Caring for the Little Ones: Updates on Clinical Issues in Pediatrics

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Objectives

- Identify key updates in the pediatric surviving sepsis campaign guidelines.
- Describe the appropriate use of L-glutamine, crizanlizumab, and voxelotor.
- Compare and contrast fish oil lipid emulsion with other commercially available lipid products.

Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children

Update in the Management of Pediatric Septic Shock and Sepsis-Associated Organ Dysfunction

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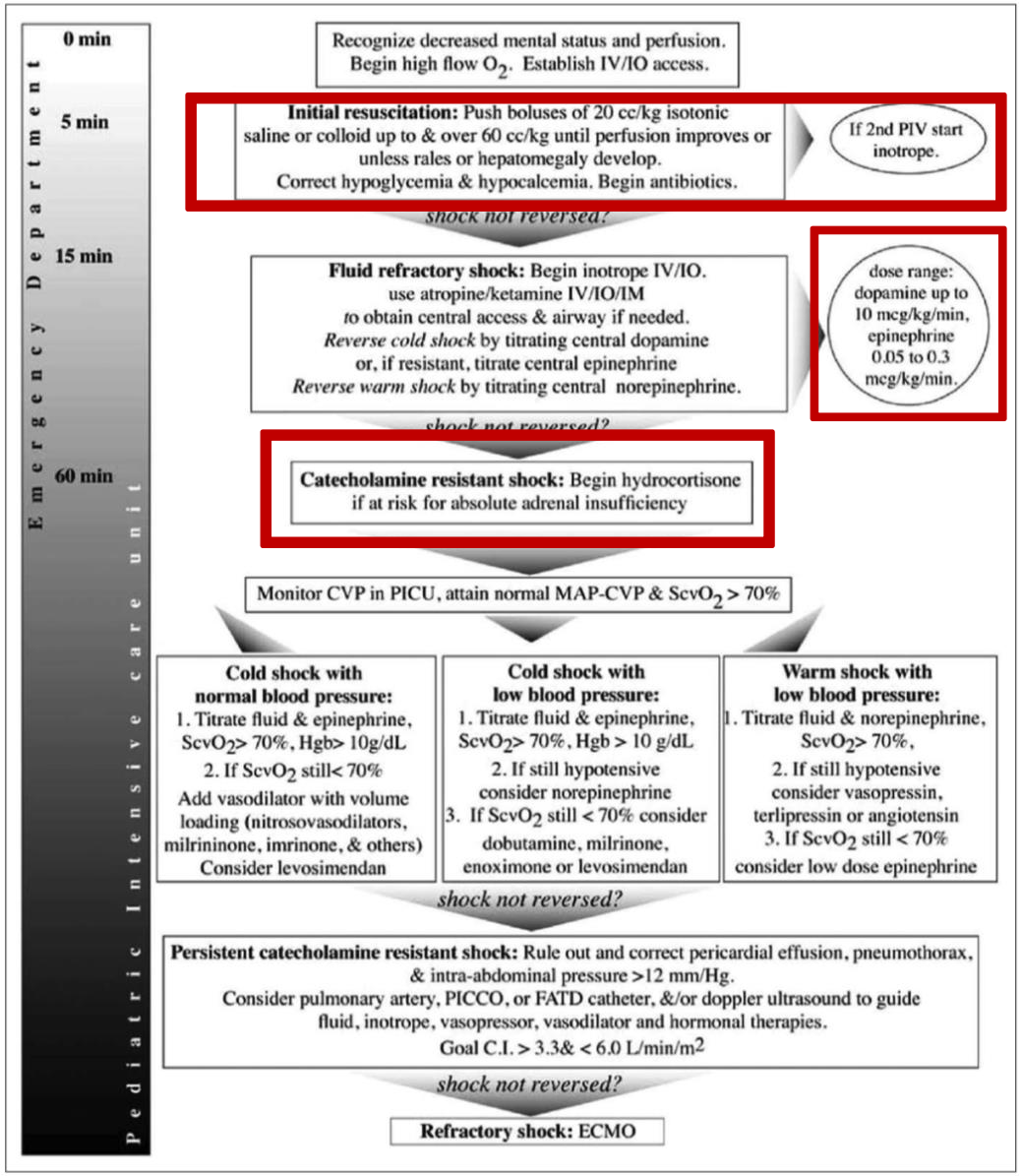
Pediatric Sepsis

- 2005 International Pediatric Sepsis Consensus Conference
  - Published definitions and criteria for sepsis, severe sepsis, and septic shock
- 2012 Surviving Sepsis Campaign
  - Provided recommendations regarding sepsis management
- 2016 Surviving Sepsis Campaign Guidelines
  - Redefined sepsis in adults; gave no guidance for pediatrics
- 2020 Surviving Sepsis Campaign Guidelines for Pediatrics
  - Provides updated guidance for management of pediatric patients with septic shock and sepsis-associated organ dysfunction in children

2012 Treatment Algorithm



Crit Care Med 2013: 41(2): 590-337.

Timing of Antimicrobial Therapy

2012 Recommendation	2020 Recommendation
B. 1. Empiric antibiotics should be administered within 1 hour of the identification of severe sepsis (grade 1D).	5. In children with septic shock, we recommend starting antimicrobial therapy as soon as possible, within 1 hour of recognition (strong recommendation, very low quality of evidence). 6. In children with sepsis-associated organ dysfunction but without shock, we suggest starting antimicrobial therapy as soon as possible after appropriate evaluation, within 3 hours of recognition (weak recommendation, very low quality of evidence).

- Recommendation based off of pooled estimate of two retrospective, observational studies
  - Possible reduction in mortality associated with faster antibiotic administration
  - Larger of the two studies assessed the impact of a bundle
    - Initiation of antimicrobials alone was not associated with significant mortality reduction

Crit Care Med 2013: 41(2): 590-337.
Ped Crit Care Med 2020; 21 (2): e52-106.

Empiric Antibiotics

2012 Recommendation	2020 Recommendation
B. 1. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (grade 1D).	7. We recommend empiric broad spectrum therapy with one or more antimicrobials to cover all likely pathogens (best practice statement). 8. Once pathogens and sensitivities are available, we recommend narrowing empiric antimicrobial therapy coverage (best practice statement). 9. If no pathogen is identified, we recommend narrowing or stopping empiric antimicrobial treatment according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice (best practice statement).

- "Institutions or regions should identify the most appropriate first-line single-agent antimicrobial, taking into account anatomic site of infection, age, local epidemiology, and host comorbidity and risk factors"
  - e. g. NICE recommends ceftriaxone for community acquired sepsis
- "Initial choice of empiric antimicrobials should take into account the specific clinical history (e.g. age, site of infection, concomitant disease states, comorbid conditions, indwelling devices)"
- Empiric treatment should be re-evaluated after no more than 48 hours following initiation
- The decision to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgement and indirect clinical information (clinical presentation, site, type of infection, host risk factors, and adequacy of clinical improvement)

Crit Care Med 2013: 41(2): 590-337. Ped Crit Care Med 2020; 21 (2): e52-106.

Empiric Antibiotic Selection

Condition	Suggested Antimicrobial Regimen
Previously healthy children with community-acquired sepsis	Third generation cephalosporin (e.g. ceftriaxone)
Previously healthy children with community-acquired sepsis in areas where MRSA or ceftriaxone-resistant pneumococci are prevalent	Third generation cephalosporin (e.g. ceftriaxone) PLUS vancomycin
Previously healthy children with community-acquired sepsis in areas where ceftriaxone resistant gram negative bacteria is common	Third generation cephalosporin (e.g. ceftriaxone) PLUS aminoglycoside OR substitute a carbapenem
Immunocompromised patients or hospital acquired sepsis	Anti-pseudomonal third- or higher generation cephalosporin (e.g. cefepime), a broad spectrum carbapenem (e.g. meropenem, imipenem/cilastatin), or an extended range penicillin/β-lactamase inhibitor combination (e.g. piperacillin-tazobactam)
Neonates	Ampicillin for listeria coverage Consider empiric acyclovir if clinical concern for HSV
Intra-abdominal source	Include broad coverage for gastrointestinal pathogens, including anaerobic bacteria with wither an extended range penicillin/β-lactamase inhibitor combination or a carbapenem, or addition of clindamycin or metronidazole
Toxic shock syndrome or necrotizing fasciitis	Clindamycin or lincomycin

Ped Crit Care Med 2020; 21 (2): e52-106.

Fluid Resuscitation

2012 Recommendation	2020 Recommendation
C. 1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins **with infusion of isotonic crystalloids or albumin with boluses up to 20 mL/kg crystalloids (or albumin equivalent) over 5-10 minutes titrated to reversing hypotension**,…without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In non-hypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises) blood transfusion is considered superior to crystalloid or albumin bolusing (grade 2C).	17. In healthcare systems **with availability of intensive care, we suggest administering up to 40-60 mL/kg in bolus fluid (10-20 mL/bolus) over the first hour, titrated to clinical markers of cardiac output** and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, low quality of evidence). 18. In healthcare systems with **no availability of intensive care and in the absence of hypotension, we recommend against fluid bolus administration while starting maintenance fluids** (strong recommendation, high quality of evidence). 19. In healthcare systems with **no availability of intensive care, if hypotension is present, we suggest administering up to 40 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour with titration to clinical markers of cardiac output** and discontinued if signs of fluid overload develop (weak recommendation, low quality of evidence).

Crit Care Med 2013: 41(2): 590-337.
Ped Crit Care Med 2020; 21 (2): e52-106.

FEAST Trial

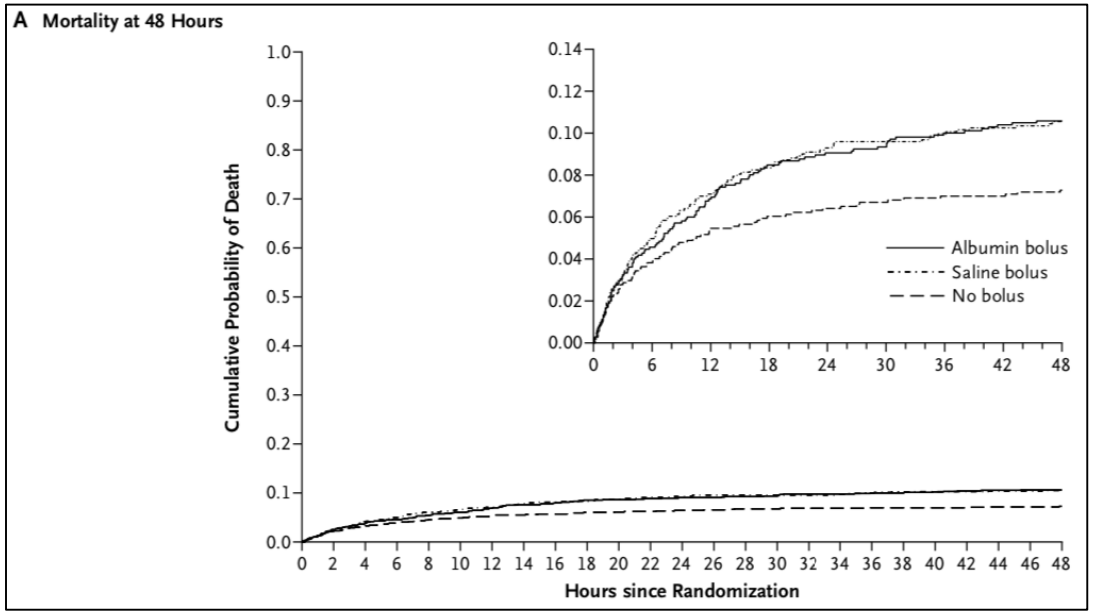
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

- Multicenter, open-label, randomized, controlled study conducted in Kenya, Tanzania, and Uganda
- 3141 children without severe hypotension between 60 days and 12 years old were randomized by a 1:1:1 ratio to receive:
  - Normal saline (NS) bolus 20 mL/kg over 1 hour
  - Albumin 5% 20 mL/kg over 1 hour
  - No bolus (control group)
    - If unresponsive to initial bolus at 1 hour, another 20 mL/kg bolus of either NS or albumin was given (no crossover allowed)
    - If severe hypotension developed, a 40 mL/kg bolus of the study fluid (NS for the control group) was given
- All children received IV maintenance fluids (2.5-4 mL/kg/hr), antibiotics, antimalarials, antipyretics, anticonvulsants, treatment for hypoglycemia (if blood glucose < 45mg/dL), and transfusion (20 mL/kg given if Hgb <5 g/dL), if needed in accordance with national guidelines

Table 2. Death and Other Adverse Event End Points at 48 Hours and 4 Weeks.

End Point	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Saline Bolus vs. No Bolus		Albumin Bolus vs. No Bolus		Albumin Bolus vs. Saline Bolus		Albumin and Saline Boluses vs. No Bolus	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
		no. (%)									
48 Hours											
Death — no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.44 (1.09–1.90)	0.01	1.45 (1.10–1.92)	0.008	1.00 (0.78–1.29)	0.96	1.45 (1.13–1.86)	0.003
Pulmonary edema — no. (%)	14 (1.3)	6 (0.6)	6 (0.6)								
Increased intracranial pressure — no. (%)	16 (1.5)	18 (1.7)	11 (1.1)								
Severe hypotension — no. (%)*	1 (0.1)	2 (0.2)	3 (0.3)								
Allergic reaction — no. (%)	3 (0.3)	4 (0.4)	2 (0.2)								
Pulmonary edema, increased intracranial pressure,	27 (2.6)	23 (2.2)	17 (1.6)	1.34 (0.72–2.51)	0.34	1.57 (0.87–2.88)	0.10	1.17 (0.68–2.03)	0.49	1.46 (0.85–2.53)	0.17



N Engl J Med 2011; 364(26): 2483-95.

Type of Fluid Resuscitation

2012 Recommendation	2020 Recommendation
C. 1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins **with infusion of isotonic crystalloids or albumin with boluses up to 20 mL/kg crystalloids (or albumin equivalent) over 5-10 minutes titrated to reversing hypotension**,…without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In non-hypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises) blood transfusion is considered superior to crystalloid or albumin bolusing (grade 2C).	20. We suggest using crystalloids, rather than albumin, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, moderate quality of evidence). 21. We suggest using balanced/buffered crystalloids, rather than 0.9% saline, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction (weak recommendation, very low quality of evidence).

- No benefit to using albumin found; increased cost and administration barriers
- Adult studies of high-chloride containing crystalloids (e.g. NS) is associated with hyperchloremic acidosis, systemic inflammation, acute kidney injury (AKI), coagulopathy, and mortality when compared to balanced/buffered crystalloids (e.g. Lactated ringer's, PlasmaLyte)
  - Two observational studies in children with sepsis showed lower mortality (but not AKI) for children receiving balanced/buffered crystalloids

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Vasoactive Medications

2012 Recommendation	2020 Recommendation
D. 1. We suggest beginning peripheral inotropic support until ventral venous access can be attained in children who are not responsive to fluid resuscitation (grade 2C). "Dopamine-refractory shock may reverse with epinephrine or norepinephrine infusion."	28. We suggest using epinephrine, rather than dopamine, in children with septic shock (weak recommendation, low quality of evidence). 29. We suggest using norepinephrine, rather than dopamine, in children with septic shock (weak recommendation, very low quality of evidence). 30. We were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock. 31. We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock. 32. We suggest either adding vasopressin or further titrating catecholamines in children with septic shock who require high-dose catecholamines (weak recommendation, low quality of evidence).

- Two RCTs have compared epinephrine with dopamine in children with fluid refractory septic shock
  - Epinephrine was associated with lower risk of mortality and more organ failure-free days among survivors by day 28
- Norepinephrine has not been studied in children with septic shock
- An RCT of of norepinephrine versus saline in sedated, mechanically ventilated children showed no difference in mortality but higher urine output and improved blood pressure in children receiving norepinephrine

Crit Care Med 2013; 41(2): 590-337. Ped Crit Care Med 2020; 21 (2): e52-106.

Corticosteroids

2012 Recommendation	2020 Recommendation
F. 1. We suggest timely hydrocortisone therapy in children with fluid-refractory, catecholamine resistant shock and suspected or proven absolute (classic) adrenal insufficiency (grade 1A).	44. We suggest against using IV hydrocortisone to treat children with septic shock if fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability (weak recommendation, low quality of evidence). 45. We suggest that either IV hydrocortisone or no hydrocortisone may be used if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability (weak recommendation, very low quality of evidence).

- RCTs in children have enrolled a small number of subjects, reported inconsistent conclusions, had methodological limitations, and did not demonstrate an overall mortality reduction
- Observational cohort studies have reported either harm or no benefit with hydrocortisone in children with septic shock
- Use of random cortisol or stimulation tests to guide corticosteroid prescription in children with septic shock cannot be recommended at this time
  - Patients with clinical concern for primary adrenal insufficiency, a high-dose cosyntropin-stimulation test should be performed

Crit Care Med 2013: 41(2): 590-337.
Ped Crit Care Med 2020; 21 (2): e52-106.

Stress Ulcer Prophylaxis

2012 Recommendation	2020 Recommendation
N. 1. We make no graded recommendations on stress ulcer prophylaxis.	76. We suggest against the routine use of stress ulcer prophylaxis in critically ill children with septic shock or other sepsis-associated organ dysfunction, except for high risk patients (weak recommendation, very low quality of evidence).

- Increased risk of pneumonia or *C. difficile* infection
- Rather than routine, universal administration of stress ulcer prophylaxis, individual patients should be assessed for the presence of risk factors of clinically appropriate gastrointestinal bleeding:
  - Multiple organ dysfunction
  - Prolonged mechanical ventilation (>48 hours)
  - Coagulopathy
  - Persistent shock
  - Treatment with corticosteroids and non-steroidal anti-inflammatory agents
- Early enteral nutrition may be a viable alternative to pharmacological stress-ulcer prophylaxis

Crit Care Med 2013: 41(2): 590-337.
Ped Crit Care Med 2020; 21 (2): e52-106.

Deep Vein Thrombosis (DVT) Prophylaxis

2012 Recommendation	2020 Recommendation
M. 1. We make no graded recommendations on the use of DVT prophylaxis in prepubertal children with severe sepsis.	77. We suggest against routine deep vein thrombosis (DVT) prophylaxis (mechanical or pharmacologic) in critically ill children with septic shock or sepsis-associated organ dysfunction, but potential benefits may outweigh risks and costs in specific populations (weak recommendation, low quality of evidence).

- Central venous catheters are the main risk factor for DVT in infants
- Older children may also have risk factors:
  - Adolescence
  - Obesity
  - Cancer
  - Multiple medical conditions (especially renal and cardiac disease)

Crit Care Med 2013: 41(2): 590-337.
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Polling Question 1

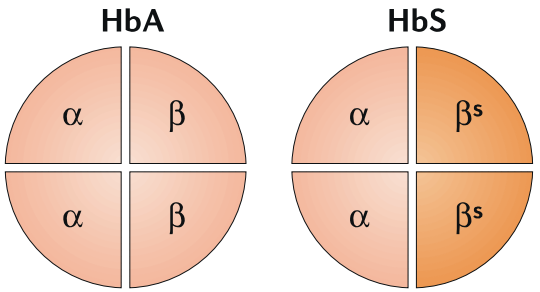
- A 3 year old, 12 kg female is admitted to the PICU with community-acquired sepsis. She has a past medical history of eczema and reactive airway disease and no past surgical history. She received a bolus of 20 mL/kg lactated ringer's, her blood pressure is now stable, and she is afebrile. Her current medication list is below:
  - Ceftriaxone 1200 mg (100 mg/kg) IV Q24h
  - Acetaminophen 180 mg (15 mg/kg) PO Q6h PRN fever >100.4°F
  - Dextrose 5& + 0.45% sodium chloride + 20 mEq/L Potassium chloride IV @ 46 mL/hr
- The team is discussing stress ulcer prophylaxis during rounds. Is stress ulcer prophylaxis indicated for this patient?

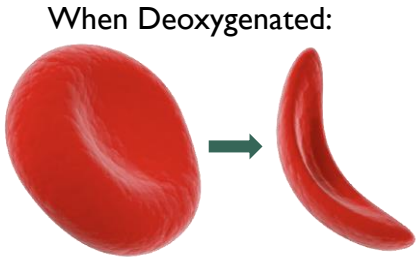
Update in the Management of Sickle Cell Disease

LIU Pharmacy

Sickle Cell Disease

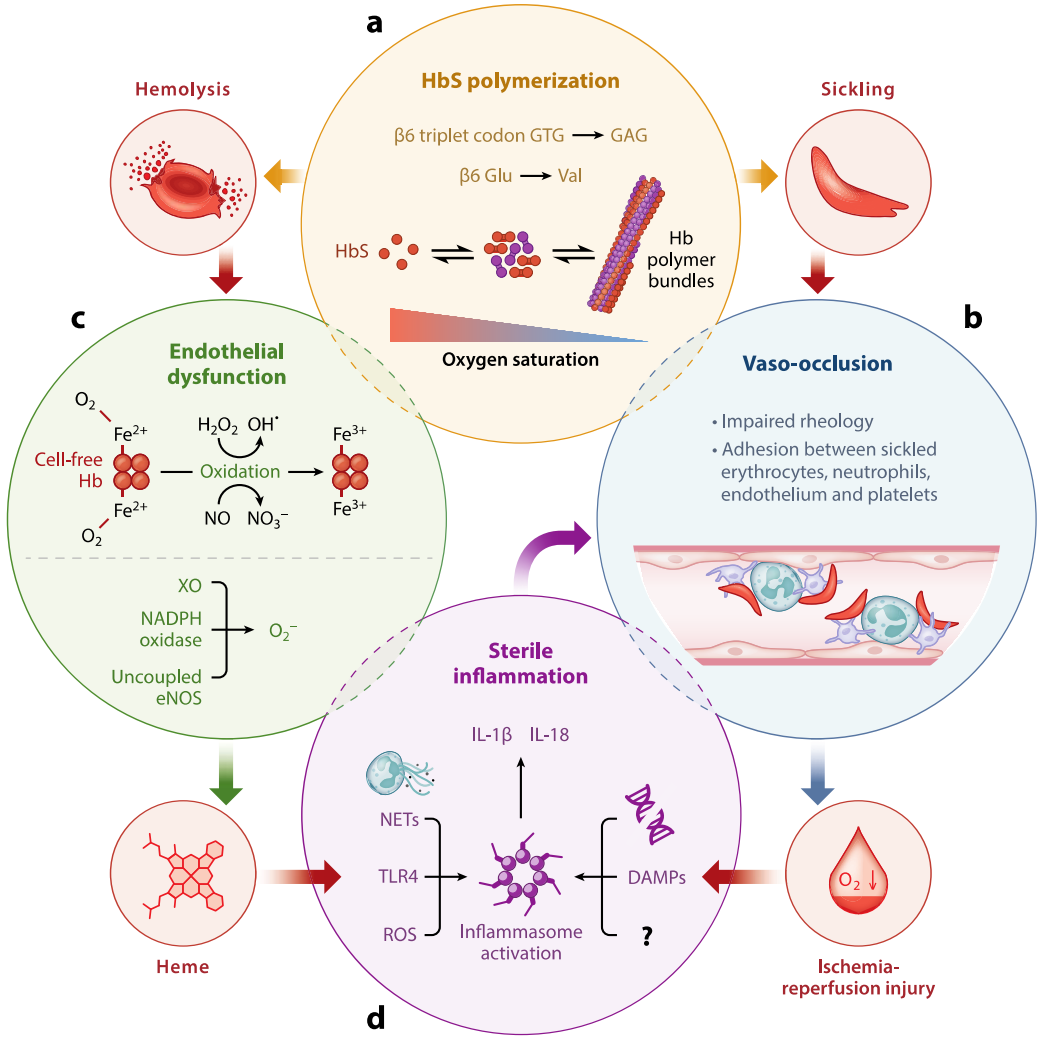
- Genetic disorder that affects 90,000-100,000 Americans
  - Millions of people affected worldwide, especially in Africa, the Middle East, and India
  - Globally, 176,000 people die each year from sickle cell disease (SCD) complications
- Single nucleotide polymorphism in the β-globulin gene leads to a substitution of valine for glutamic acid on the β-globulin chain of hemoglobin
  - Substitution allows for polymerization when the red blood cell becomes deoxygenated, leading to the 'sickle shape'
- Many subtypes of disease result when other β-globulin mutations are coinherited with sickle hemoglobin (Hemoglogin S, HgbS)
  - Hemoglobin C, β-Thalassemia





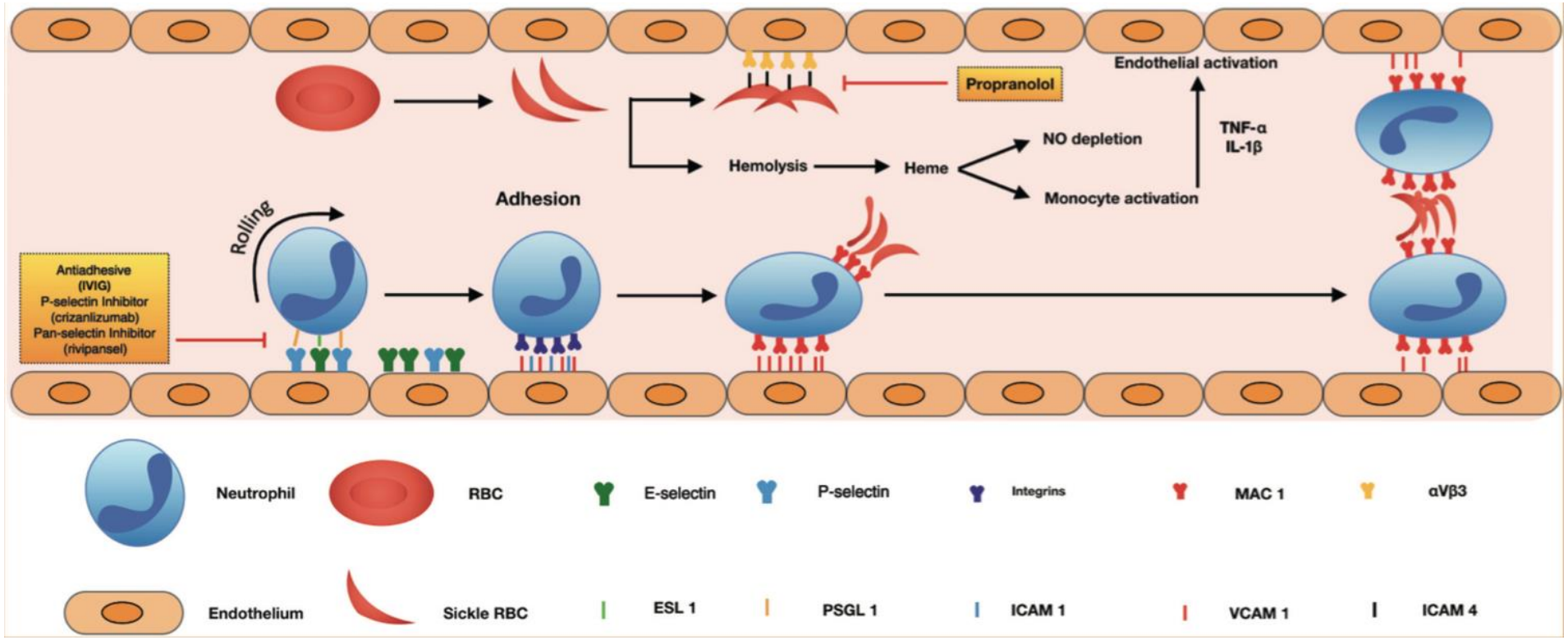
Pediatrics in Review 2012; 33(5): 195-206.
Annu Rev Pathol Mech Dis 2019; 14: 263-92.
Mayo Clin Proc 2018: 93(12): 1810-1824.
Nat Rev Drug Disc 2019: 18: 139-158.

Sickle Cell Disease



Annu Rev Pathol Mech Dis 2019; 14: 263-92.

Vaso-Occlusion



Mayo Clin Proc 2018: 93(12): 1810-1824.

Selected Complications of SCD

Vasco-occlusive plan crisis

Acute chest syndrome (ACS)

Sequestration (splenic, hepatic)

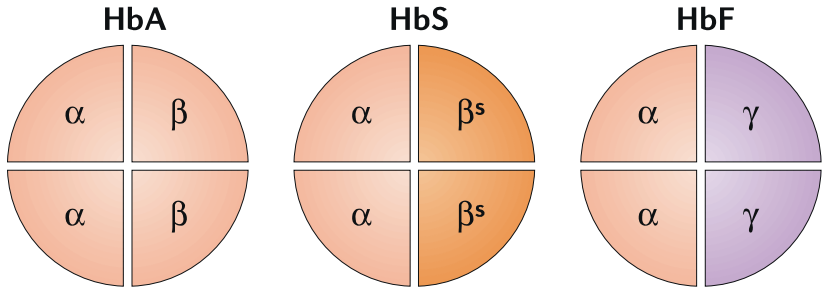
Priapism

Stroke

Cholelithiasis

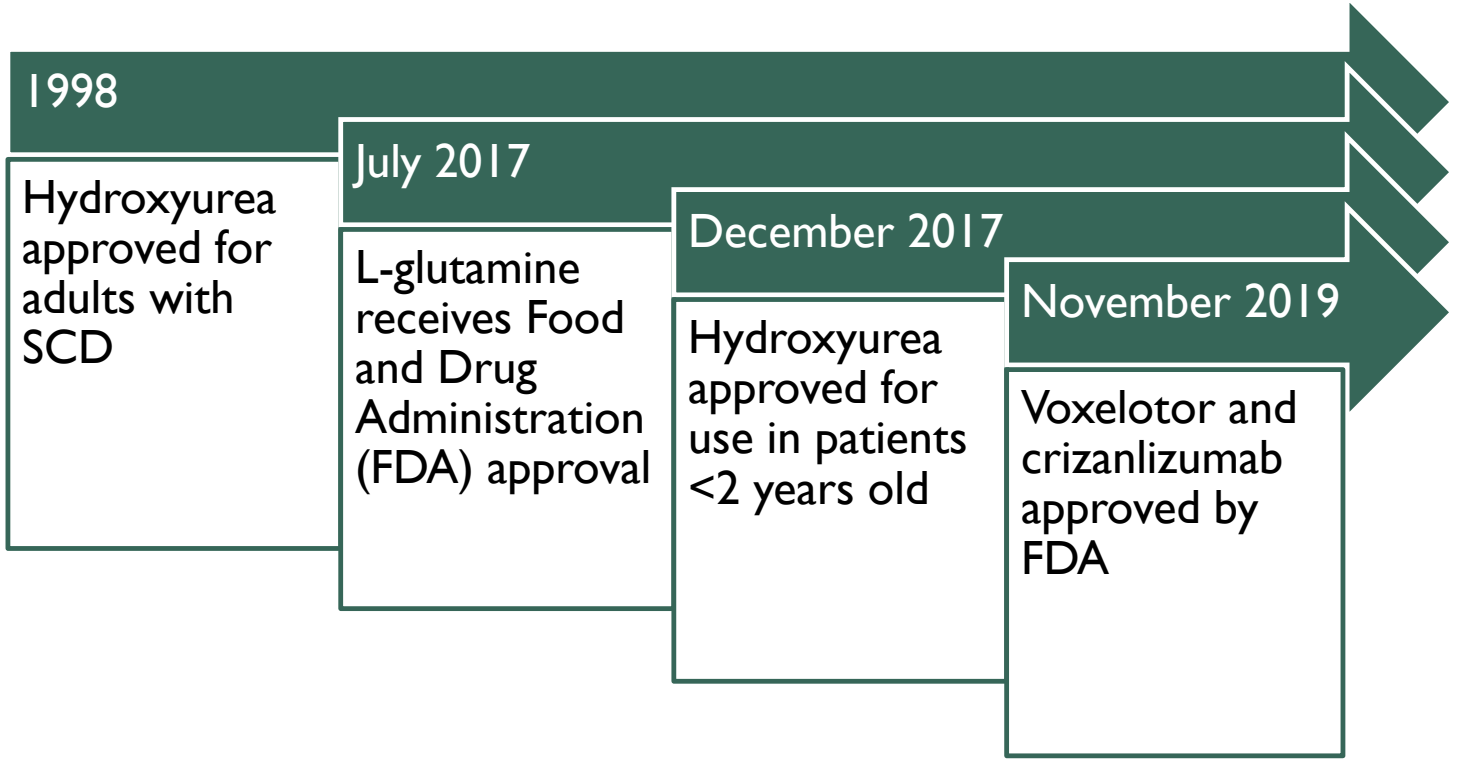
‘Traditional’ Therapies for SCD

- Chronic Management
  - Penicillin prophylaxis
  - Immunizations
  - Hydroxyurea
  - Folic acid
- Acute Management
  - Pain medications (opioids, ketorolac)
  - Fluid provision
  - Antibiotics (sepsis, ACS)



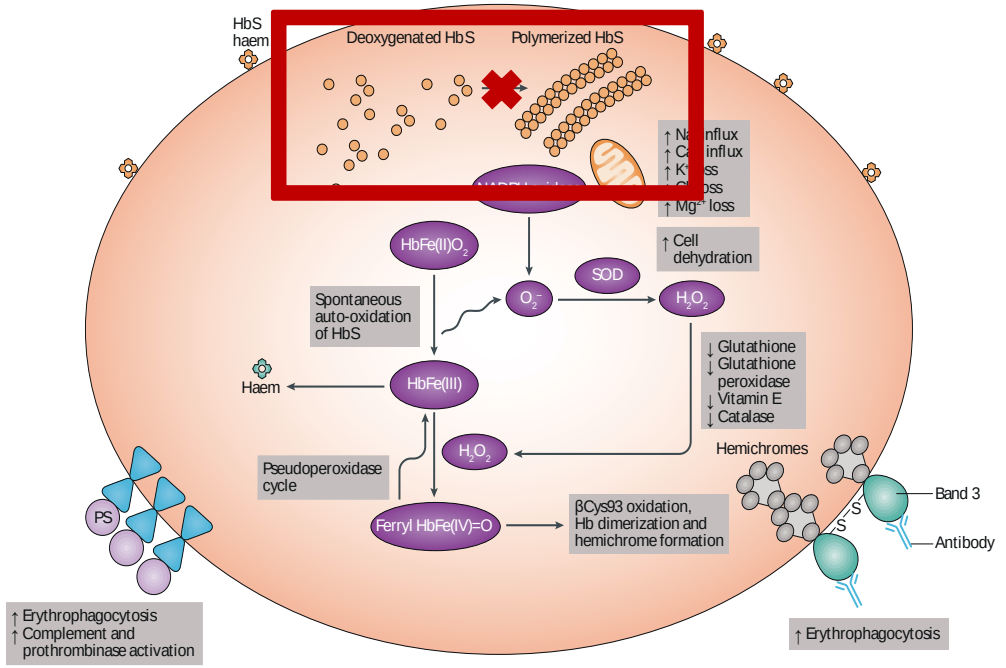
Pediatrics in Review 2012; 33(5): 195-206.
Mayo Clin Proc 2018: 93(12): 1810-1824.

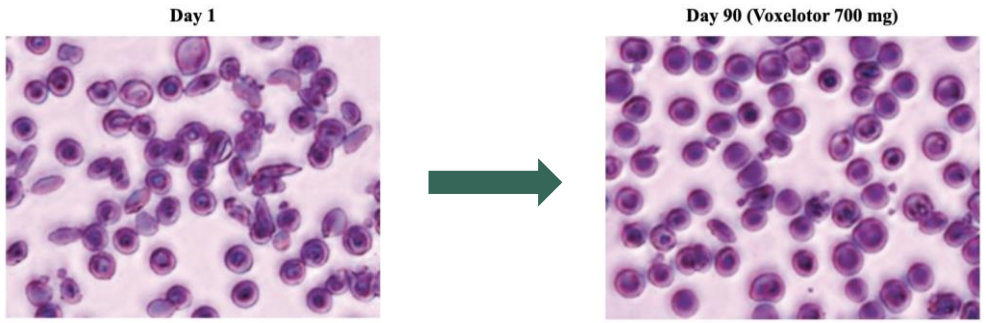
Sickle Cell Disease (SCD) Drug Approval



Voxelotor

- HbS polymerization inhibitor
- Reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state
- Clinical effects:
  - Reduces red-cell sickling
  - Reduces blood viscosity
  - Extends red-cell half-life
  - Reduces anemia and hemolysis





N Engl J Med 2019; 381(6): 509-519.
Nat Rev Drug Disc 2019: 18: 139-158.
https://www.sec.gov/Archives/edgar/data/1629137/000119312518060818/d518438d10k.htm

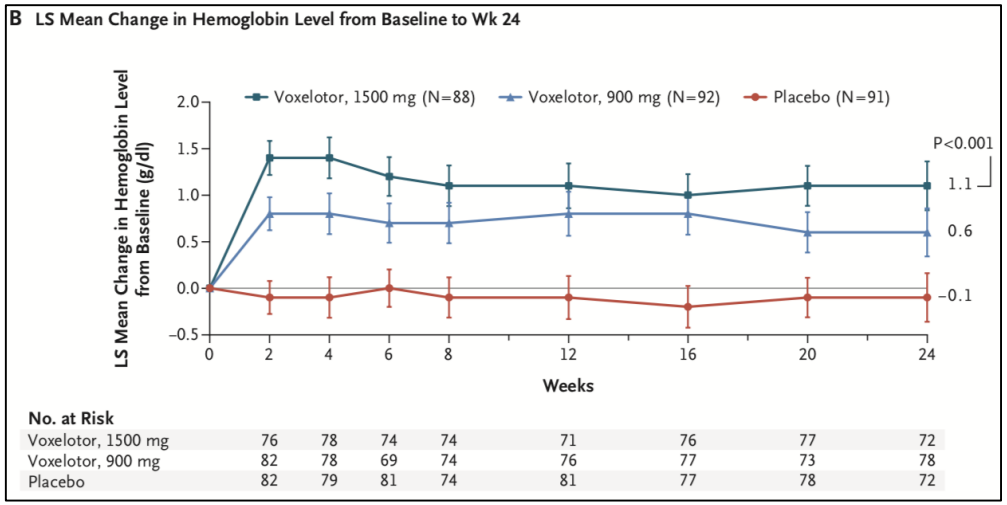
Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) Trial

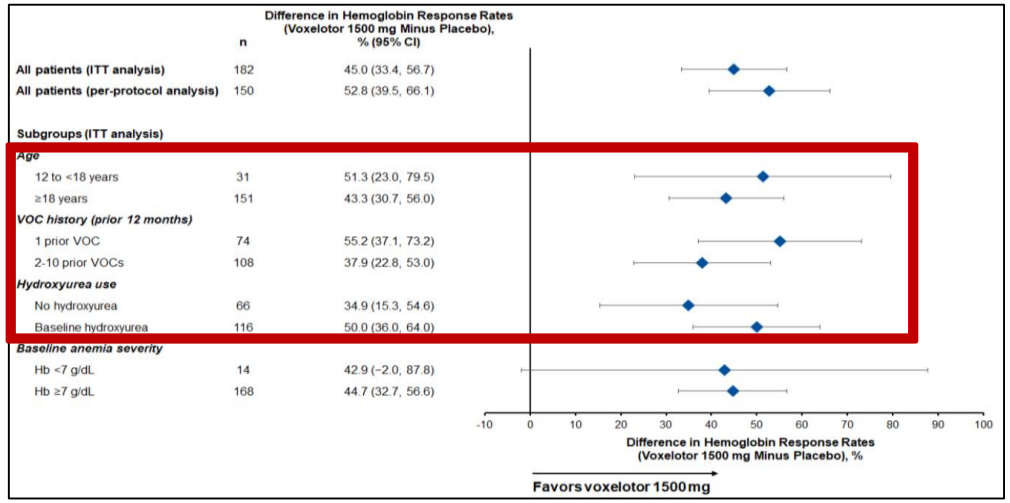
- International, multicenter, randomized, placebo controlled, double-blind, parallel-group trial
- Included patients 12 to 65 years of age with sickle cell disease, a hemoglobin between 5.5 and 10.5 g/dL at screening, and had 1 to 10 vaso-occlusive crisis (VOC) in the past 12 months
  - 'Vaso-occlusive crisis' included pain crisis and ACS
  - Patients were allowed to enroll if they were receiving a stable dose of hydroxyurea for at least 3 months
- Excluded patient that received regular blood cell transfusions, received a transfusion in the past 60 days, or required hospitalization within 2 weeks of enrollment
- Randomized in a 1:1:1 fashion to receive:
  - 1500 mg voxelotor orally once a day (n = 90)
  - 900 mg voxelotor orally once a day (n = 92)
  - Placebo orally once a day (n = 92)
- Study treatment period was 72 weeks

N Engl J Med 2019; 381(6): 509-519.

HOPE Trial

- Primary endpoint: Hemoglobin response (increase in hemoglobin of 1 mg/dL from baseline) at week 24
  - Significantly greater in the voxelotor group (51%; 46 of 90 patients) vs. placebo (7%; 6 of 92 patients) (p<0.001)
  - Benefit seen in patients independent of age group, history of VOC, and use of hydroxyurea prior to enrollment





N Engl J Med 2019; 381(6): 509-519.

HOPE Trial

Table 3. Annualized Incidence Rate of Vaso-Occlusive Crisis and the Most Common Adverse Events That Occurred or Worsened during the Treatment Period.

Variable	Voxelotor, 1500 mg (N=88)	Voxelotor, 900 mg (N=92)	Placebo (N=91)
Annualized incidence rate of vaso-occlusive crisis — no. of crises per person-yr (95% CI)*	2.77 (2.15 to 3.57)	2.76 (2.15 to 3.53)	3.19 (2.50 to 4.07)
Participants with ≥1 vaso-occlusive crisis — no. (%)	59 (67)	61 (66)	63 (69)
Total no. of vaso-occlusive crises	179	183	219

- No significant reduction in VOC episodes within the study period
- Longer-term follow up may be required to see a difference

N Engl J Med 2019; 381(6): 509-519.

HOPE Trial: Safety

- Most common adverse events: headache and diarrhea
- Four patients had fatal adverse events
  - 1 patient has pulmonary sepsis, sickle cell anemia with crisis, and acute sickle hepatic crisis (1500 mg group)
  - 1 patient had sickle cell anemia with crisis (900 mg group)
  - 1 patient had sickle cell anemia with crisis (placebo group)
  - 1 patient had cardiac arrest (placebo group)

Table 3. Annualized Incidence Rate of Vaso-Occlusive Crisis and the Most Common Adverse Events That Occurred or Worsened during the Treatment Period.

Adverse events not related to sickle cell disease — no. (%)†			
Incidence of adverse events of any grade	83 (94)	86 (93)	81 (89)
Adverse events with ≥10% incidence			
Headache	23 (26)	14 (15)	20 (22)
Diarrhea	18 (20)	16 (17)	9 (10)
Nausea	15 (17)	15 (16)	9 (10)
Arthralgia	13 (15)	11 (12)	11 (12)
Upper respiratory tract infection	12 (14)	17 (18)	10 (11)
Abdominal pain	12 (14)	13 (14)	7 (8)
Fatigue	12 (14)	12 (13)	9 (10)
Rash‡	12 (14)	10 (11)	9 (10)
Pyrexia	11 (12)	10 (11)	6 (7)
Pain in extremity	10 (11)	18 (20)	16 (18)
Back pain	10 (11)	13 (14)	10 (11)
Vomiting	10 (11)	12 (13)	11 (12)
Pain	8 (9)	10 (11)	6 (7)
Noncardiac chest pain	7 (8)	12 (13)	8 (9)
Upper abdominal pain	6 (7)	11 (12)	6 (7)

N Engl J Med 2019; 381(6): 509-519.

Pediatric Trial

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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Save this study

Study to Evaluate the Effect of GBT440 on TCD in Pediatrics With Sickle Cell Disease (HOPE Kids 2)

ClinicalTrials.gov Identifier: NCT04218084

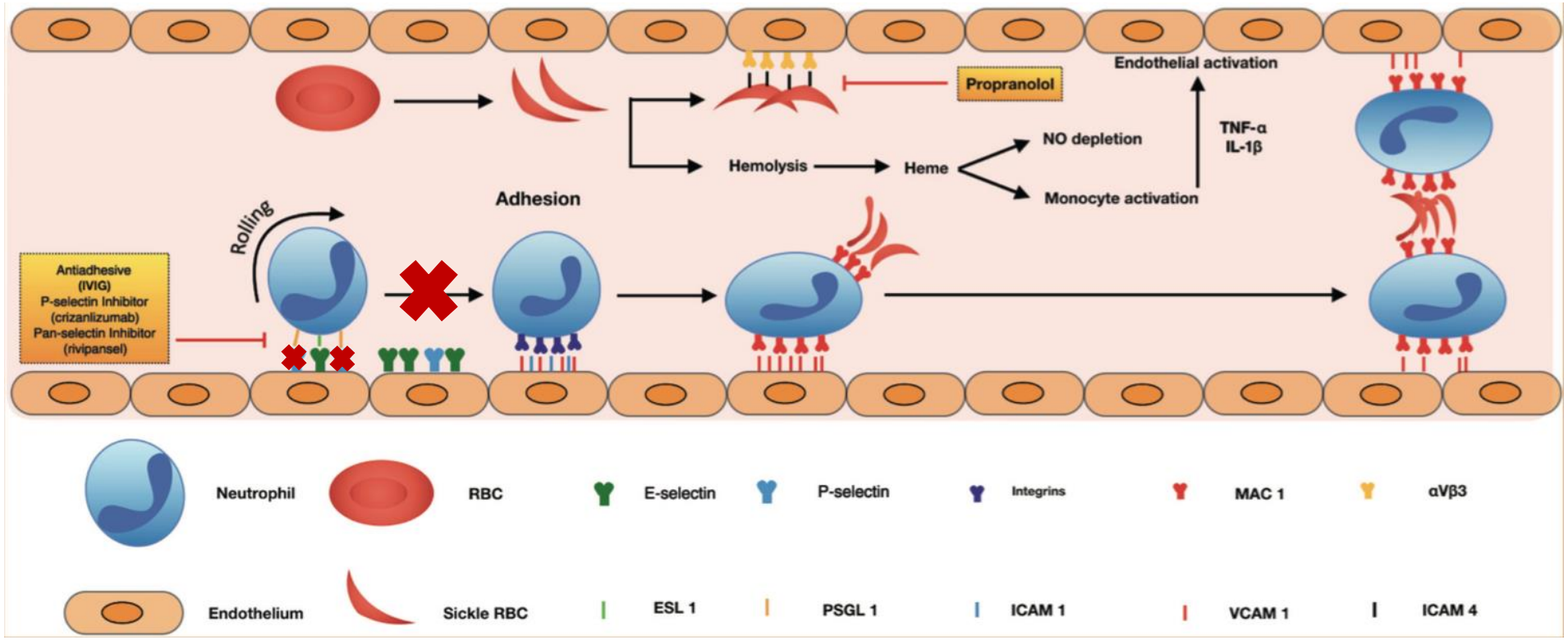
Study Start Date: February 3, 2020
Anticipated Completion: March 2026

Recruitment Status : Recruiting
First Posted : January 6, 2020
Last Update Posted : March 27, 2020

See Contacts and Locations

https://clinicaltrials.gov/ct2/show/NCT04218084

Crizanlizumab



Mayo Clin Proc 2018: 93(12): 1810-1824.

SUSTAIN Trial

- "Phase 2, multicenter, randomized, placebo controlled, double blind, 12-month study to assess safety and efficacy of crizanlizumab (SelG1) with or without hydroxyurea therapy in sickle cell disease patients with sickle cell related pain crisis"
- Enrolled patients 16 to 65 years old who had 2 to 10 SCD pain crisis in the prior 12 months
  - Patients on a stable dose of hydroxyurea for 6 months were eligible for enrollment
- Excluded patients requiring long-term red-cell transfusion therapy
- Patients randomized in a 1:1:1 fashion to receive:
  - High-dose crizanlizumab (5 mg/kg) (n = 67 patients)
  - Low-dose crizanlizumab (2.5 mg/kg) (n = 66 patients)
  - Placebo (n = 65 patients)
- Patients received two doses, two weeks apart (loading doses), followed by doses every 4 weeks for a total of 14 doses (52 weeks total)
- Administered IV over 30 minutes

N Engl J Med 2017; 376(5): 429-39.

SUSTAIN Trial

- Primary endpoint: annual rate of sickle cell disease pain crisis

$$= \frac{\text{Total number of crises} \times 365}{\text{End date} - \text{date of randomization} + 1}$$

- End date was the day of the last dose plus 14 days
- 'Pain crisis' included acute episodes of pain, acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism
- Statistically significant reduction in the annual rate of sickle cell disease crisis
- Medial number of pain crisis per year was consistently lower, regardless of hydroxyurea use or number of pain crisis in the previous 12 months

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
Annual rate of crises in the per-protocol population			
No. of patients	40	44	41
Median rate of crises per year (IQR)	1.04 (0.00–3.42)	2.00 (1.00–3.02)	2.18 (1.96–4.96)
Difference from placebo — %	−52.3	−8.3	—
P value	0.02	0.13	—
No. of patients with crisis rate of zero at end of trial	15	7	5
Subgroup analyses in the intention-to-treat population			
According to concomitant hydroxyurea use			
Use			
No. of patients	42	41	40
Median rate of crises per year (IQR)	2.43 (0.00–4.01)	2.00 (1.00–3.93)	3.58 (1.13–6.23)
Difference from placebo — %	−32.1	−44.1	
No use			
No. of patients	25	25	25
Median rate of crises per year (IQR)	1.00 (0.00–2.00)	2.16 (1.89–3.98)	2.00 (1.63–3.90)
Difference from placebo — %	−50.0	8.0	—
According to no. of crises in previous 12 mo			
2–4 crises			
No. of patients	42	41	41
Median rate of crises per year (IQR)	1.14 (0.00–3.96)	2.00 (1.00–3.02)	2.00 (1.00–3.90)
Difference from placebo — %	−43.0	0.0	—
5–10 crises			
No. of patients	25	25	24
Median rate of crises per year (IQR)	1.97 (0.00–3.98)	3.02 (2.00–5.19)	5.32 (2.01–11.05)
Difference from placebo — %	−63.0	−43.2	—

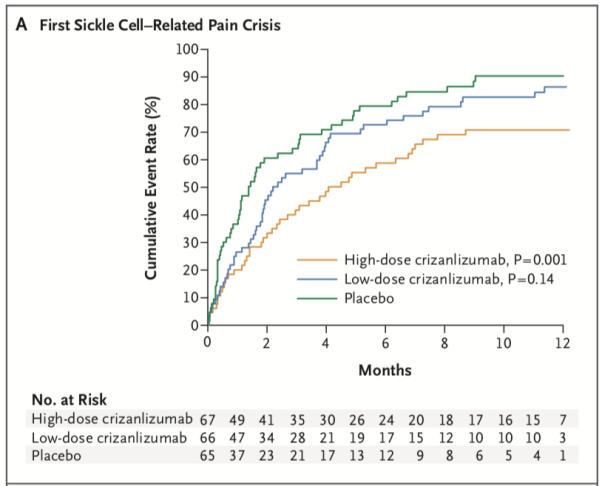
N Engl J Med 2017; 376(5): 429-39.

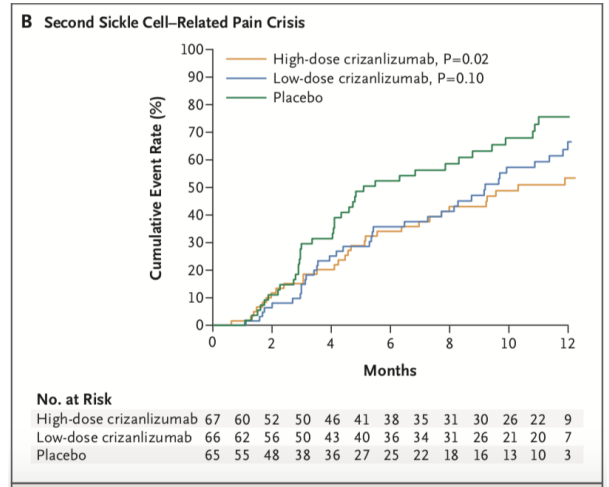
SUSTAIN Trial

- No difference seen in the annual rate of days hospitalized or the annual rate of acute chest syndrome
- Time to first and second sickle cell pain crisis was significantly longer in patients receiving high-dose crizanlizumab versus placebo
- No significant differences were observed for markers of hemolysis (hemoglobin, lactate dehydrogenase, reticulocyte count, haptoglobin, or indirect bilirubin)

Table 3. Secondary End Points in the Intention-to-Treat Population.*

End Point	High-Dose Crizanlizumab (N=67)	Low-Dose Crizanlizumab (N=66)	Placebo (N=65)
Annual rate of days hospitalized			
Median rate per year (IQR)	4.00 (0.00–25.72)	6.87 (0.00–18.00)	6.87 (0.00–28.30)
Difference from placebo — %	−41.8	0.0	—
P value†	0.45	0.84	—
Time to first sickle cell–related pain crisis			
Median time to first crisis (IQR) — mo	4.07 (1.31–NR)‡	2.20 (0.95–6.60)	1.38 (0.39–4.90)
Hazard ratio (95% CI)	0.50 (0.33–0.74)	0.75 (0.52–1.10)	—
P value§	0.001	0.14	—
Time to second sickle cell–related pain crisis			
Median time to second crisis (IQR) — mo	10.32 (4.47–NR)‡	9.20 (3.94–12.16)	5.09 (2.96–11.01)
Hazard ratio (95% CI)	0.53 (0.33–0.87)	0.69 (0.44–1.09)	—
P value§	0.02	0.10	—
Annual rate of uncomplicated sickle cell–related pain crises			
Median rate per year (IQR)	1.08 (0.00–3.96)	2.00 (0.00–3.02)	2.91 (1.00–5.00)
Difference from placebo — %	−62.9	−31.3	—
P value†	0.02	0.12	—
Annual rate of the acute chest syndrome			
Median rate per year (IQR)	0 (0.00–0.00)	0 (0.00–0.00)	0 (0.00–0.00)
Difference from placebo — %	0.0	0.0	—
P value†	0.78	0.87	—





N Engl J Med 2017; 376(5): 429-39.

SUSTAIN Trial

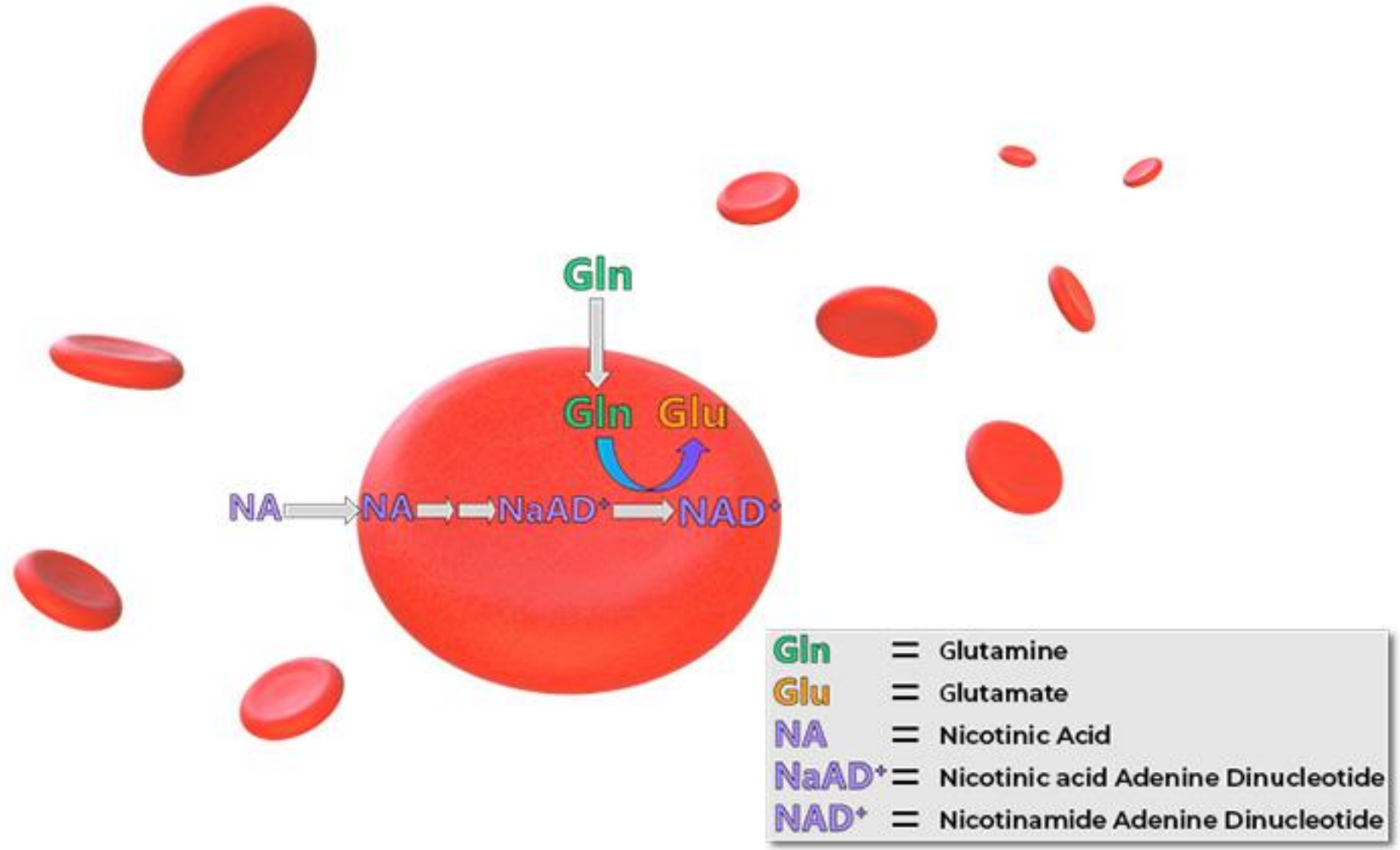
- Pyrexia and influenza occurred at a higher frequency in a treatment group than the placebo group
- 5 patients died during the trial
  - 2 receiving high-dose crizanlizumab (acute chest syndrome and endocarditis/sepsis)
  - 1 receiving low-dose crizanlizumab acute chest syndrome with aspiration/respiratory failure and progressive vascular congestion)
  - 2 receiving placebo (right ventricular heart failure and vaso-occlusive crisis/ischemic stroke, coma, sepsis, and venous thromboembolism)
- Antibodies against crizanlizumab were not detected during the study

Table 4. Adverse Events in the Safety Population.*

Variable	High-Dose Crizanlizumab (N=66)	Low-Dose Crizanlizumab (N=64)	Placebo (N=62)
		no. of patients (%)	
Serious adverse events			
No. of patients with ≥1 serious adverse event	17 (26)	21 (33)	17 (27)
Most frequent serious adverse events†			
Pyrexia	2 (3)	0	1 (2)
Influenza	0	3 (5)	0
Pneumonia	3 (5)	2 (3)	3 (5)
Adverse events			
No. of patients with ≥1 adverse event	57 (86)	56 (88)	55 (89)
Most frequent adverse events‡			
Headache	11 (17)	14 (22)	10 (16)
Back pain	10 (15)	13 (20)	7 (11)
Nausea	12 (18)	11 (17)	7 (11)
Arthralgia	12 (18)	9 (14)	5 (8)
Pain in extremity	11 (17)	8 (12)	10 (16)
Urinary tract infection	9 (14)	7 (11)	7 (11)
Upper respiratory tract infection	7 (11)	7 (11)	6 (10)
Pyrexia	7 (11)	6 (9)	4 (6)
Diarrhea	7 (11)	5 (8)	2 (3)
Musculoskeletal pain	8 (12)	4 (6)	6 (10)
Pruritus	5 (8)	7 (11)	3 (5)
Vomiting	5 (8)	7 (11)	3 (5)
Chest pain	1 (2)	7 (11)	1 (2)

N Engl J Med 2017; 376(5): 429-39.

L-Glutamine



$$\frac{NADH}{NAD^{+}+NADH}$$

https://www.endarirx.com/how-ENDARI-works

Phase 3 Trial of L-Glutamine in Sickle Cell Disease

- Randomized, placebo controlled, double-blind, parallel-group trial
- Enrolled patients 5 years old or older with SCD who had at least 2 episodes of pain crisis during the previous year
  - Patients on a stable dose of hydroxyurea for 3 months were eligible for enrollment
- Excluded patients if they required hospitalization for a non-SCD related reason in the 2 months before screening, received blood products within 3 weeks of screening, received L-glutamine within 30 days of screening, had an international normalized ratio of >2 or a serum albumin <3 g/dL
- Patients randomized in a 2:1 ratio to receive:
  - L-glutamine 0.3 mg/kg/dose (maximum = 30 g/day) (n = 152 patients)
  - Placebo (n = 78 patients)
- Patients given doses for 48 weeks and tapered over 3 weeks
- Powder mixed with a nonheated food and consumed immediately

N Engl J Med 2018; 379(3): 226-35.

Phase 3 Trial of L-Glutamine in Sickle Cell Disease

- Primary endpoint: Significantly less number of pain crisis at week 48
- Significantly less hospitalizations at week 48 and less days in the hospital
- No difference in ED visits that did not result in hospitalization
- Fewer episodes of acute chest syndrome
- No significant differences regards to hemoglobin level, hematocrit level, or reticulocyte count

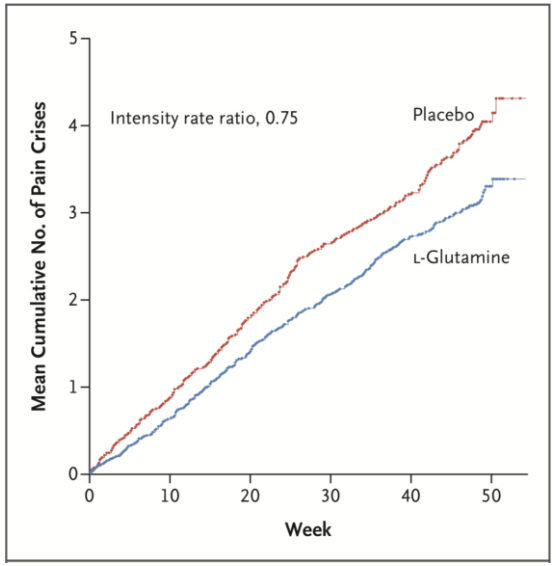
Table 2. End-Point and Additional Analyses.

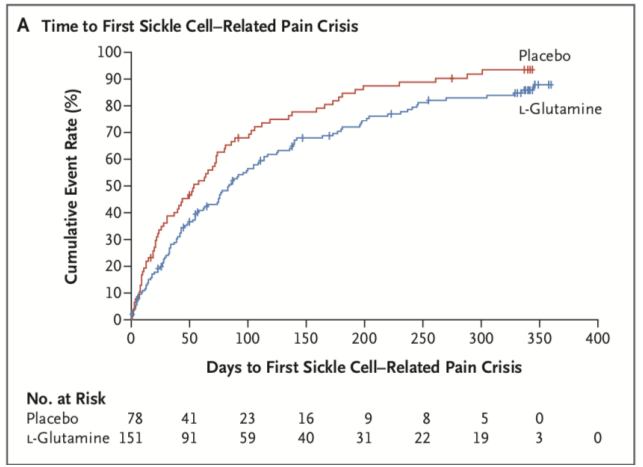
Through Week 48	L-Glutamine (N=152)	Placebo (N=78)	P Value
Primary end point			
No. of pain crises			0.005*
Mean	3.2±2.24	3.9±2.54	
Median (range)	3 (0–15)	4 (0–15)	
Secondary end points			
No. of hospitalizations for sickle cell–related pain			0.005*
Mean	2.3±1.99	3.0±2.33	
Median (range)	2 (0–14)	3 (0–13)	
No. of emergency department visits for sickle cell–related pain			0.09*
Mean	1.1±1.49	1.5±2.29	
Median (range)	1 (0–12)	1 (0–15)	
Additional analyses			
Cumulative no. of days in hospital			0.02†
Mean	12.1±16.6	18.1± 27.4	
Median (range)	6.5 (0–94)	11 (0–187)	
Median no. of days to first pain crisis (95% CI)	84 (62–109)	54 (31–73)	0.02‡
Median no. of days to second pain crisis (95% CI)	212 (153–250)	133 (115–179)	0.03‡
Episodes of acute chest syndrome — no. (%)			0.003*
0	139 (91.4)	60 (76.9)	
≥1	13 (8.6)	18 (23.1)	
1	10 (6.6)	13 (16.7)	
2	3 (2.0)	4 (5.1)	
3	0	1 (1.3)	

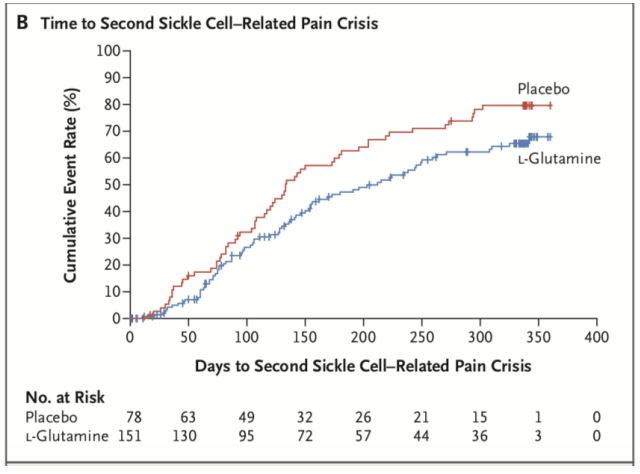
N Engl J Med 2018; 379(3): 226-35.

Phase 3 Trial of L-Glutamine in Sickle Cell Disease

- Sickle cell-related pain crisis over time was also measured by the intensity rate ratio
  - Ratio of the recurrent event rates in each group
  - Indicates that the cumulative number of painful crisis was 25% lower in the L-glutamine group than in the placebo group over the 48 weeks of treatment
- Median time to first pain crisis (p = 0.02)
  - L-glutamine group: 84 days
  - Placebo group: 54 days
- Median time to second pain crisis (p = 0.03)
  - L-glutamine group: 212 days
  - Placebo group: 133 days







N Engl J Med 2018; 379(3): 226-35.

Phase 3 Trial of L-Glutamine in Sickle Cell Disease

- Overall adverse events and serious adverse events were more common in the placebo group than the L-glutamine group
- Largest difference between groups was nausea, arm or leg pain, or back pain
- 2 patients in the L-glutamine group died from sudden cardiac death (long history of organ failure and coexisting medical conditions)
- 5 patients in the L-glutamine group withdrew from the study due to adverse effects:
  - Hyperplenism and abdominal pain
  - Dyspepsia
  - Burning sensation in feet
  - Hot flashes
  - Pregnancy

Table 3. Adverse Events (Safety Population).*

Adverse Event	L-Glutamine (N=151)	Placebo (N=78)
	no. of patients (%)	
Cardiac disorders		
Tachycardia	8 (5.3)	4 (5.1)
Gastrointestinal disorders		
Constipation	38 (25.2)	19 (24.4)
Nausea	34 (22.5)	13 (16.7)
Vomiting	22 (14.6)	10 (12.8)
Abdominal pain upper	16 (10.6)	6 (7.7)
Diarrhea	12 (7.9)	5 (6.4)
General disorders and administration site conditions		
Chest pain (noncardiac)	21 (13.9)	7 (9.0)
Fatigue	9 (6.0)	1 (1.3)
Infections and infestations		
Urinary tract infection	10 (6.6)	3 (3.8)
Musculoskeletal and connective tissue disorders		
Pain in extremity	24 (15.9)	6 (7.7)
Back pain	20 (13.2)	5 (6.4)
Nervous system disorders		
Headache	32 (21.2)	14 (17.9)
Dizziness	8 (5.3)	4 (5.1)
Respiratory, thoracic, and mediastinal disorders		
Nasal congestion	11 (7.3)	5 (6.4)

N Engl J Med 2018; 379(3): 226-35.

Summary

- Voxelotor is a polymerization inhibitor that is FDA approved for children ages 12 and older. It was shown to increase hemoglobin in patients with SCD, but had no effect on the incidence of vaso-occlusive crisis.
- Crizanlizumab is a P-selectin inhibitor that is FDA approved for children ages 16 and older. It was shown to reduce the rate of sickle cell pain crisis, but has no effect on hemoglobin or annual rate of days hospitalized.
- L-glutamine improves NAD redox potential and is FDA approved for children ages 5 and older. Is was shown to reduce the number of pain crisis and hospitalizations, but has no effect on hemoglobin.

www.accessdata.fda.gov

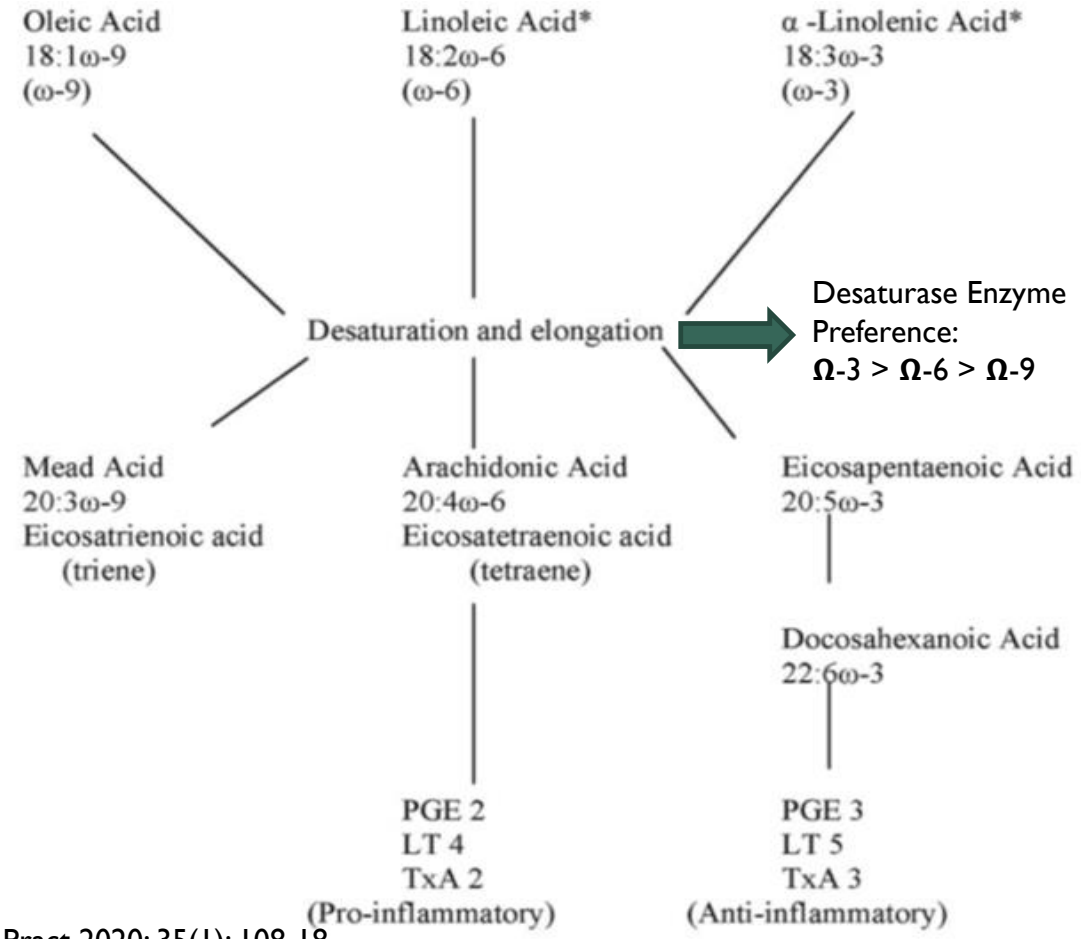
Polling Question 2

- Which medication demonstrated the ability to improve hemoglobin concentrations in patients with sickle cell disease?
  - Folic acid
  - Crizanlizumab
  - Voxelotor
  - L-glutamine

Update in Neonatal Lipid Emulsions

LIU Pharmacy

Essential Fatty Acids



- Essential fatty acids are fatty acids that cannot be synthesized by the body
  - α-linolenic acid
  - Linoleic acid
- Needs can be met through exogenous (dietary) sources or lipolysis of adipose tissue
- More recent data has questioned the essential nature of α-linolenic acid and linoleic acid
  - Arachidonic acid and DHA may be just as effective at preventing essential fatty acid deficiency and promoting growth

Nutr Clin Pract 2020; 35(1): 108-18.
Nutr Clin Pract 2006; 21: 387-394.

Comparison of Lipid Products

	Soybean Oil Lipid Emulsion (SOLE)	Soy-Medium Chain Triglyceride-Olive-Fish Oil Lipid Emulsion (SMOF)	Fish Oil Lipid Emulsion (FOLE)
Arachadonic acid	7.5%	-	0.2-2%
Linoleic acid (Ω-6)	44-62%	14-25%	1.5%
α-linolenic acid (Ω-3)	4-11%	1.5-3.5%	1.1%
Eicosapentaenoic acid (EPA)	-	1-3.5%	13-26%
Docosahexanoic acid (DHA)	-	1-3.5%	14-27%
Vitamin E	0 mg/mL	0.163-0.225 mg/mL	0.3 mg/mL
Typical Dose	Adult: 1-2 g/kg/day Pediatric: 2-3 g/kg/day	Adult: 1-2 g/kg/day Pediatric: 2-3 g/kg/day	Pediatric: 1 g/kg/day

SMOFlipid Package Insert. Fresinius Kabi. 2016.
Omegavan Package Insert. Fresinius Kabi. 2018.
Intralipid Package Insert. Fresinius Kabi. 2015.

Hepatobiliary Complications of Parenteral Nutrition

Steatosis

- Hepatic fat accumulation
  - Elevations in transaminases that occur within 2 weeks of initiating PN
  - Can manifest as a benign lesion or may lead to fibrosis and cirrhosis
- More common in adult patients

Cholestasis

- Impaired secretion of bile or biliary obstruction
  - Elevations in alkaline phosphatase, γ-glutamyl transpeptidase (GGT), and conjugated/direct bilirubin (>2 mg/dL)
  - May progress to jaundice, cirrhosis, and liver failure
- Most common in children

Gallbladder Stasis/Sludge

- Due to lack of enteral stimulation
- Impaired cholecystokinin (CCK) release
  - Impairs bile flow and gallbladder contractility
  - Acalculous cholecystitis

ASPEN Parenteral Nutrition Handbook, 2nd Ed. 2014. Chapter 8: Complications of Parenteral Nutrition, p. 200.

Fish Oil Lipid Emulsion

- FDA approved in 2018 as a source of calories and fatty acids in pediatric patients with parenteral nutrition associated liver disease
  - Previously available through investigational new drug (IND) application and specific sites
  - Most data in the US comes from a compassionate use program
- Dosing (maximum): 1 g/kg/day
- FOLE is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition associated cholestasis (PNAC)
- Limitations of use (from package insert):
  - FOLE is not indicated for the prevention of PNAC. It has not been demonstrated that FOLE prevents PNAC in parenteral nutrition dependent patients
  - It has not been demonstrated that the clinical outcomes observed in patients treated with FOLE are a result of the Ω-6:Ω-3 fatty acid ratio of the product

Omegavan. [Package Insert]. Fresinius Kabi. Graz, Austria. 2018.

Comparison of Growth Patterns (FOLE vs. SOLE)

- Included patients with intestinal failure that were <2 years old, had a direct bilirubin of >2 mg/dL, and prospectively received FOLE (1 g/kg/day) (n = 82)
- Compared to similar retrospective patients who received SOLE (up to 3 g/kg/day) (n = 41)
- No difference in age-adjusted body weight, height/length, or head circumference at the time of cholestasis resolution or study conclusion
- FOLE recipients shower higher mean prealbumin concentrations, substantially lower mean triglyceride concentrations, and more normal glucose concentrations compared to SOLE recipients

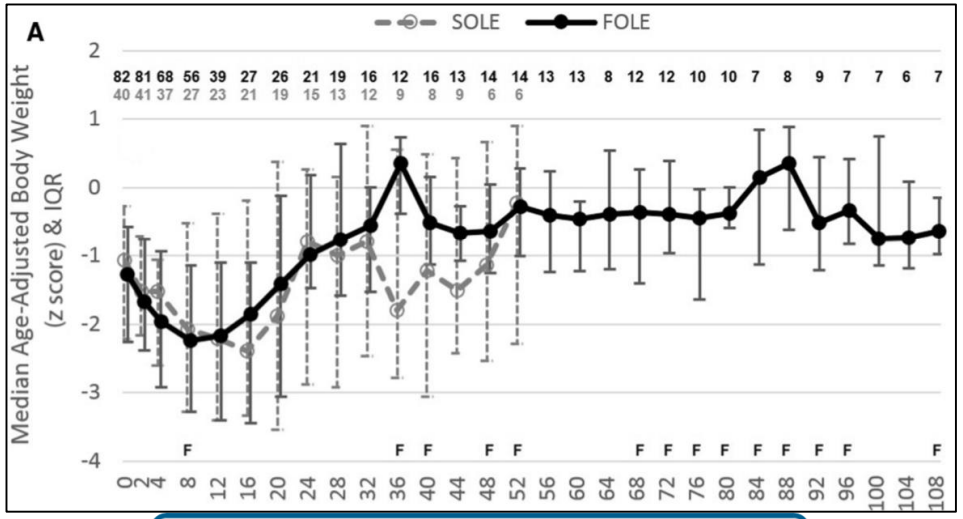


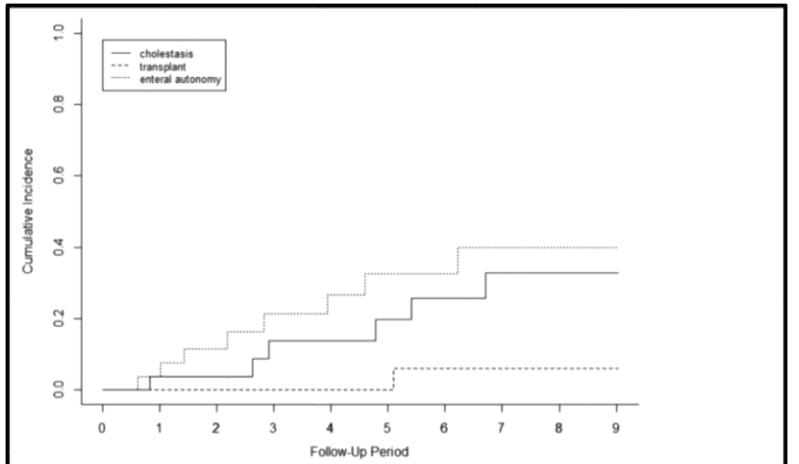
Table III. Nutrition received during treatment*

Categories (units)†	Integrated pair-matched population		
	FOLE	SOLE	*P* value
PN lipid calories (kcal/kg/d)	n = 75 10.13 (9.72, 10.57)	n = 21 23.07 (18.23, 26.94)	<.001
PN lipid dose (g/kg/d)	n = 75 0.92 (0.88, 0.96)	n = 21 2.31 (1.82, 2.69)	<.001
PN amino acid dose (g/kg/d)	n = 59 2.45 (2.09, 2.85)	n = 16 2.17 (1.56, 2.85)	.132
PN dextrose dose (g/kg/d)	n = 59 15.61 (11.12, 19.0)	n = 16 12.37 (9.23, 12.71)	.010
PN total calories (kcal/kg/d)	n = 75 71.19 (56.27, 85.86)	n = 21 72.80 (59.46, 88.05)	.791
EN total calories (kcal/kg/d)	n = 59 14.06 (3.02, 32.89)	n = 16 23.12 (10.51, 37.31)	.162

J Pediatr 2020; 219: 98-105.

Long Term Use of FOLE

- Prospective, observational study of children with intestinal failure associated liver disease who received FOLE for 6 months, followed by a switch back to SOLE (n = 27)
  - During FOLE treatment, the median time to resolution of cholestasis was 13 weeks (range: 4-24 weeks)
- Cumulative incidence rate of cholestasis redevelopment was 26% when SOLE was resumed



Cumulative Incidence Rates	Year 1	Year 2	Year 3
Cholestasis	0.04 (0.003–0.16)	0.14 (0.03–0.32)	0.26 (0.08–0.47)
Transplant	0	0	0.06 (0.003–0.25)
Enteral Autonomy	0.12 (0.03–0.27)	0.27 (0.10–0.47)	0.40 (0.17–0.62)

Table 3. Liver Function, Nutrition, and Growth During Follow-Up.

Variable	Start of Follow-Up	End of Follow-Up	*P*-Value[a] n = 27	Mean Change[b] (95% CI)	*P*-Value n = 27
CB, mg/dL	0.2 (0.1, 1.5)	0.2 (0.1, 8.8)	.06[c]	0.005 (0.003, 0.008)[c]	<.001[c]
AST, IU/L	47 (23, 155)	55 (16, 553)	.67	0.16 (0.03, 0.28)[c]	.01
ALT, IU/L	55 (17, 197)	47 (14, 231)	.98	0.06 (−0.06, 0.18)[c]	.4
GGT, IU/L	69 (12, 445)	79 (18, 536)	.19[c]	0.63 (0.36, 0.90)[c]	<.001[c]
Platelets, K (×1000)	289 (93, 705)	200 (27, 446)	.003	−0.21 (−0.38, −0.05)[c]	.01
AP, IU/L	338 (218, 1012)	266 (90, 672)	.002	−0.73 (−1.04, −0.41)[c]	<.001
Serum albumin, mg/dL	3.9 (2.8, 4.9)	3.6 (1.7, 4.6)	.11	−0.0004 (−0.0015, 0.0007)[c]	.5
PN, kcal/kg/d	66 (41, 103)	64 (12, 81)	.005	−2.1 (−3.70, −0.52)[d]	.01
Fat, g/kg/wk	6.8 (6.1, 7.3)	6.6 (0, 15.0)	.87	−0.11 (−0.40, 0.18)[d]	.5
Weight *z*-score	−0.4 (−2.4, 1.2)	−0.60 (−2.4, 1.4)	.81	0.16 (0.04, 0.27)[d]	.01
Height *z*-score	−1.2 (−4.7, 0.8)	−1.1 (−3.9, 2.9)	.10	0.18 (0.02, 0.34)[d]	.03

J Parenter Enteral Nutr 2019: 43(6): 708-16.

Additional Pharmacy Considerations

- Non-di-2-ethylhexyl phthalate (DEHP) infusion sets and containers are preferred
  - Intravenous lipid emulsions may extract the DEHP plasticizer
  - Do not use polyvinyl chloride containers
- Infuse over 8 to 24 hours
  - If >12 hours, two separate containers should be used
- Maximum infusion rate: 0.17 g/kg/hr
- 1.2 micron in-line filter should be used
- Limited compatibility information (can not infer compatibility from other lipids sources)

Nutr Clin Pract 2020; 35(1): 108-18.

Polling Question 3

- A 10 month old, 4.5 kg male with short bowel syndrome is receiving home parenteral nutrition. Early in his clinical course, he developed parenteral nutrition associated cholestasis presumably from a soybean oil lipid emulsion (SOLE). He was switched to the fish oil lipid emulsion (FOLE), has been receiving this for 6 months. His cholestasis has now reversed. What risks may be associated with changing him back to SOLE at this time?
  - Reduction is growth velocity
  - Essential fatty acid deficiency
  - Return of cholestasis
  - Aluminum toxicity

Summary

- Updates guidelines for pediatric sepsis suggest new strategies for fluid provision and vasopressor support while discouraging the use of corticosteroids, stress ulcer prophylaxis, and DVT prophylaxis.
- Voxelotor, crizanlidumab, and L-glutamine are new therapies for sickle cell disease that can improve hemoglobin or reduce vaso-occlusive crisis and days hospitalized.
- FOLE provides adequate calories for growth and development in children with hepatobiliary complications of parenteral nutrition administration; discontinuation may lead to rebound cholestasis.

Caring for the Little Ones: Updates on Clinical Issues in Pediatrics

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