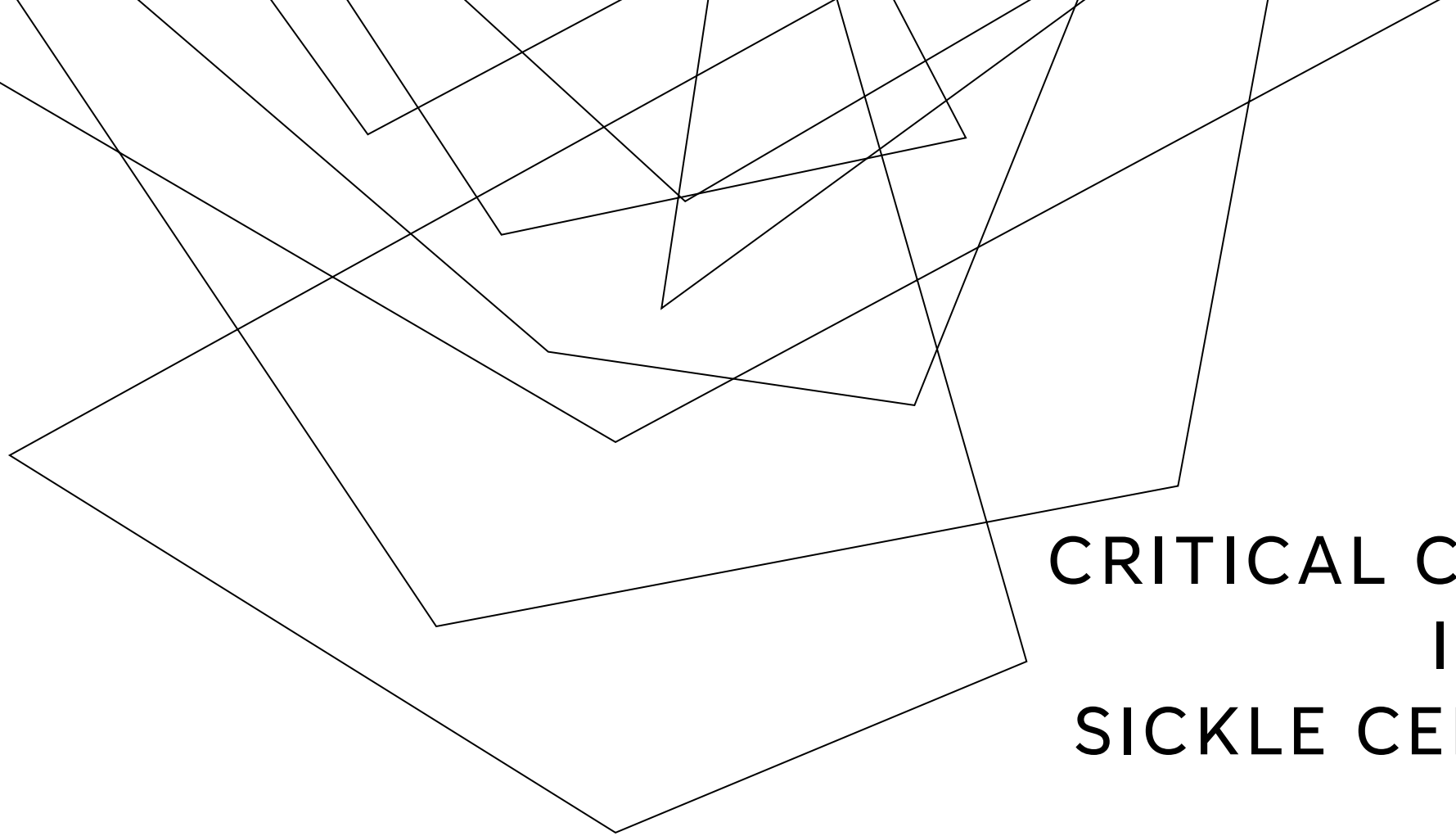

CRITICAL CARE ISSUES IN SICKLE CELL DISEASE

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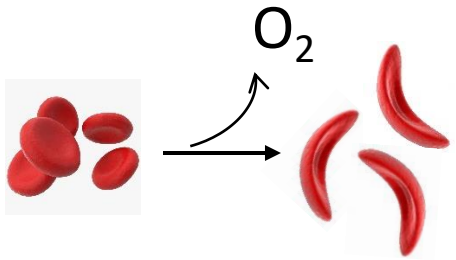
Director, Comprehensive Sickle Cell Center
Associate Professor, Harvard Medical School

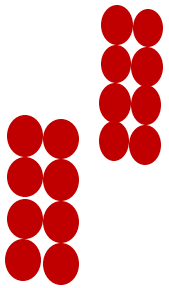
OUTLINE

- BACKGROUND ON SICKLE CELL DISEASE
- ACUTE CHEST SYNDROME
- ACUTE ISCHEMIC/HEMORRHAGIC STROKES
- SICKLE HEPATOPATHY
- DELAYED HEMOLYTIC TRANSFUSION REACTIONS

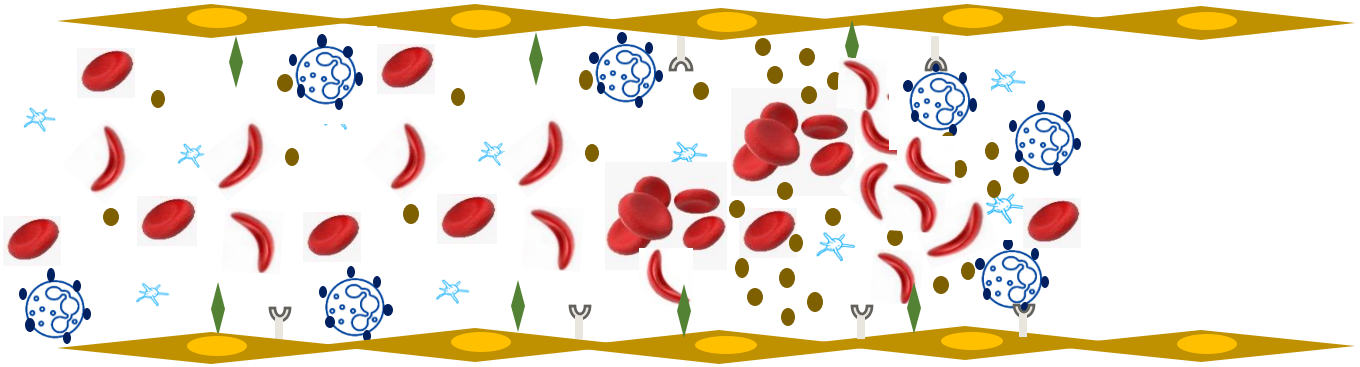
BACKGROUND

CENTRAL PATHOPHYSIOLOGY AND SICKLE VASCULOPATHY





HbS polymerization

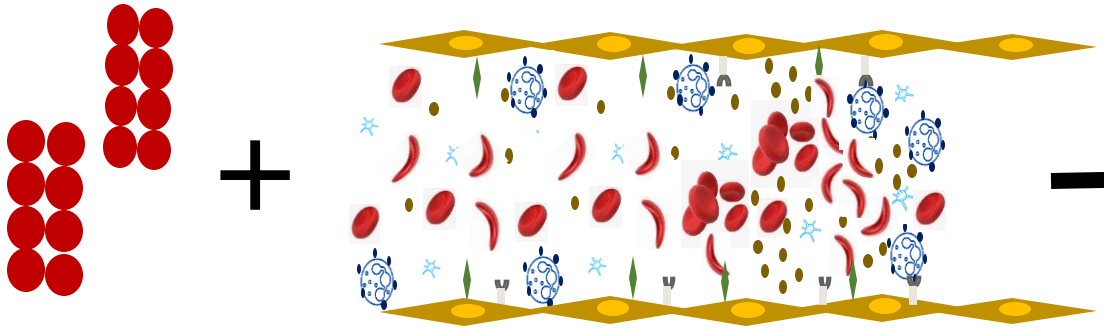


heme
platelets
Neutrophil with adhesion molecule
Endothelial adhesion molecule
P-selectins and von Willebrand factor

Modified from Dutra, FF and Bozza, MT. Front Pharmacol 2014;5:15

(SOME) CLINICAL MANIFESTATIONS OF SCD

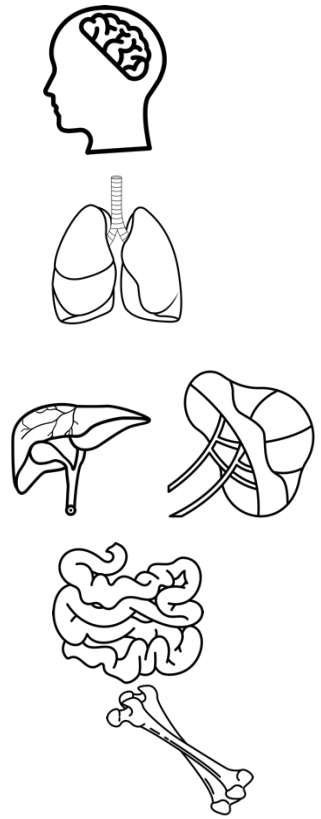
Complex Pathophysiology



HbS polymerization

Sickle vasculopathy

Acute vaso-occlusive Episodes (VOE)	Chronic hemolysis	Chronic organ damage
pain	**Anemia**	
Acute chest syndrome	**Jaundice**	
Acute ischemic stroke	**Sickled RBCs**	
	↑ LDH	
	Thrombosis risk	
	Tissue inflam.	

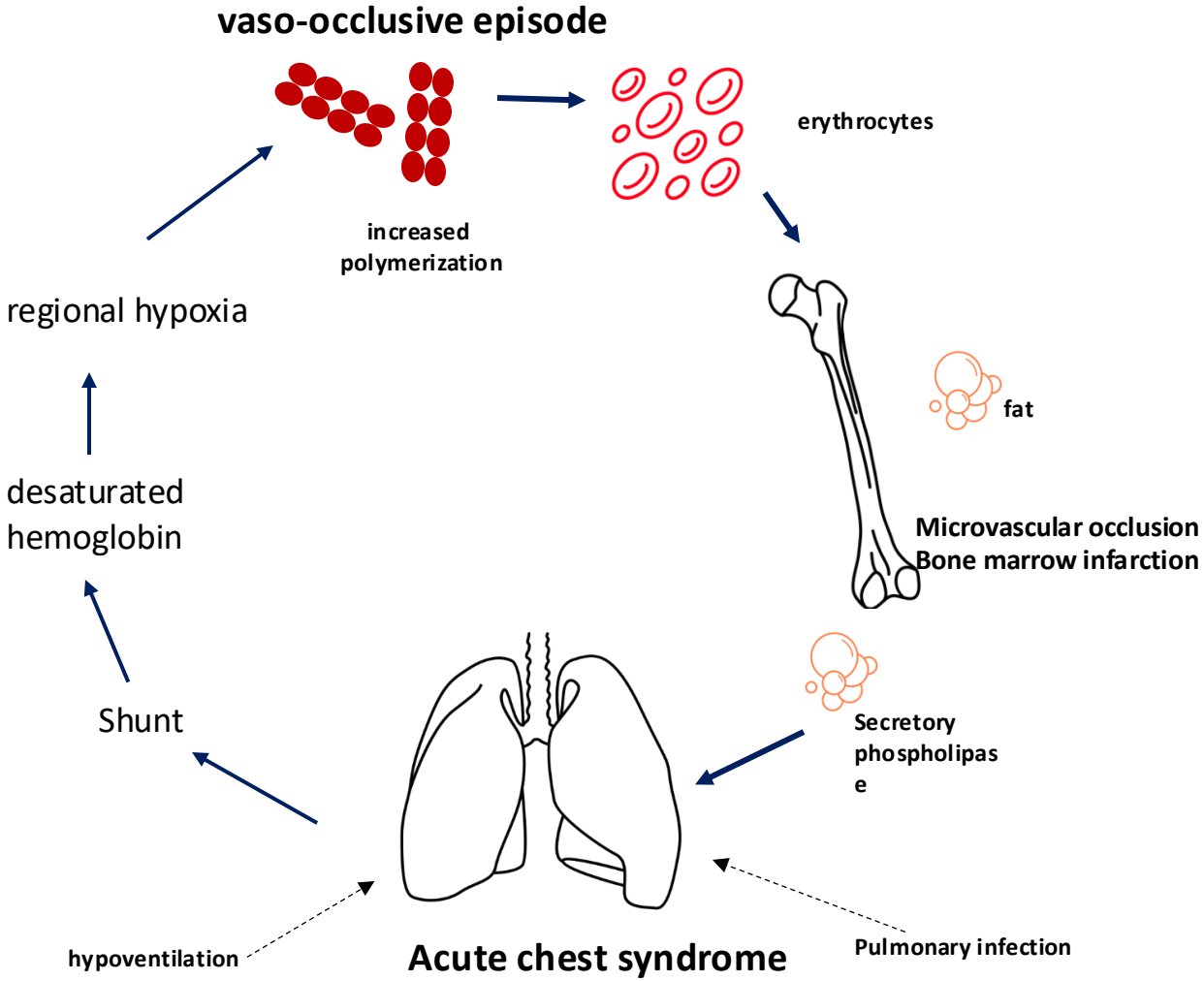


Modified from Dutra, FF and Bozza, MT. Front Pharmacol 2014;5:15

ACUTE CHEST SYNDROME

ACUTE CHEST SYNDROME

- Acute illness
- New infiltrate on CXR
- ≥ new respiratory signs or symptoms
  - chest pain
  - Temp >38.5 °C
  - SOB/tachypnea
  - hypoxemia (>3% ↓, or <94%)
  - Wheezing or cough



Modified from Gladwin and Vichinsky. NEJM 2008; 359:2254

ORIGINAL ARTICLE

Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease

Elliott P. Vichinsky, M.D., Lynne D. Neumayr, M.D., Ann N. Earles, R.N., P.N.P., Roger Williams, M.D., Evelyne T. Lennette, Ph.D., Deborah Dean, M.D., M.P.H., Bruce Nickerson, M.D., Eugene Orringer, M.D., Virgil McKie, M.D., Rita Bellevue, M.D., Charles Daeschner, M.D., Miguel Abboud, M.D., et al., for the National Acute Chest Syndrome Study Group*

- Prospective 30-center study of 671 episodes of ACS in 538 pts.
- **Findings:**
  - **PE and resp. infection** were main etiologies
  - Mean LOS in hospital was **10.5 days**
  - 13% pts required vent. support
  - **3% died**
  - 1% acquired RBC alloimmunization

TABLE 4. CAUSES OF THE ACUTE CHEST SYNDROME.*

CAUSE	ALL EPISODES (N=670)	AGE AT EPISODE OF ACUTE CHEST SYNDROME		
		0–9 YR (N=329)	10–19 YR (N=188)	≥20 YR (N=153)
	no. of episodes (%)			
Fat embolism, with or without infection†	59 (8.8)	24	16	19
Chlamydia‡	48 (7.2)	19	15	14
Mycoplasma§	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	5	12
Mixed infections	25 (3.7)	16	6	3
Legionella	4 (0.6)	3	0	1
Miscellaneous infections¶	3 (0.4)	0	3	0
Infarction‖	108 (16.1)	50	43	15
Unknown**	306 (45.7)	139	88	79

Vichinsky et al. N Eng J M 2000; 342:1855-1865

CLASSIFICATIONS OF ACUTE CHEST SYNDROME

2 categories

- ***Non- rapidly progressive ACS***
  - pulmonary infiltrate on CXR
- ***Rapidly progressive ACS***
  - decreased O2 needing 3L to maintain O2 sat >90%
  - intubation and mechanical ventilation within 24 hours of the onset of respiratory symptoms

3 Categories

- ***Mild:*** ≤ 1L to keep O2sat >95%
- ***Moderate:*** > 1L < 3L to keep O2sat >95%
- ***Severe:*** >3L to keep O2sat >95%

PLATELET COUNT PREDICTS POOR OUTCOMES IN ACS

Study		Patients	Platelet count	Poor outcome
Alkindi 2020	Retrospective Case-control	96 cases:20 controls	lower Hb, higher WBC, lower O2	
Alhandalous 2015	Retrospective	71 hospital SCD adults	Decline in plts >10%	2:1
Shome 2018	Retrospective	136 SCD pts in ICU	**ICU day 1** plts ∝ prognostic scores Significant ↓plts in non-survivors	
Chaturvedi 2016	Retrospective	173 SCD pts (97 kids; 76 adults)	Hospital day 1 plt ≤ 150,000 or 50% ↓ from baseline	OR 4.82

MANAGEMENT OF ACS

Potential classification and management of ACS.

	Fever	Lung	Platelet count drop from baseline	Hemoglobin drop from baseline	Possible treatment options
Mild	≥38.3 °C	New pulmonary infiltrate Chest pain that improves with adequate pain management Improvement in symptoms with bronchodilators if patient has underlying asthma. ≤1L of oxygen needed to keep O_2 sat ≥95%	≤10%	<1 g/dL	Adequate pain control Antibiotics Incentive spirometry Improve ambulation. Avoid overhydration. Thromboprophylaxis (adults) if Platelets >50,000
Moderate	≥38.3 °C	New pulmonary infiltrate Chest pain that improves with adequate pain management Requiring >1 L but <3L of oxygen to maintain O_2 sats >95%	11%-20%	1-2 g/dL	Adequate pain control Antibiotics Incentive spirometry Improve ambulation. Avoid overhydration. Thromboprophylaxis (adults) if Platelets >50,000 Transfusion[a]
Severe	≥38.3 °C	New pulmonary infiltrate Severe chest pain with a need for intubation or mechanical ventilation within 24 hours of the onset of respiratory symptoms Requiring ≥3 L of oxygen to maintain O2 sats >95%	≥20% with no concerns for splenomegaly	>2 g/dL	Adequate pain control Consider transfer to intensive care unit if mechanical ventilation is indicated Antibiotics Incentive spirometry Avoid overhydration. Medical Thromboprophylaxis (adults) if Platelets >50,000 Transfusion[a]

Bhasin N, Sarode R. ACS in SCD. Transfus Med Rev. 2023 Jul;37(3):150755.

MANAGEMENT OF SEVERE ACS

- Management is symptomatic
- Frequently develops in hosp.
- Be attentive

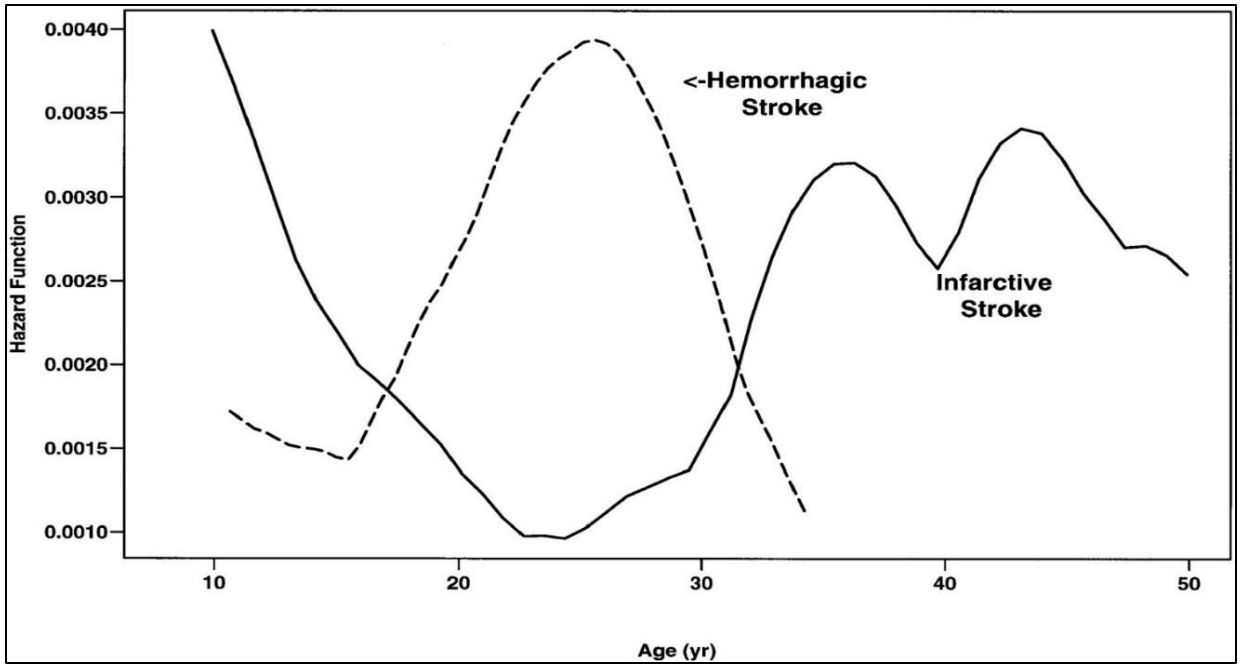
GOAL	INTERVENTION/MANAGEMENT
HBS <30% Hgb 30 – 33%	RBC Exchange transfusion Simple transfusions
O2sat >95%	Intubation and mechanical ventilation Incentive spirometry/bronchodilaton
Antibiotic coverage	Community-acquired Atypical organisms (Mycoplasma, Chlamydophila)
Correction of negative fluid balance	IV fluids Do not overhydrate
Pain management (to minimize chest splinting)	IV opioids + adjuvant meds Avoid oversedation
Prevent VTE	Thromboprophylaxis (plts >50,000)

ACUTE ISCHEMIC STROKE

STROKES IN SCD

- Ischemic strokes in adults with SCD aged 35–64 years and >65 years, have rates of 1.16 and 4.7 per 100 PYO, **(3X the general population)**
- Intraparenchymal, intraventricular, subarachnoid and subdural hemorrhages have been described in SCD pts
- Cerebral hemorrhage in SCD is commonly related to aneurysms
- Hemorrhage has the highest incidence in young adults (20–30 years)

Incidence of first CVA in SS patients

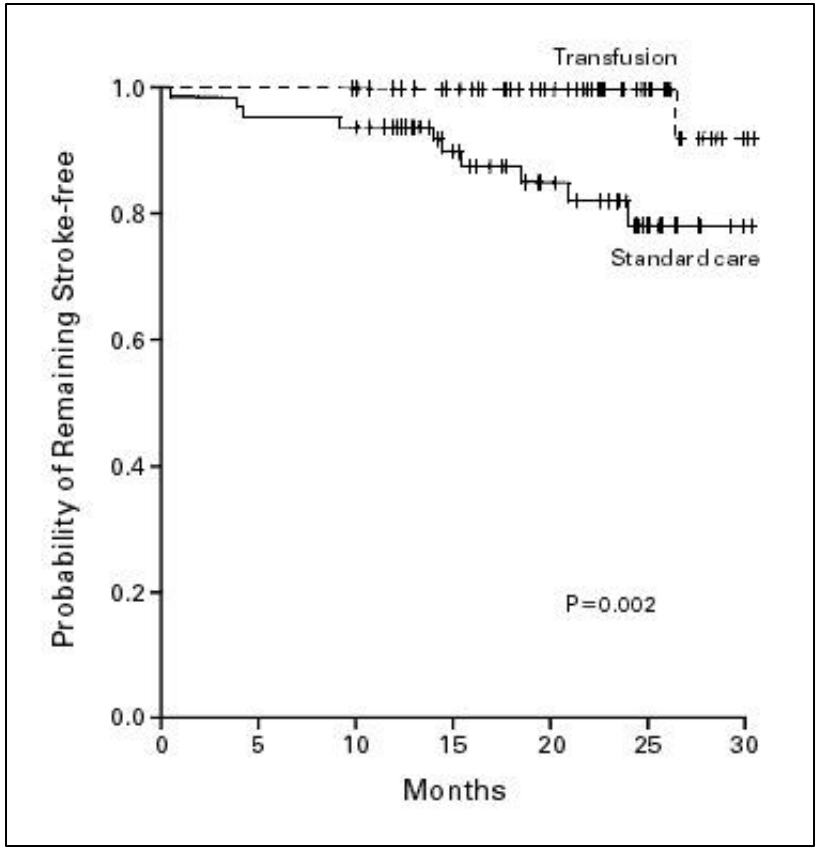


Smoothed hazard rates of infarctive and hemorrhagic stroke in SS pts by age.

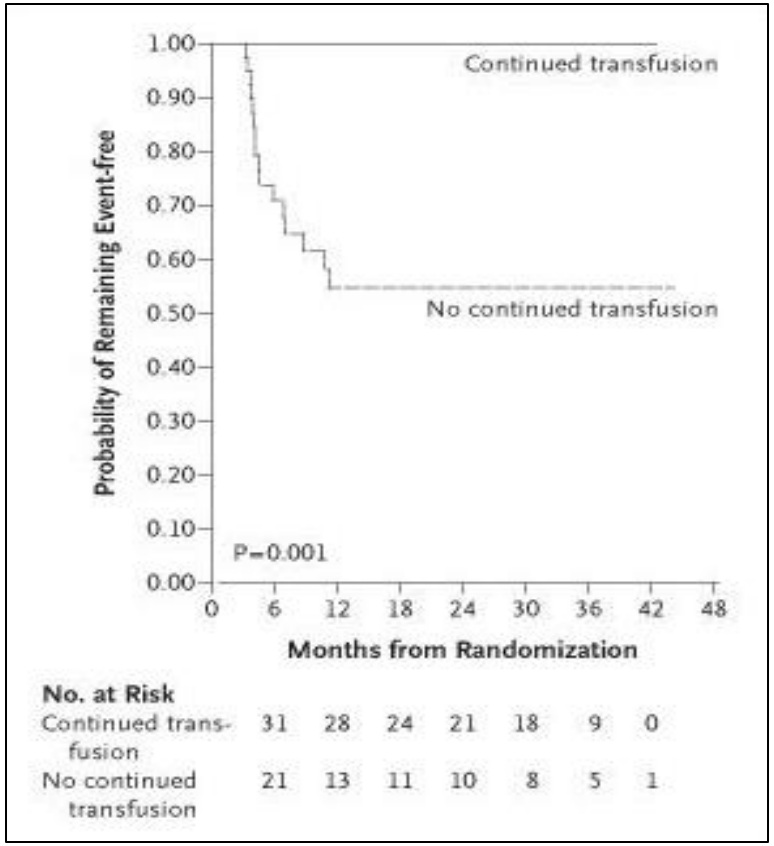
Ohene-Frempong K et al. Blood 1998;91:288-294

PRIMARY PREVENTION TRIALS IN SCD

Prevention of a First Stroke by Transfusions in Children with Sickle Cell Anemia and Abnormal Results on TCD (**STOP 1**). Adams RJ et al. **N Engl J Med 1998;339:5-11**.



The Optimizing Primary Stroke Prevention in Sickle Cell Anemia (**STOP 2**) Trial Investigators. Adams RT et al. **N Engl J Med 2005;353:2769-2778.**



MANAGEMENT OF ACUTE STROKE AND TRANSIENT ISCHEMIC ATTACK

- **Prompt** blood transfusion given immediately **without delay > 2 hours**.
- Exchange RBC transfusion is preferred over simple transfusion.
- Type of transfusion depends on patient factors; goal is **Hct ~ 30-33%; HbS <30%**

- For Moya moya syndrome – evaluate for revascularization surgery
- IV tPA may be considered in adults' with SCD (usual tPA criteria)

MANAGEMENT OF STROKE

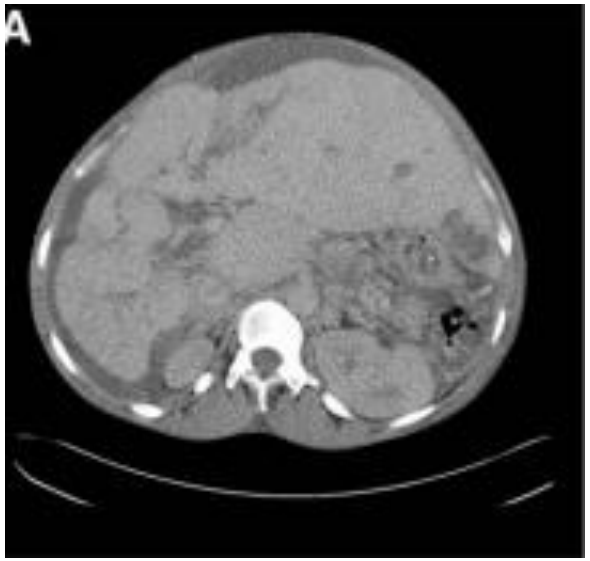
- Chronic management: Long-term transfusion to maintain HbS 30%-50%
- **Trials for secondary stroke prevention:**
  - Stroke With Transfusion Changing to Hydroxyurea (**SWiTCH**) study was a multicenter randomized trial: hydroxyurea arm inferior to transfusions. Closed early.
  - Chronic transfusion (2.2/100 pt yrs[1]) > HU(3.6/100 pt yrs[2]) > stopping RBCs(50% recur[3])

1. Scothorn et al. J. Pediatr. 2002;140:348-54.
2. Ware et al. J Pediatr 2004;145:346-52.
3. Wang, Kovnar, Tonkin. J. Pediatr. 1991:118:377-82

SICKLE HEPATOPATHY

SICKLE HEPATOPATHY

- An umbrella term describing various patterns of liver injury seen in patients with sickle cell disease



CLINICAL SPECTRUM OF SICKLE HEPATOPATHY

- Liver involvement in SCD has not been well characterized in terms of its natural history and pathogenesis

Ischemic injury sickling in hepatic sinusoids

Gall stone disease

Venous outflow obstruction

Sickle cell intrahepatic Cholestasis (SCIC)

Hepatic sequestration

Cirrhosis in 16-29% of pts

- Several patients (up to a third) will have more than one pathophysiological abnormality

ACUTE INTRAHEPATIC CHOLESTATIS/SCIC

- It is the most severe of acute hepatic manifestations of SCD
- Resembles Acute liver failure (ALF)

- It carries **high mortality.**
- More common in males; only 26% patients are female.

- Presents as acute hepatic crisis:
  - fever, RUQ pain, severe hyperbilirubinemia, mainly **conjugated**
  - Transaminitis: significantly elevated levels, up to 1000 IU/L.
  - Rapid progression to Acute Liver Failure; increased INR, decreased fibrinogen, hepatic encephalopathy, renal failure, multi-organ failure

MANAGEMEMENT OF ACUTE SCIC

- Can be rapidly fatal.
- Exchange RBC transfusions have dramatically decreased mortality
- Target : maintaining **HbS < 20–30% and Hb 10 (Hct 30)**

- Reversals of liver failure by aggressive RBC exchange transfusion and fresh frozen plasma have been reported

Ahn et al. Pediatr Blood Canc. 2005;45:184–190

MANAGEMEMENT OF ACUTE INTRAHEPATIC CHOLESTASIS/SCIC

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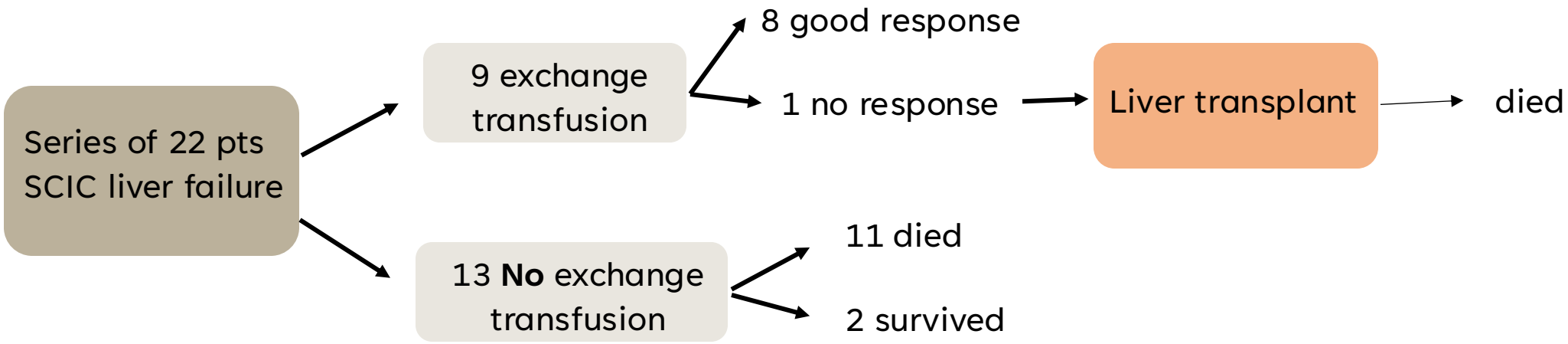


Ahn et al. Pediatr Blood Canc. 2005;45:184–190

ROLE OF LIVER BIOPSY IN ACUTE SICKLE HEPATOPATHY

- Percutaneous liver biopsy in the acute setting is noted to have high risk of bleeding complications

- Zakaria et al: 36% of pts undergoing percutaneous liver biopsy developed bleeding complications; 28% died

- Institute of Liver Studies at King's College Hospital,
  - 14 patients, biopsy in acute setting – 5 bleeding complication
  - 9 patients, biopsy as elective procedure – 0 bleeding complication

- Hepatic venous congestion is an important risk factor for post-biopsy hemorrhage

LIVER TRANSPLANT IN ACUTE INTRAHEPATIC CHOLESTATIS/SCIC

- Experience is limited
- Only 22 cases of liver transplantation have been reported, majority adults

- Two clinical phenotypes that benefit most:
  - end-stage SCD-related liver disease, without significant damage of other organs
  - liver disease (eg AIH) coincident to SCD

Retrospective series of 6 adult patients with liver transplants
- 5 SCIC ALF
- 1 AIH ALF

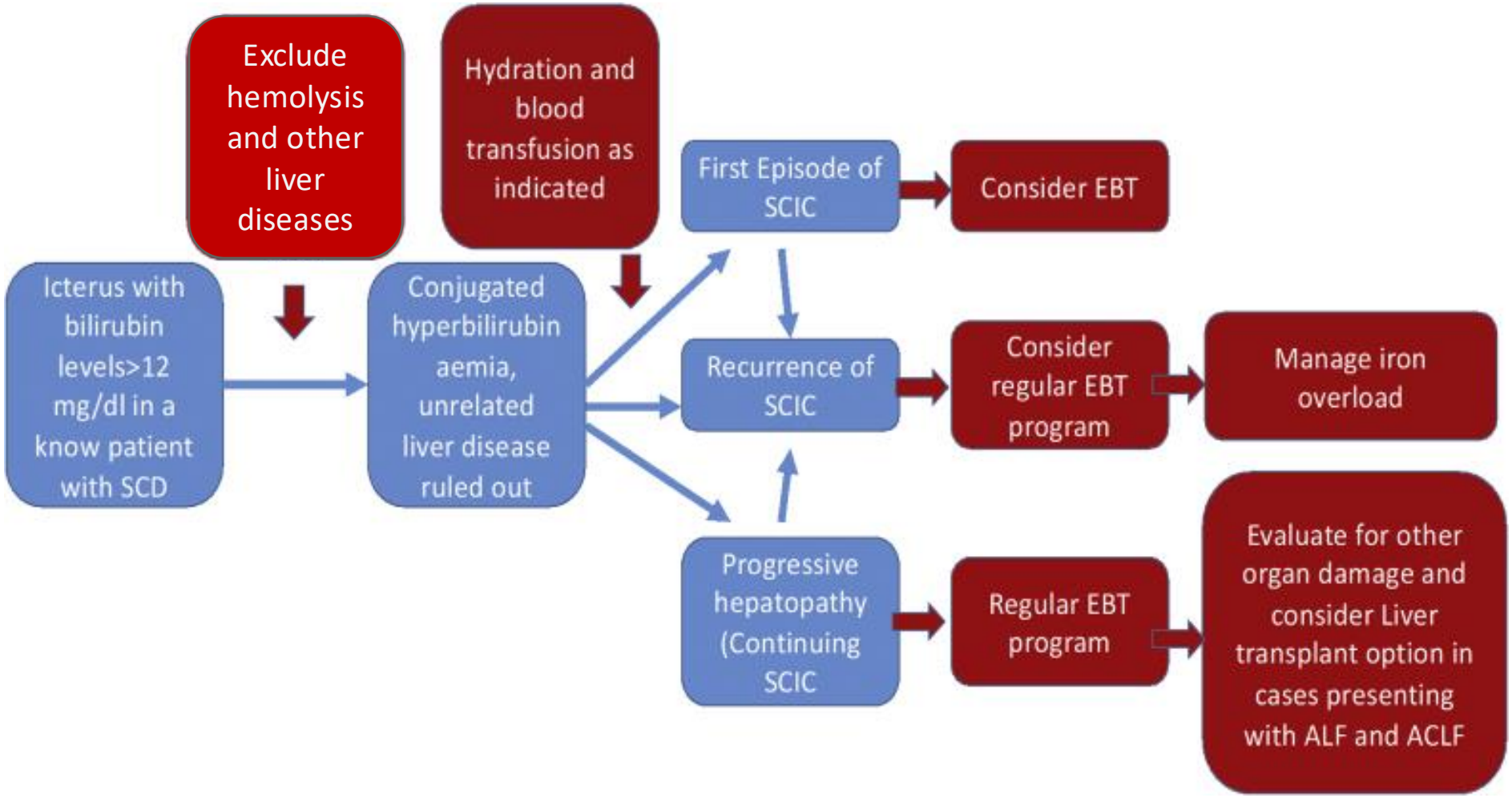
→ 1 severe rejection immediate post-op death on day 10

→ 5 others:
1-yr survival was 83.3%
5-yr survival was 44.4%
10-yr survival was 44.4%

All explanted livers were cirrhotic

Hurtova M, et al Liver Transpl. 2011 Apr;17(4):381-92.
Gardner K, et al. Blood. 2014 Apr 10;123(15):2302-7.

MANAGEMENT OF ACUTE SICKLE HEPATOPATHY

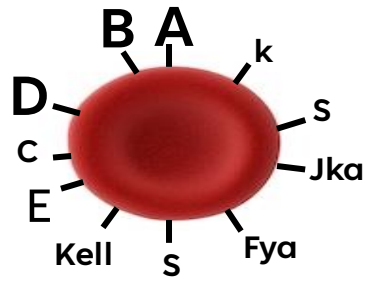


Praharaj et al. J Clin Exp Hepatol. 2021 Jan-Feb;11(1):82-96

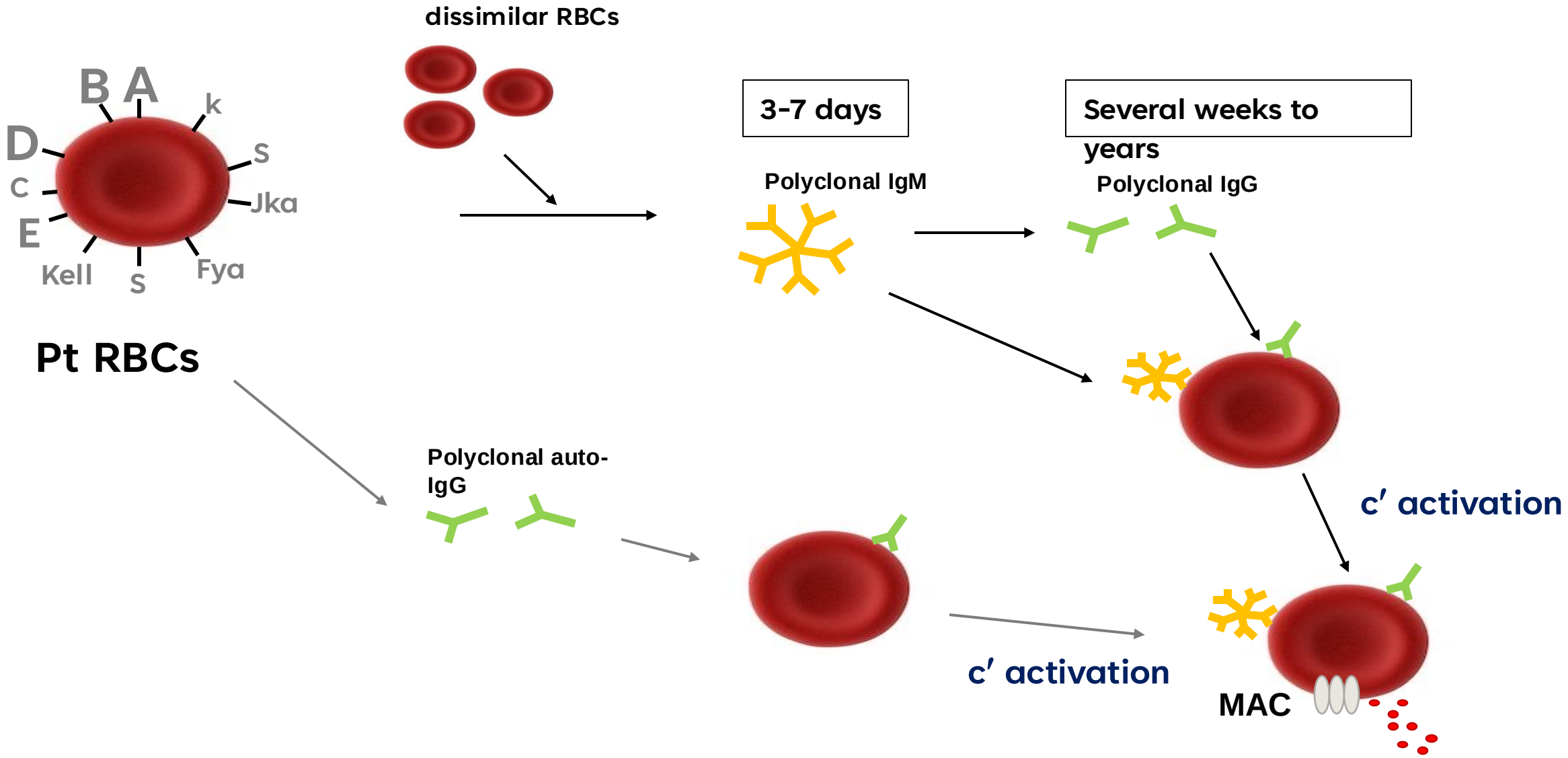
DELAYED HEMOLYTIC TRANSFUSION REACTION

DELAYED HEMOLYTIC TRANSFUSION REACTIONS (DHTR)

- DHTR is a feared adverse outcome of transfusion in SCD
- The reported incidence of DHTR in SCD is 4.8-7.7%.
- Occurs after re-exposure to RBC antigen that the pt had previously been immunized against



DELAYED HEMOLYTIC TRANSFUSION REACTION



CLINICAL DIAGNOSIS OF DHTR

- Making the diagnosis relies on a High Index of suspicion
- Clinical Presentation:
  - Anemia and Pain – **don't mistake this for a pain episode**
  - Fever
  - Hemoglobinuria **(Coca-cola colored urine)**
  - RBC transfusion in the last few weeks.

- The recent ASH guidelines defined DHTR as a significant drop in Hb, within 21 days after transfusion in the presence of hemoglobinuria, newly detected alloAbs, accelerated increase in HbS %, and significant change in retic % or increase in LDH

Rosse. Blood 1990; (76) 7:1431-1437

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- Laboratory Findings
  - Hemolysis
  - Indirect Coombs (+)
  - Urinalysis – Blood (+++), with few RBCs
  - Direct Coombs (+) in 80% of cases, if complicated by severe AIHA
  - Newly detected RBC Ab (in 25-60% cases)

Rosse. Blood 1990; (76) 7:1431-1437

DELAYED HEMOLYTIC TRANSFUSION REACTIONS (DHTR)

- ~80% of alloantibodies in patients with SCD become undetectable
- 30-40% of DHTR are associated with no identifiable antibodies
- One-third of cases, autoantibodies or antibodies of unclear specificity are the only detectable finding
- The most severe complication is hyperhemolysis

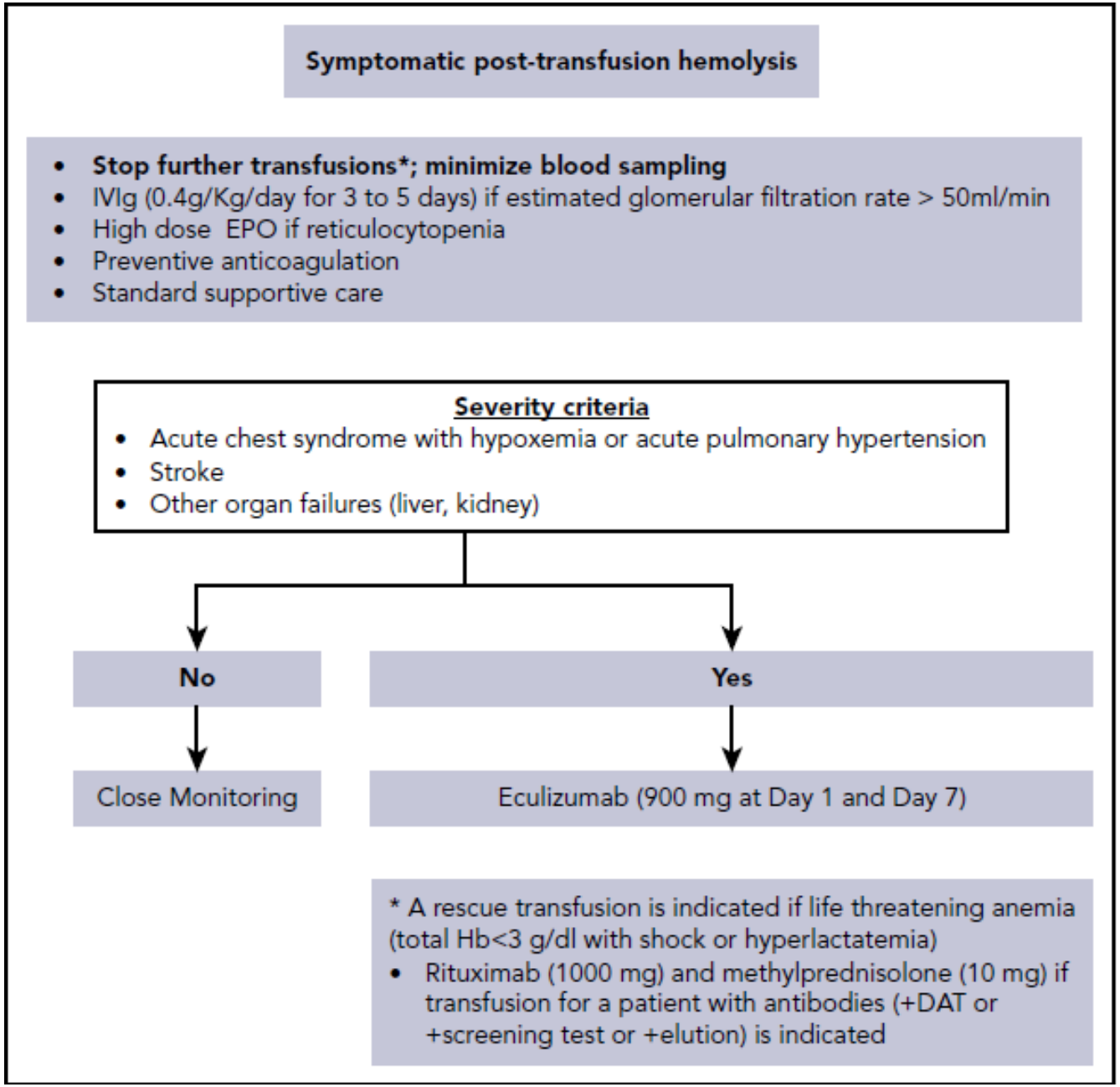
MANAGEMENT OF DHTR

- First, do **NOT** transfuse RBCs

- Genetic diversity of the *RH* locus in recipients of African ancestry - **less is more**
- IVIG and high dose steroids, rituximab, eculizumab, tocilizumab
- Supportive care:
  - Hydration, Oxygen
  - ESA therapy
  - Pain medication

- Transfuse extended Ag-matched RBCs - C/c, E/e, K, Jka/Jkb, Fya/Fyb, and S/s, **only if hemodynamically unstable**

How I Treat DHTR



Pirenne, R. Blood 2018(131)25:2773

ECULIZUMAB/TOCILIZUMAB FOR DHTR & HYPERHEMOLYSIS

Study	Drug investigated	Dose	Number of patients	Adverse events
Boonyasampant *et al.* 2015	Eculizumab	1200 mg weekly x 4 weeks followed by every 2 weeks for 2 more doses	1	None reported
Dumas *et al.* 2016	Eculizumab	900 mg x 2 dosed 1 week apart	3	1 death secondary to severe pulmonary infection
Chonat *et al.* 2018	Eculizumab	600 mg x 2	1	None reported
Vlachaki *et al.* 2018	Eculizumab	900 mg x 1	1	None reported
Unnikrishnan *et al.* 2019	Eculizumab	900 mg x 1	1	None reported
Chonat *et al.* 2020	Eculizumab	600 mg weekly x 4 weeks	1	None reported
Floch *et al.* 2020	Eculizumab	1-3 doses	18	3 patient deaths (2 from complications of encapsulated bacterial infection)
Mpinganzima *et al.* 2020	Eculizumab	900 mg x 2 dosed 6 days apart	1	None reported
Sivapalaratnam *et al.* 2019	Tocilizumab	8 mg/kg daily x 2 days	1	None reported
Lee *et al.* 2020	Tocilizumab	8 mg/kg daily x 4 days	1	Seizure (in the setting of methemoglobinemia secondary to hemoglobin-based oxygen carrier)
Hair *et al.* 2021	Eculizumab and Tocilizumab	900 mg x 3 8 mg/kg x 1	1	None reported

Linder GE, Chou ST. Haematologica. 2021 Jul 1;106(7):1805-1815.

TAKE AWAYS

- SCD is a chronic hemolytic disease defined by HbS polymerization and vasculopathy that causes chronic organ damage and acute complications that are potentially fatal.

- Emergency [exchange] RBC transfusions to target **HbS <30% and Hct ~30**

- Delayed hemolytic transfusion reactions – **Do not transfuse**

- Therapeutics to address acute complications of SCD are needed.


THANK
YOU