (62)	40 (62)
No	25 (37)	25 (38)	25 (38)
Sickle cell–related pain crises during previous 12 mo — no. (%)			
2–4 crises	42 (63)	41 (62)	41 (63)
5–10 crises	25 (37)	25 (38)	24 (37)

Table 2. Annual Rates of Sickle Cell–Related Pain Crises.*

Variable	High-Dose Crizanlizumab	Low-Dose Crizanlizumab	Placebo
Primary end point: annual rate of crises in the intention-to-treat population			
No. of patients	67	66	65
Median rate of crises per year (IQR)	1.63 (0.00–3.97)	2.01 (1.00–3.98)	2.98 (1.25–5.87)
Difference from placebo — %	–45.3	–32.6	—
P value	0.01	0.18	—
No. of patients with crisis rate of zero at end of trial	24	12	11

CRIZANLIZUMAB

- Primary endpoint was the annual rate of sickle cell related pain crisis with high dose Crizanlizumab versus placebo
- Crizanlizumab given at 5mg/kg dose had a statistically significant reduction in median annual rate of VOC compared to placebo of 45.3%

THERAPEUTIC INTERVENTIONS

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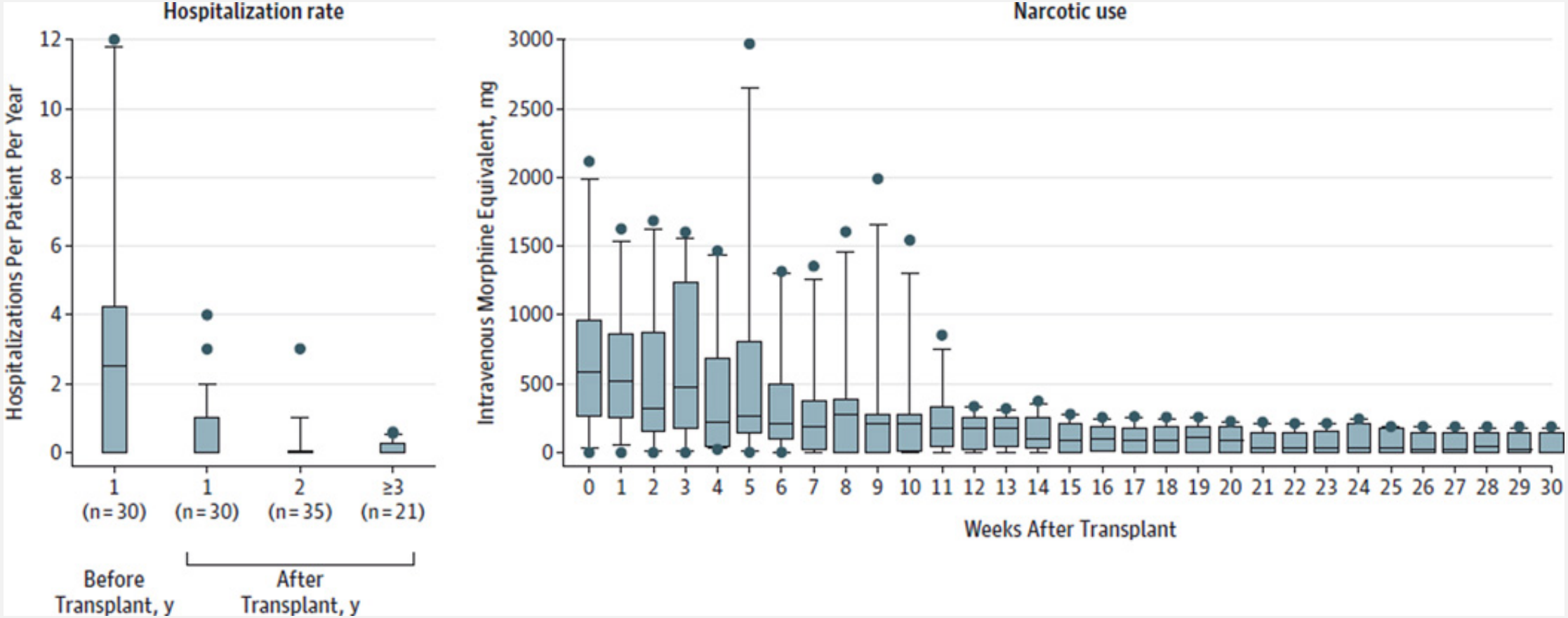
SICKLE CELL AND TRANSPLANT

- **1984: AN 8 YEAR OLD GIRL WITH SICKLE CELL DISEASE AND ACUTE MYELOID LEUKEMIA HAD A STEM CELL TRANSPLANT**
- MATCHED SIBLING DONOR, RECEIVED A MYELOABLATIVE REGIMEN, CURED FROM SICKLE CELL DISEASE AND ACUTE MYELOID LEUKEMIA
- 2014 NIH ADULT STUDY NONMYELOABLATIVE REGIMEN ON MATCHED SIBLING DONORS
- 30 PATIENTS, 26 ENGRAFTED, AND 25 PATIENTS FULL DONOR HGB



Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-Matched Sibling Allogeneic Hematopoietic Stem Cell Transplantation for Severe Sickle Cell Phenotype. *JAMA*. 2014;312(1):48–56. doi:10.1001/jama.2014.7192

TRANSPLANT

- PROS
  - FIRST AND ONLY CURRENT CURE
  - MIXED CHIMERISM ABLE TO REVERSE SICKLE PHENOTYPE
  - GOOD OUTCOMES WITH MATCHED RELATED DONORS
  - NONMYELOABLATIVE CONDITIONING REGIMENS HAVE DECREASED END ORGAN DAMAGE AND MORTALITY IN ADULTS
- CONS
  - ALLOGENEIC
  - AVAILABILITY OF MATCHED RELATED DONORS
  - HAPLOIDENTICAL-HIGHER RISK OF REJECTION
  - NONMYELOABLATIVE REGIMENS-HIGH RISK OF GRAFT FAILURE
  - GVHD

Kassim AA, Sharma D. Hematopoietic stem cell transplantation for sickle cell disease: The changing landscape. Hematol Oncol Stem Cell Ther. 2017;10(4):259–66. doi: 10.1016/j.hemonc.2017.05.008.

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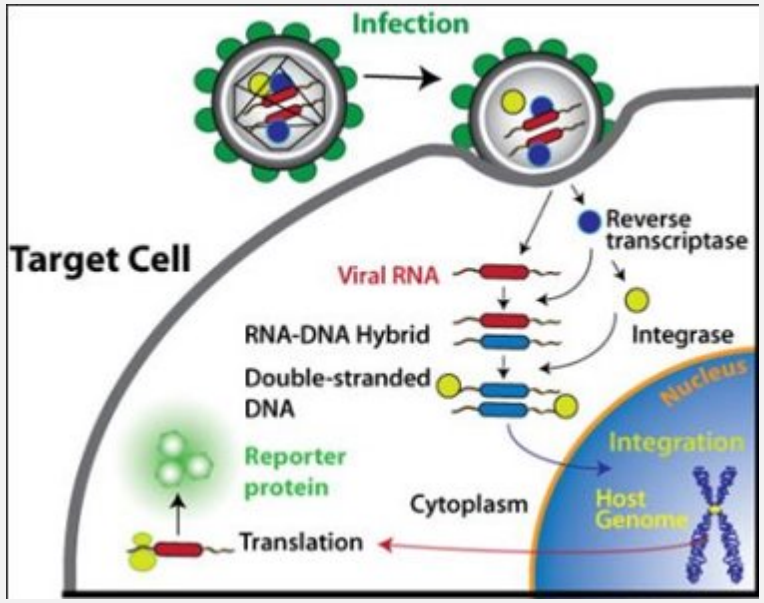
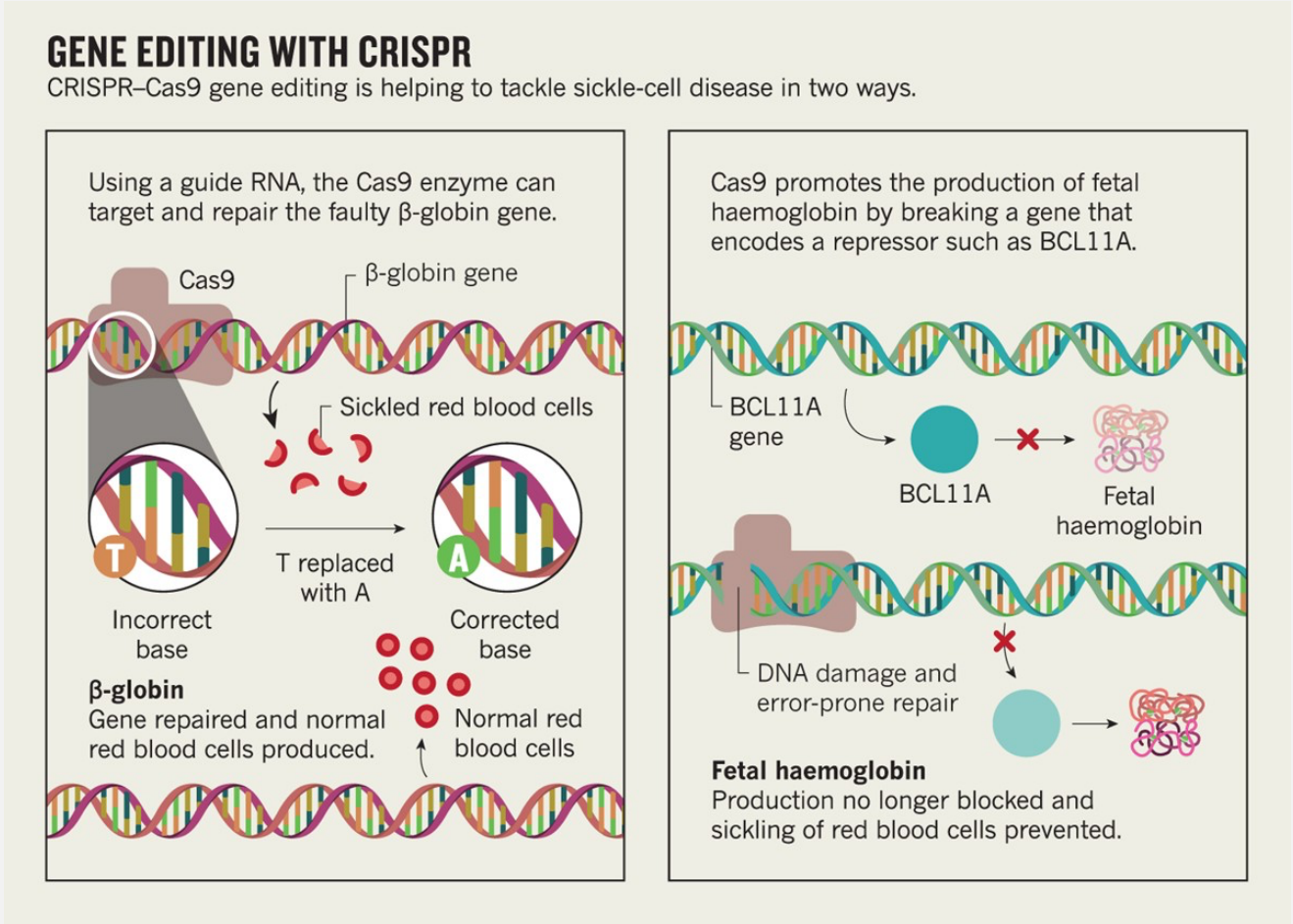
GENE THERAPY

- **Gene addition strategy**
- **Introduce genes to produce non sickled hemoglobin**
- **Introduction process**
  - Vectors insert DNA into host genome
  - Retroviruses like lentivirus
    - contain RNA genes,
    - reverse transcriptase: transcribe RNA into DNA
    - Integrase: to an integrate viral DNA into a host
- Stem cells containing new DNA or transduced cells are transplanted into patient
- Bluebird Bio T87Q



GENE THERAPY

- GENE EDITING
- BCL11A REPRESSOR GENE OF HGB F
- CRISPR TARGETS AND REPAIRS BCL11A GENE TO INCREASE PRODUCTION OF HGB F
- PERSISTENCE OF HGB F CHANGES PHENOTYPE



Bourzac, K. Gene therapy: Erasing sickle-cell disease. *Nature* **549,** S28–S30 (2017). https://doi.org/10.1038/549S28a

OUTLINE

- Pathophysiology
- Therapeutic Interventions
- ASH Guidelines 2020
- COVID-19

NEW ASH GUIDELINES

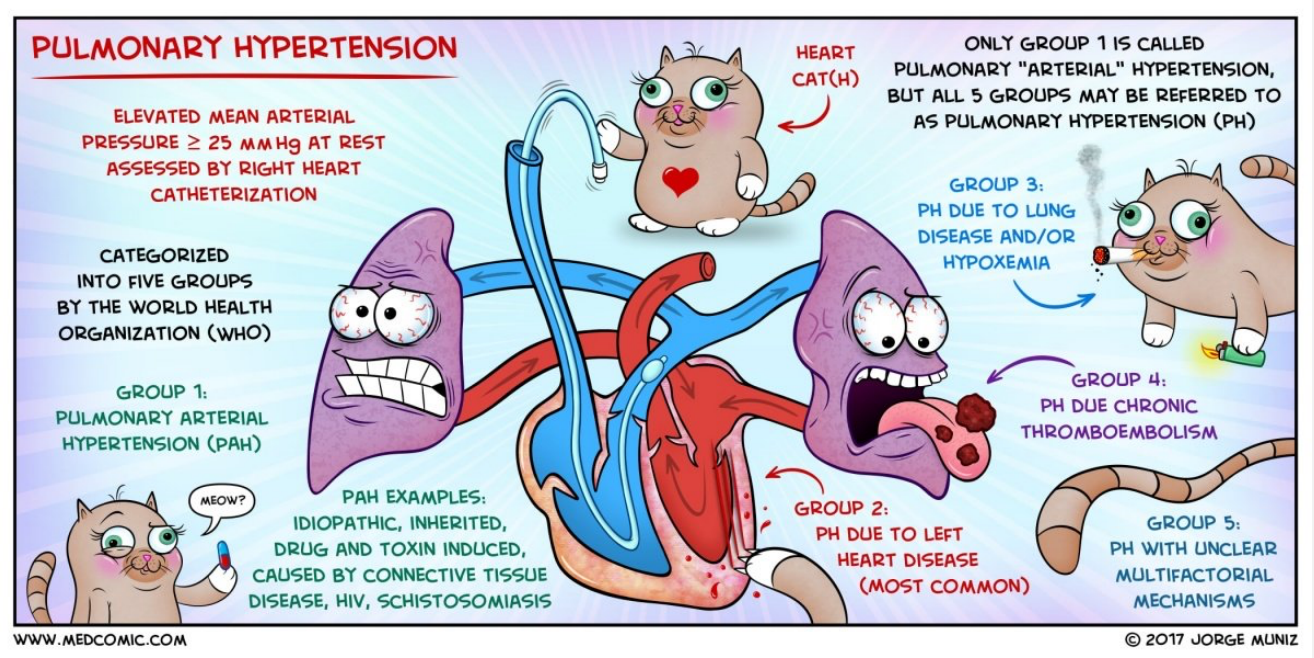
- Ongoing Process
  - Available data and evidence to form guidelines
  - Some guidelines based on low quality evidence with expert opinion
  - Long overdue, last update 2014
- Dec 2019-released new updates
  - Cardiopulmonary
  - Kidney Disease
  - Transfusion
  - Cerebrovascular Disease

CARDIOPULMONARY GUIDELINES

- Screening for pulmonary hypertension
- Management of VTE

PULMONARY HYPERTENSION

- Asymptomatic patients
  - Do not do screening echo
- Symptomatic patients
  - Echo or referral to PAH consultant
    - SOB/ Hypoxia/ Chest pain at rest/exertion
    - Unexplained exercise limitation
    - Sleep disordered breathing
    - Syncope/presyncope
    - Heart failure or fluid overload on exam
    - Pulmonary embolism history



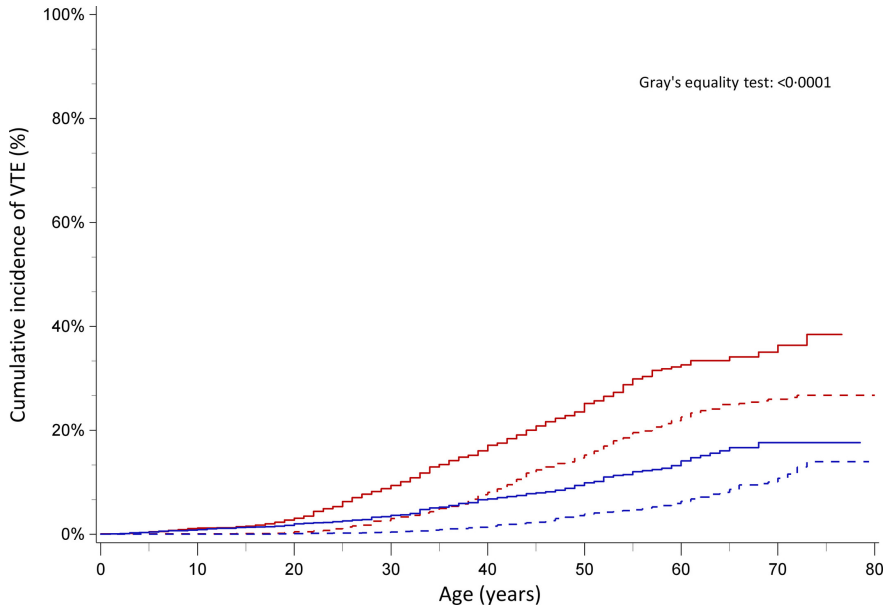
HYPERTENSION AND VTE

Blood Pressure goal of <130/80

VTE

- First unprovoked VTE→indefinite anticoagulation
- First provoked VTE→3-6 months of anticoagulation
- Recurrent provoked VTE→indefinite anticoagulation

British Journal of Haematology, Volume: 178, Issue: 2, Pages: 319-326, First published: 03 April 2017, DOI: (10.1111/bjh.14655)



Cumulative incidence of incident acute venous thromboembolism (VTE) among African-American sickle cell disease (SCD) patients compared to matched hospitalized African-American asthma patients, by SCD severity/average hospitalizations, California, 1991–2013. SCD patients with severe disease (solid red line); Asthma patients averaging ≥3 hospitalizations per year (dashed red line); SCD patients with less severe disease (solid blue line); Asthma patients averaging <3 hospitalizations per year (dashed blue line). African-American SCD patients matched 1:3 on sex, age (±2 years), and year (±2 years) and hospital frequency to African-American asthma patients.

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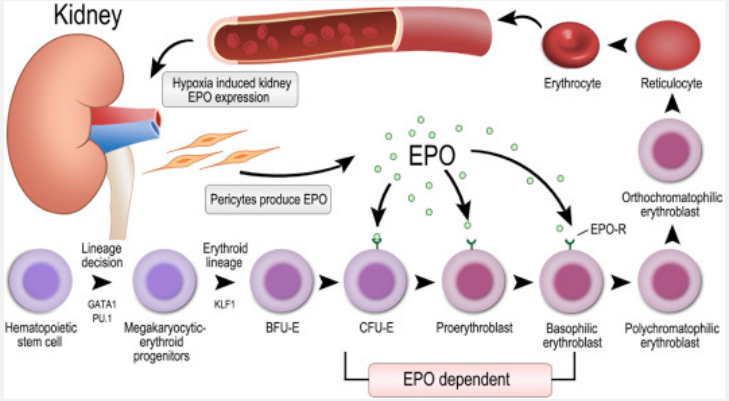
KIDNEY DISEASE

- Management or albuminuria
  - Suggests use of ACE inhibitor and ARBs for albuminuria
- Management of End-Stage Renal Disease
  - For Advanced CKD or ESRD, refer to transplant
- CKD and anemia
  - Combination of EPO agents and hydroxyurea
    - Consider if Drop in Hemoglobin and Retic Count
    - Maximizes Hemoglobin F
    - Don't exceed 10g/dl due to risk of stroke or VTE



Lin et al, Physiology and pathophysiology of renal erythropoietin-producing cells https://doi.org/10.1016/j.jfma.2018.03.017.

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TRANSFUSIONS

- Transfusion Support
- Exchange Transfusions
- Pregnancy
- Surgeries
- Iron Overload

TRANSFUSION SUPPORT

- Extended red cell typing with genotyping or serology
- DHTR
  - Prevention: Immunosuppressive therapy for patients with acute need for transfusion and high risk for hemolytic transfusions reactions
  - Treatment: Immunosuppressive therapy for patients with DHRT and hyperhemolysis

- DHTR Definition
  - Drop in Hemoglobin within 21 days of transfusion plus one or more of the following:
    - New red cell alloantibody
    - Hemoglobinuria
    - HbS% increase with a concomitant fall in HbA posttransfusion
    - Relative reticulocytopenia or reticulocytosis from baseline
    - Significant LDH rise from baseline

TRANSFUSIONS

Transfusion Support

Exchange Transfusions

Pregnancy

Surgeries

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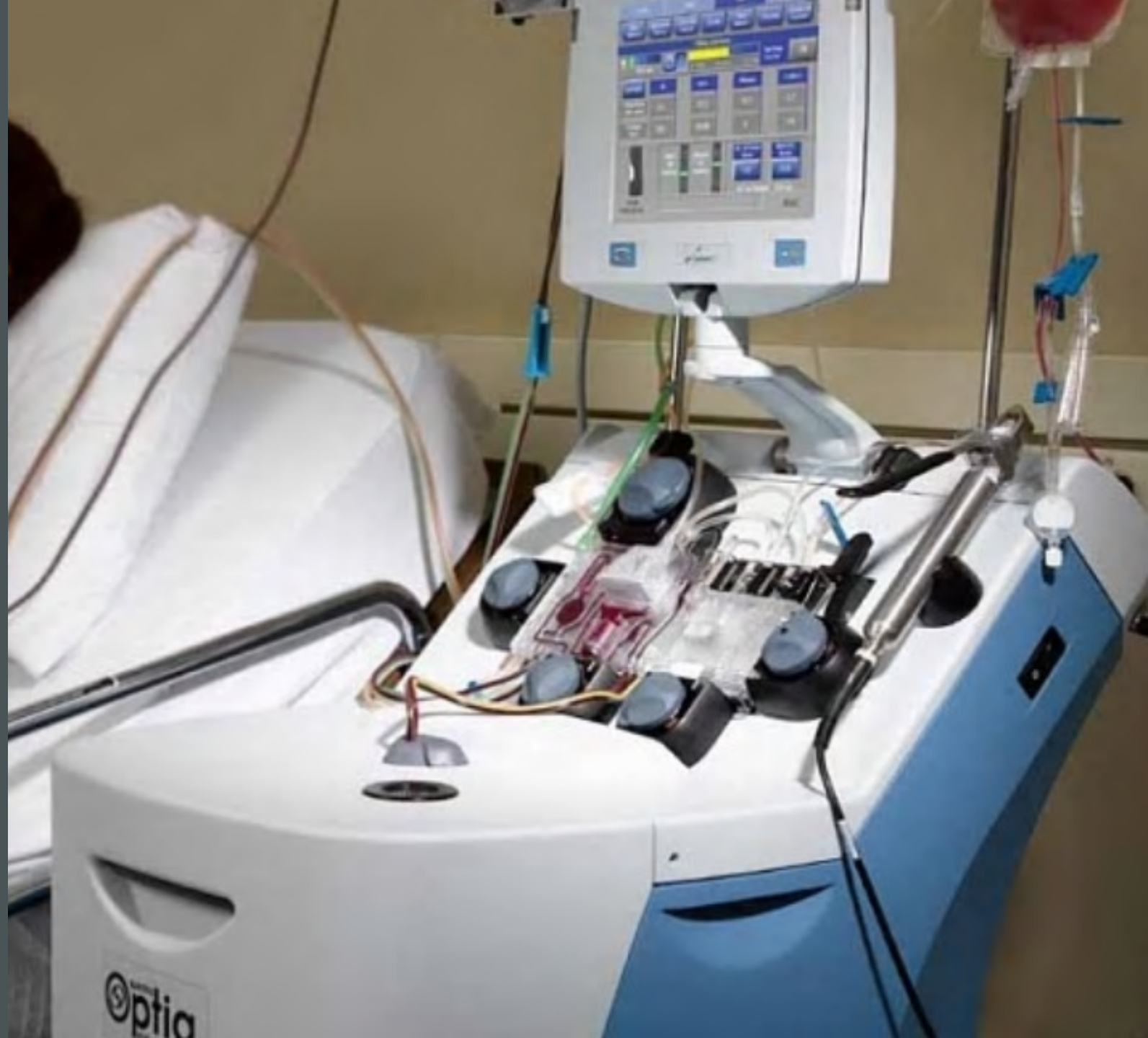
EXCHANGE TRANSFUSIONS

- Severe Acute Chest Syndrome
  - Hypoxia, Pulmonary Infiltrates, Respiratory Distress, Drop in Hemoglobin despite Simple Transfusion
- Stroke
  - Reduce Hemoglobin S below 30%
  - Automated exchange preferred over manual exchange



TRANSFUSIONS

Transfusion Support

Exchange Transfusions

Pregnancy

Surgeries

Iron Overload

TRANSFUSION AND PREGNANCY

- Standard of Care or Prophylactic Transfusions
- Prophylactic Transfusions
  - Meta-analysis of 12 observational and 1 RCT
    - Reduction of maternal mortality, VOC, pulmonary complications, perinatal mortality, preterm birth
  - History of SCD complications in prior pregnancies
    - Recurrent pain Episodes
    - Acute Chest Syndrome
    - Comorbidities

Table 4

Outcomes in cohort studies of prophylactic transfusion compared with on-demand transfusion in pregnant women with SCD (cohort studies)

Group	Outcomes	Studies, n	Study subject, n	OR (95% CI)	Significance (heterogeneity), *P* (I^2)
Maternal	Mortality	7[14,15,18,26-29]	955	0.23 (0.06-0.91)	.04 (20%)
	Vaso-occlusive pain episodes	11[10,15,17-19,26-30]	1219	0.26 (0.09-0.76)	.01 (90%)
	Pulmonary complications*	9[10,15,17-19,26-28,30]	1019	0.25 (0.09-0.72)	.01 (77%)
	Pulmonary infection	5[18,19,26-28]	792	0.26 (0.05-1.27)	.10 (83%)
	Pulmonary embolism	3[19,26,28]	237	0.07 (0.01-0.41)	<.01 (1%)
	Acute chest syndrome	2[15,17]	102	0.28 (0.06-1.26)	.10 (0%)
	Urinary tract infection	3[15,29,30]	149	1.09 (0.22-5.42)	.92 (61%)
	Pyelonephritis	6[15,19,26-29]	455	0.19 (0.07-0.51)	<.01 (34%)
	Endometritis	2[26,29]	80	0.76 (0.17-3.44)	.72 (40%)
	Preeclampsia	6[10,14,15,17,26,29]	282	1.01 (0.49-2.08)	.98 (0%)
Fetal	Perinatal mortality	8[10,15,18,19,26-28,30]	1140	0.43 (0.19-0.99)	<.05 (58%)
	Intrauterine fetal demise	8[14,15,17,19,26,28-30]	458	0.47 (0.17-1.33)	.15 (32%)
	Neonatal death	5[15,19,26,28,30]	374	0.26 (0.07-0.93)	.04 (0%)
	Small for gestational age/low birth weight	10[10,15,17-19,26-30]	1187	0.71 (0.44-1.16)	.17 (35%)
	Preterm delivery	9[10,15,17-19,27-30]	1123	0.59 (0.37-0.96)	.03 (38%)

TRANSFUSIONS

- Transfusion Support
- Exchange Transfusions
- Pregnancy
- **Surgeries**
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TRANSFUSION AND SURGERIES

- Preoperative Transfusion is indicated if General Anesthesia over 1 hour
  - Simple transfusion if Hgb<9
  - Exchange transfusion if Hgb >9 and high risk surgery(neurosurgery or cardiac surgery)
  - TAPS trial: multicenter children and adults with HgbSS and Hgb S beta thal undergoing surgery
    - Preoperative transfusions reduced complications

Table 3. Numbers of clinically important complications and serious adverse events

	No preoperative transfusion (n=33)	Preoperative transfusion (n=34)	Overall (n=67)
Number of patients with clinically important complications (%)	13 (39%)	5 (15%)	18 (27%)
Number of clinically relevant complications			
All related to sickle-cell disease	12	3	15
Acute chest syndrome	9	1	10
Acute pain crisis	3	1	4
CNS	0	1	1
Surgery-related	4	1	5
Infection-related	0	1	1
Transfusion-related	0	0	0
Other	0	1	1
Total	16*	6†	22
Number of patients with complications classified as SAEs (%)	10 (30%)	1 (3%)	11 (16%)

CNS=central nervous system. SAEs=serious adverse events.

* Three patients had two complications.

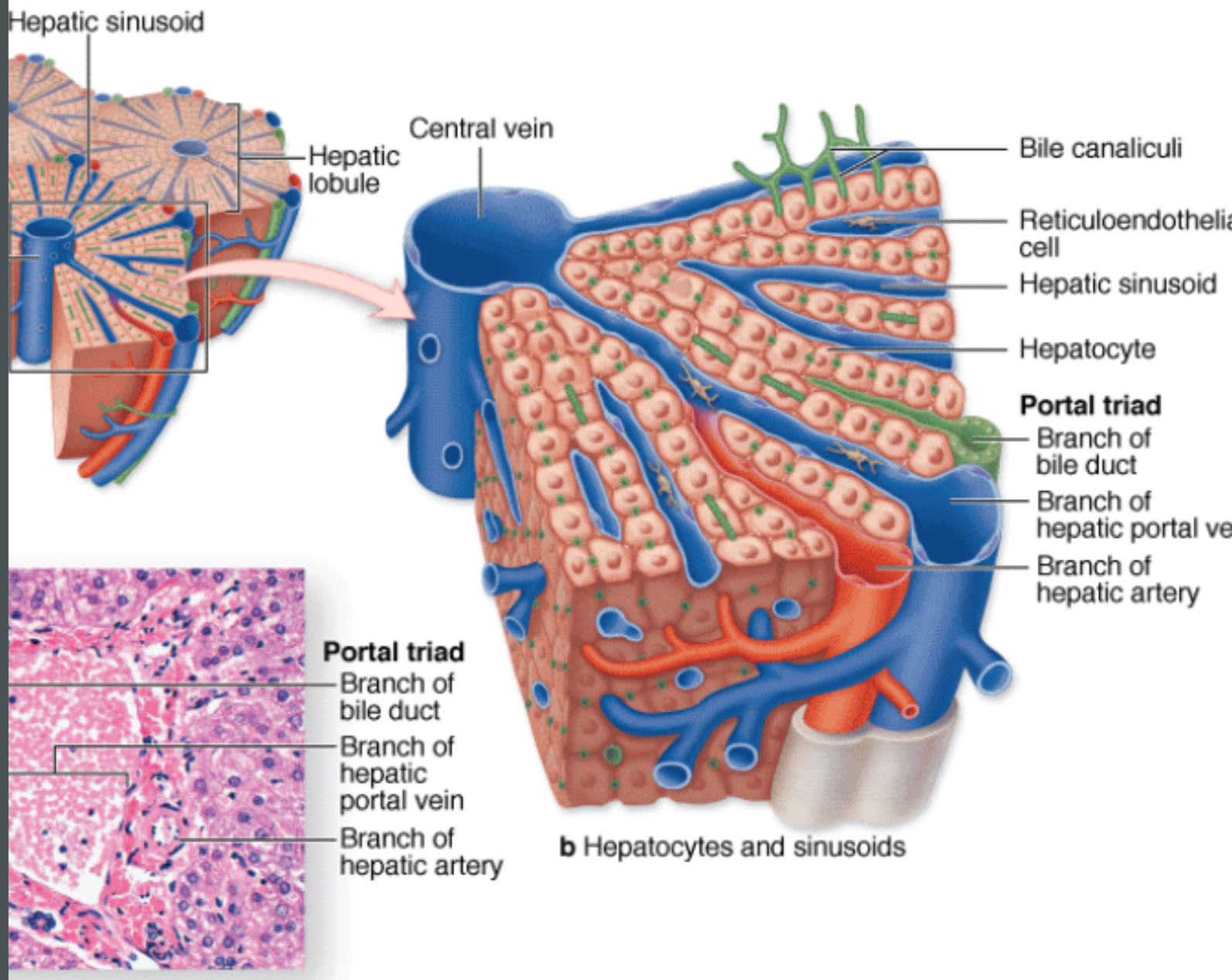
† One patient had two complications.

TRANSFUSIONS

- Transfusion Support
- Exchange Transfusions
- Pregnancy
- Surgeries
- **Iron Overload**

TRANSFUSIONS AND IRON OVERLOAD

- Screening MRI for Liver Iron Concentration every 1-2 years with ferritin in patients on chronic transfusions
- If Ferritin<1000 can consider omitting MRI
- Cardiac MRI if LIC>15mg/g/dw or cardiac dysfunction or evidence of organ damage from iron overload
- https://www.mrgscience.com/d3-function-of-the-liver-core.html



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CEREBROVASCULAR DISEASE

Treatment and Prevention

TPA?

Silent Infarcts

CVA TREATMENT AND PREVENTION

- Neurologic Deficits
  - Acute neurological change→transfusion immediately(simple or exchange) within first 2 hours
- TIA or Stroke
  - Exchange transfusion within first 2 hours
  - Simple transfusion if Hgb<8.5 and exchange is not available
- Secondary Stroke Prevention
  - Hemoglobin >9 and HgbS<30%
    - Strong recommendation on low quality evidence
  - If Moya-moya→evaluate for revascularization surgery

CEREBROVASCULAR DISEASE

Treatment and Prevention

TPA?

Silent Infarcts

TPA VS EARLY TRANSFUSION

- TPA consider
  - If Neurologic symptoms<4.5 hours
  - No hemorrhage on CT
  - Does not delay transfusion
  - Comorbidities: older age, atrial fibrillation, hypertension, hyperlipidemia, hypertension, and diabetes

for adults with sickle cell disease presenting with acute ischemic stroke having had a CT scan excluding hemorrhage within 4

Imprecision	Other considerations	Impact
not serious	none	A total of 3 out of 61 (4.9%) patients and 9 out of 290 (3.2%) patients hemorrhage in the sickle cell disease and non-sickle cell disease resp
not serious	none	None of the patients in the SCD group developed life-threatening syst (0.7%) patients in the non-SCD group developed life-threatening syst up.
not serious	none	A total of 4/61 (6.6%) patients in the SCD group developed any type o (6.0%) patients in the non SCD group developed any type of serious

me of Lytic Therapy in Acute Ischemic Stroke: Findings From Get With The Guidelines-Stroke. Stroke; 2017.

CEREBROVASCULAR DISEASE

Treatment and Prevention

TPA?

Silent Infarcts

SCREENING FOR SILENT INFARCTS

- Up to 50% of adults with SS or Sbeta thal have silent infarcts
- Presence of silent infarcts predicts future neurologic injuries
- Associated with Decrease in IQ
- Eligible of individual education plans and Disability services

- Recommendations
  - All patients should have a 1 time MRI
  - Patients with infarcts should consider
    - Transfusions or transplant
    - Cognitive screening with psychologist or PCP
    - Repeat MRI every 12-24 months to assess progression

OUTLINE

Pathophysiology

Therapeutic Interventions

ASH Guidelines 2020

COVID-19

COVID-19 IMPACT

- Sickle Cell Disease Association Advisory
  - Managing Pain
  - Screening/Triage of COVID-19
  - Treatment of COVID-19
  - Chronic Transfusions
  - Letter for Work-form letter highlighting risk of sickle cell and complications

COVID-19

- Managing Pain
  - Encourage patients to manage pain at home
  - Send prescriptions to local pharmacies
  - Encourage patients to obtain thermometers
  - Send naloxone prescriptions
  - Frequent phone calls/telemedicine visits
  - Encourage adherence to medications(Hydroxyurea, L glutamine, Voxelotor, Crizanlizumab)
- Screening/Triage
  - Fever or cough or shortness of breath
    - Schedule outpatient visit, avoid ED
    - Test patient for COVID-19
    - Test for viral infections, cultures if indicated, antibiotics if indicated as standard of care

COVID-19 POSITIVE

- Complications worsening COVID
  - Pulmonary hypertension
  - Asthma (avoid aerosol based interventions)
- Be vigilant for
  - Progressive ACS
  - Multiorgan failure
- Hydroxychloroquine
  - Consider checking G6PD level
  - Methadone patients may have prolonged QTC
- Hypercoagulability
- Discharge
  - Close follow up

SECURE-SCD

REGISTRY

Surveillance Epidemiology of Coronavirus
(COVID-19) Under Research Exclusion

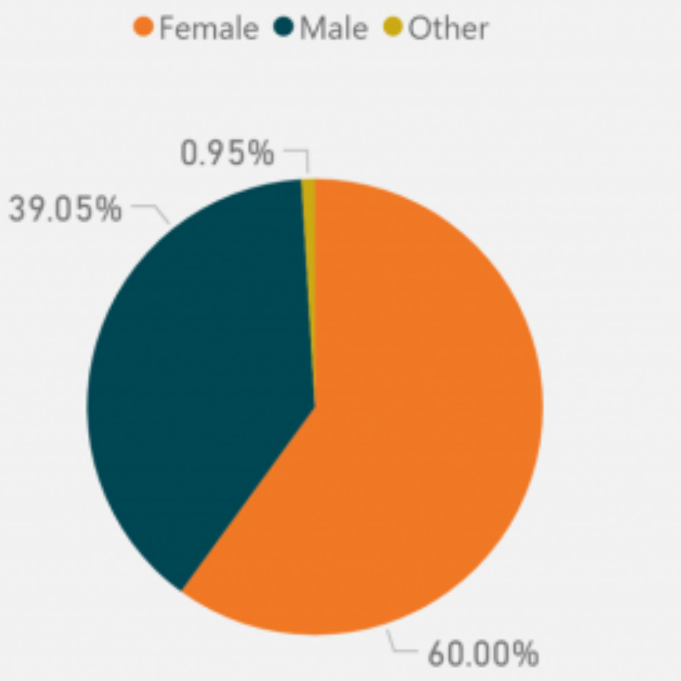
Count of Cases Reported

105

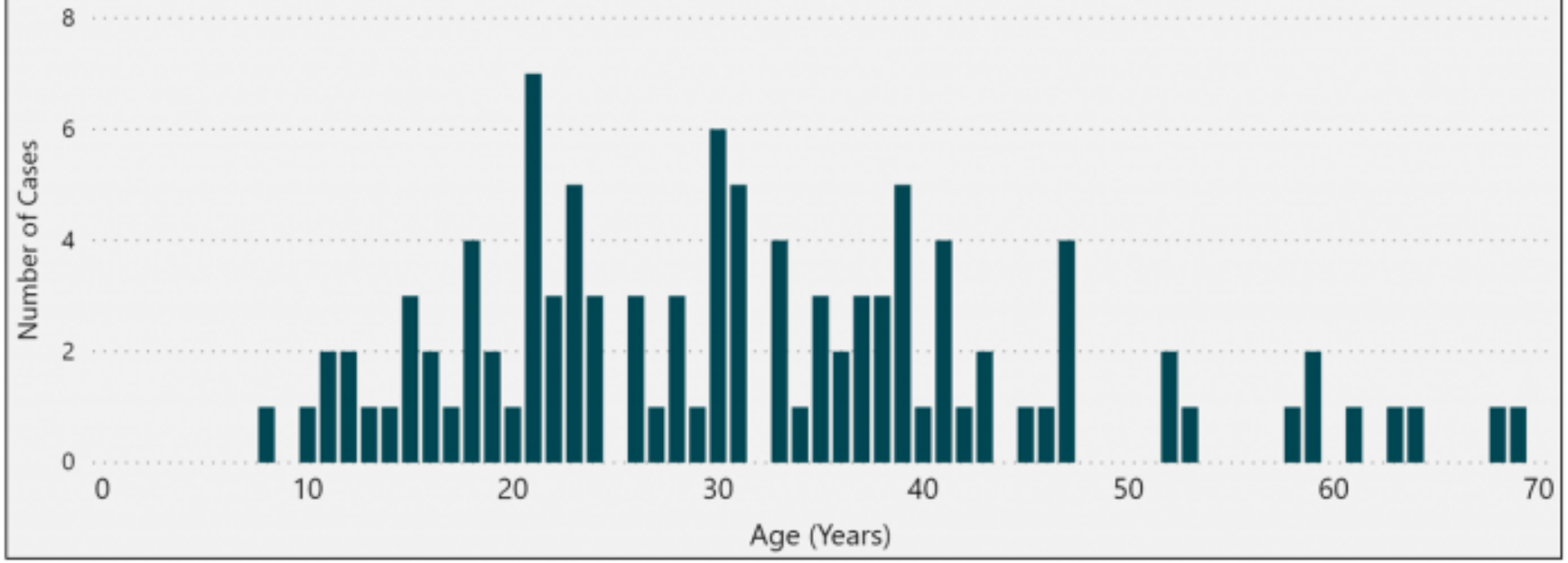
Age Summary

31.73	13.73
Average Age	Standard Deviation

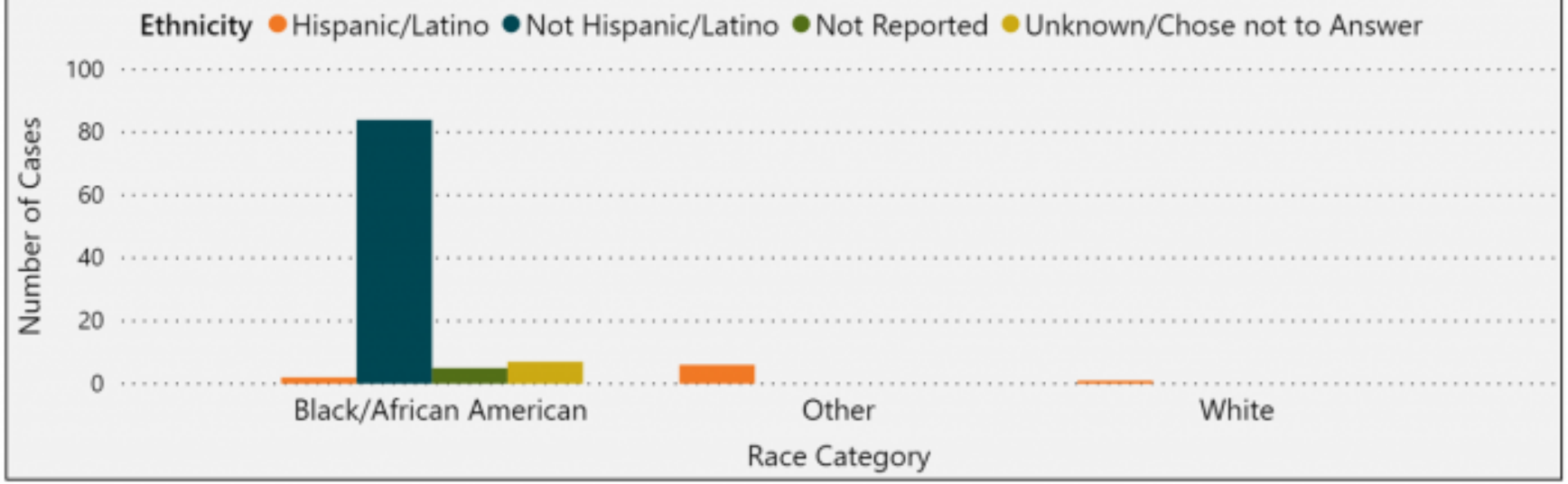
Sex



Age Distribution



Race & Ethnicity Distribution



THE END