Cases of DHTR and hyperhemolysis in Sickle Cell Disease

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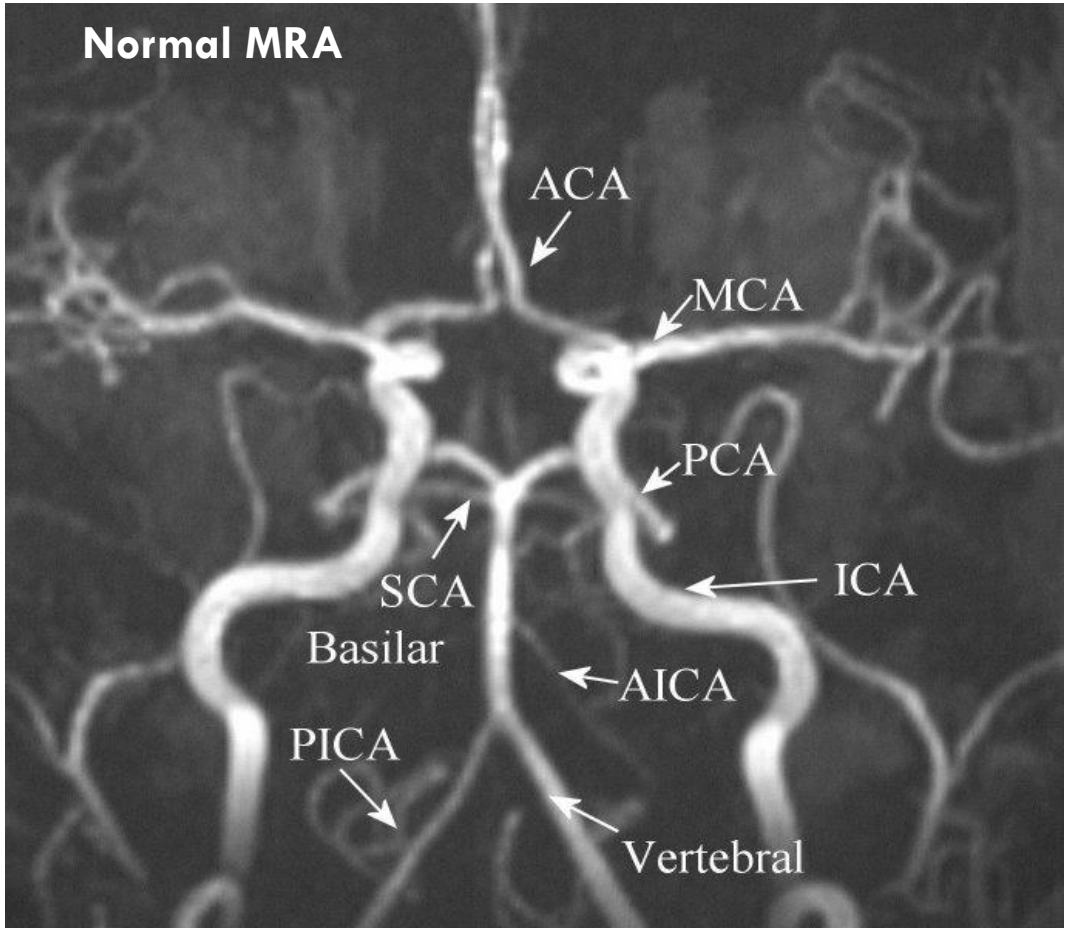
Disclosures

- No relevant conflicts

Case- presentation

- Patient presents acute VOC, with word-finding difficulties -an expressive aphasia (previous strokes presented similarly).
- PE: NIHSS 5 for (mental status questions: could not say month), RUE drift, R facial weakness, and mild anomia.
- MRI upon admission: no acute stroke and chronic L ACA/MCA distribution encephalomalacia
- **Dx: Sickle Cell Crisis/w recrudescence of old stroke symptoms (AKA no acute stroke)**
- **An emergent red cell exchange was performed with 9 units.**

Case- baseline MRA

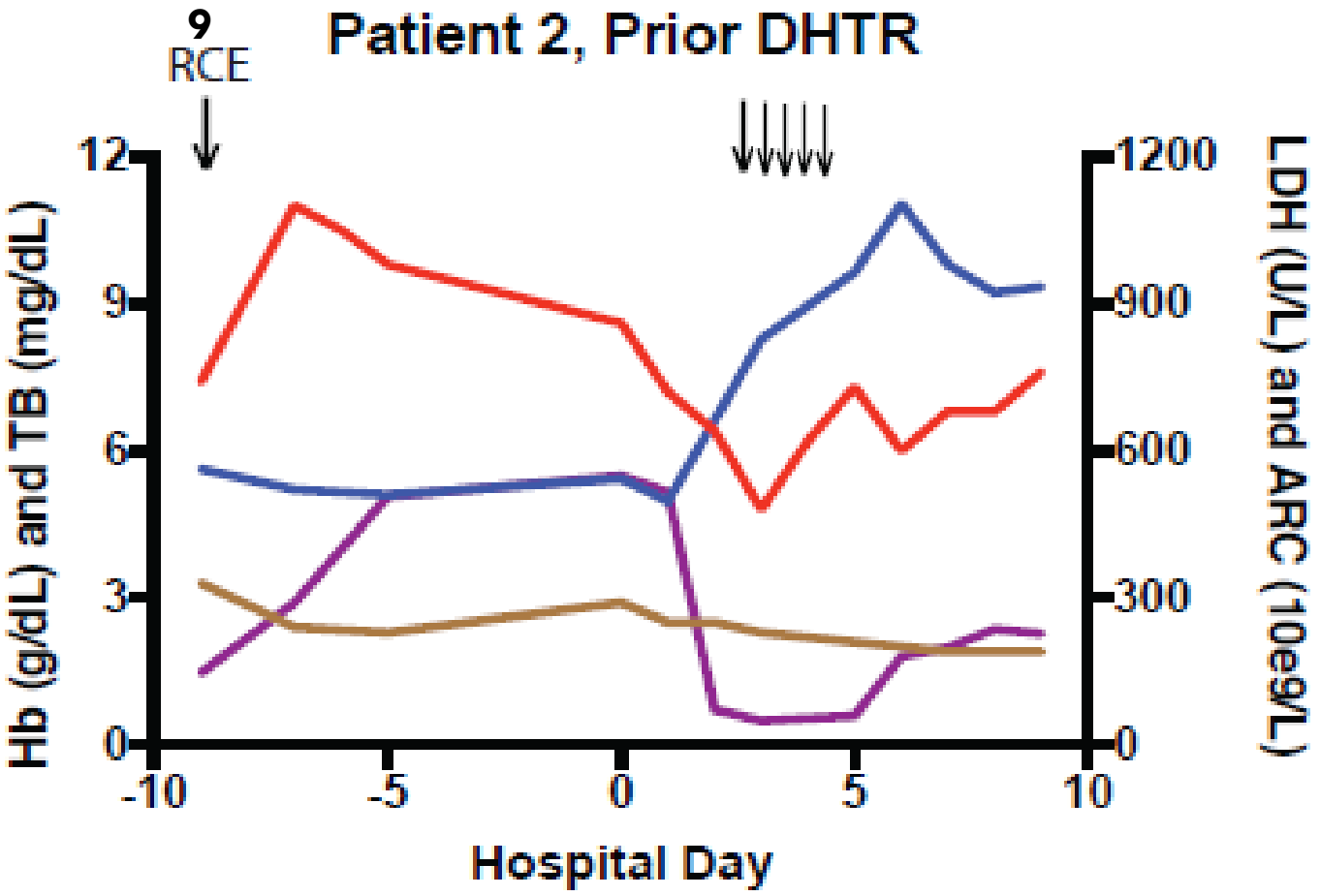


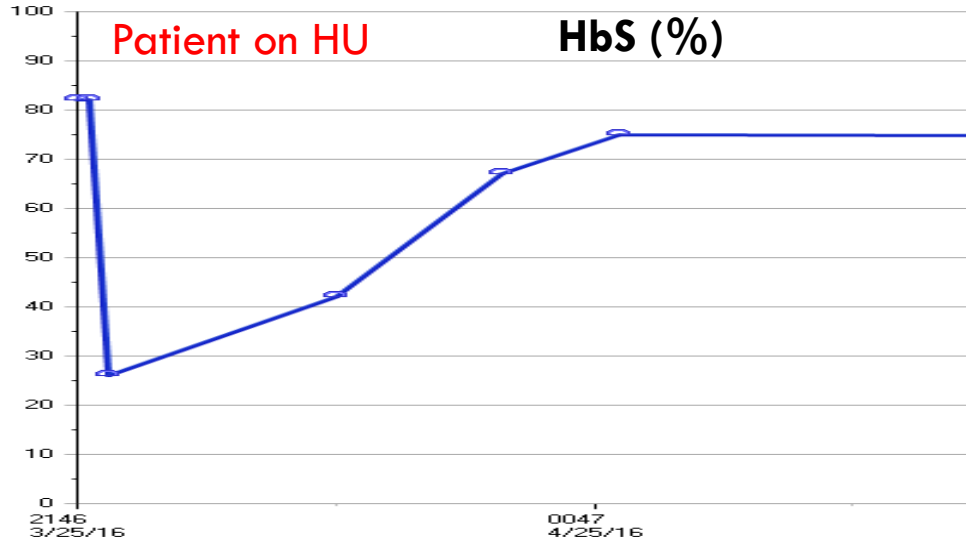
Case continued

- Patient re-presented 7 days post RBCX with diffuse intense body pain in bilateral arms, legs and back
- Received 5 more units RBCs for dropping Hb.
- UA: + hemoglobinuria (D+7, D+28). Ab screens and DAT: negative

Case- DHTR (No antibody identified)

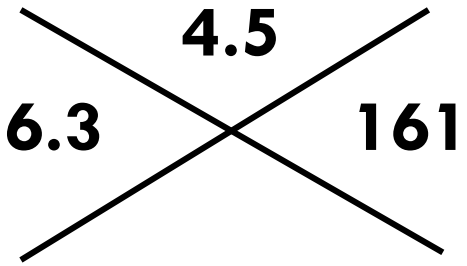
KEY: Hb TB LDH ARC ↓ Transfusion



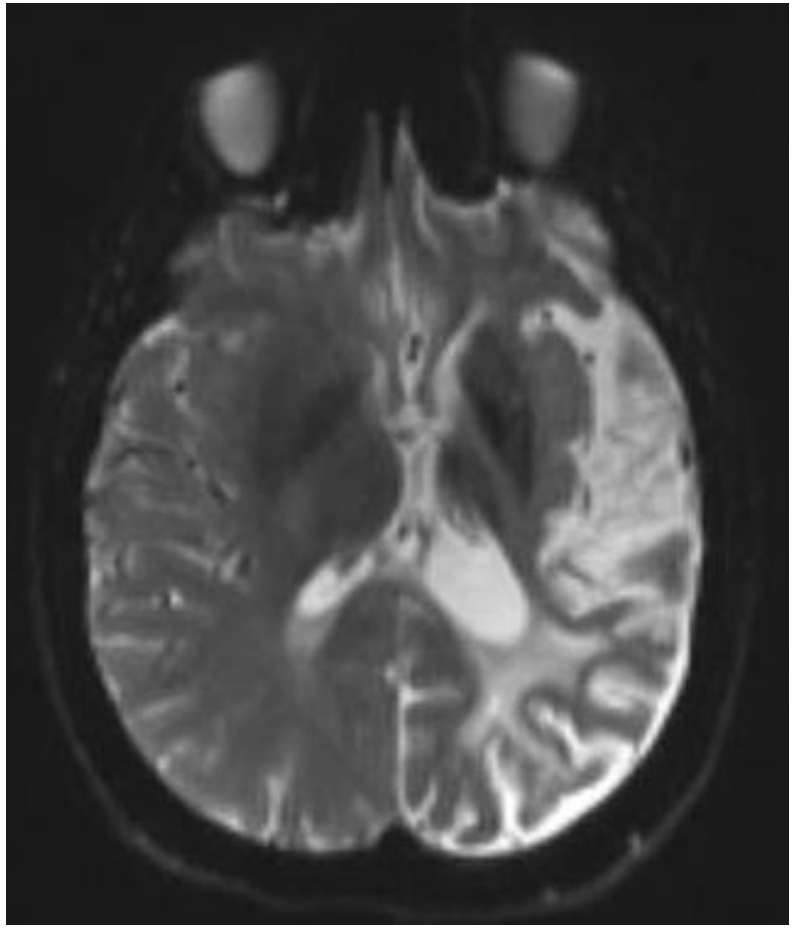


Case continued…

- Patient re-presented to clinic with pain and new worsened right hemiparesis and expressive aphasia.
- MRI showed a new left MCA ischemic stroke



ANC 2900 /µL
Retic: 1.7%
ARC: 14.8k /µL



- Dx: Aplastic crisis, new ischemic stroke

- **What to do**

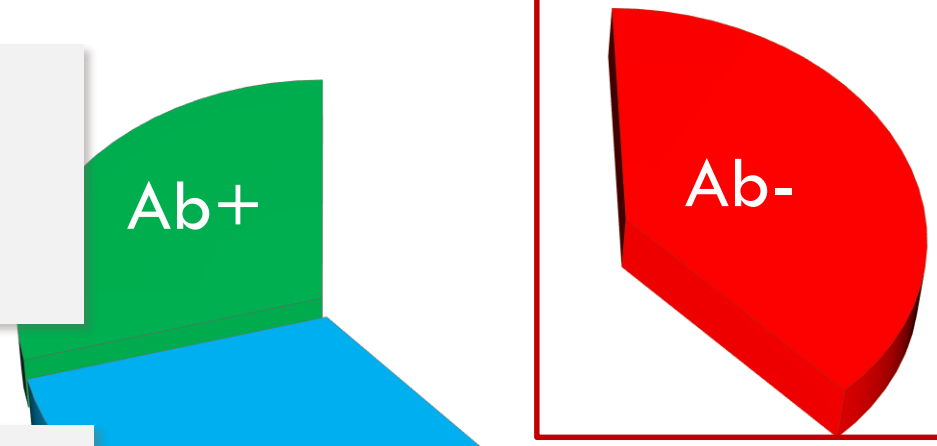
Why Rituximab?

- Rituximab targets CD20, and induces B cell depletion
  - should inhibit primary or secondary immune response to blood group antigens
- Rituximab is effective in depleting B cells in NHL
- Rituximab has been effective in treating many autoimmune disorders that Ab-dependent (e.g. AIHA, ITP, TTP, SLE, etc…)

- Is Rituximab effective in <u>Ab-negative</u> DHTRs?

DHTRs in SCD: Immunohematological Characteristics

Antibody-negative: 38%



Autoantibodies, AUS, complex Abs: 29%

New classically significant alloAb: 32%

Habibi A, et al. Am J Hematol. 2016

Prevention of DHTR with Rituximab

- Retrospective analysis of 8 SCD patients with previous history of multiple antibody-related life threatening DHTR (1 to 4 episodes of DHTR)

- **Pre-Treatment**
  - 2 different Rituximab regimens depending on the patient condition
    - Ritux 1,000 mg x2, 2 weeks apart, (D-30, D-15) before the procedure
      - planned surgery requiring transfusion
    - Ritux 1,000 mg x1
      - acute conditions requiring urgent transfusion
    - In all cases, 10 mg of methylprednisolone (usual dose 100 mg)

- **Transfusion**
  - Extended matched RBCs (Rh/K/Fy/Jk/MNS) and negative for previous antibodies

Noizat-Pirenne, Vox Sanguinis, 2015

Prevention of DHTR with Rituximab

- **Clinical course (N=8)**
  - Median drop of Hb from post-trxn Hb: **1.3 g/dl** (range 0 to 3.8 g/dl)
  - Median LDH max: **461 IU/mL** (range: 271-1180)
  - 5 patients : no DHTR
  - 3 patients : mild DHTR
    - 2 patients had mild clinical symptoms of intravascular hemolysis and/or exacerbation of VOC

- **Post transfusion serologic testing**
  - In all patients : no new formed antibodies, DAT remains negative

Noizat-Pirenne, Vox Sanguinis, 2015

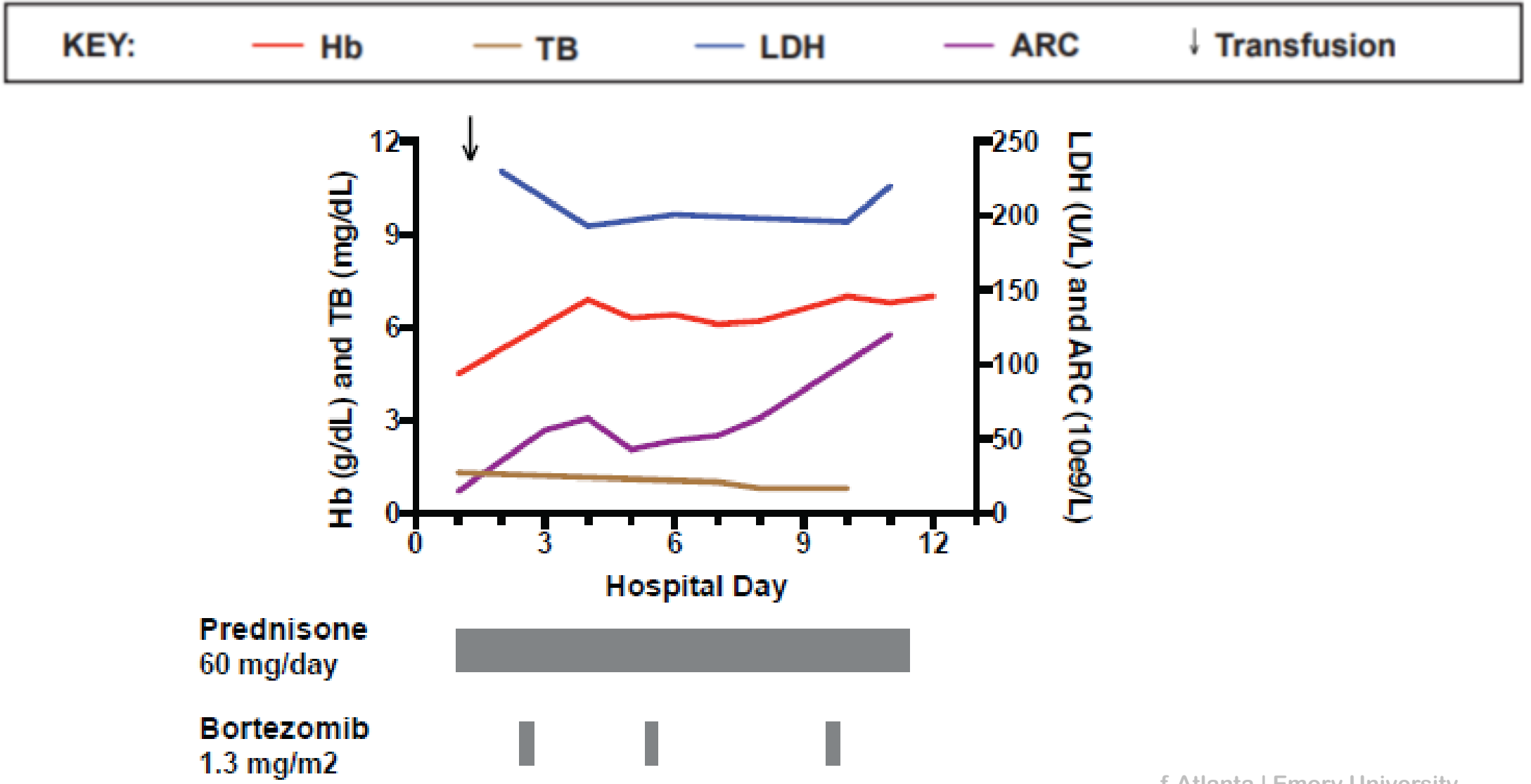
Why Bortezomib?

- Proteasome inhibitor which blocks NF-κB activation
  - Causes accumulation of misfolded proteins
  - Leads to cell apoptosis, particularly plasma cells.

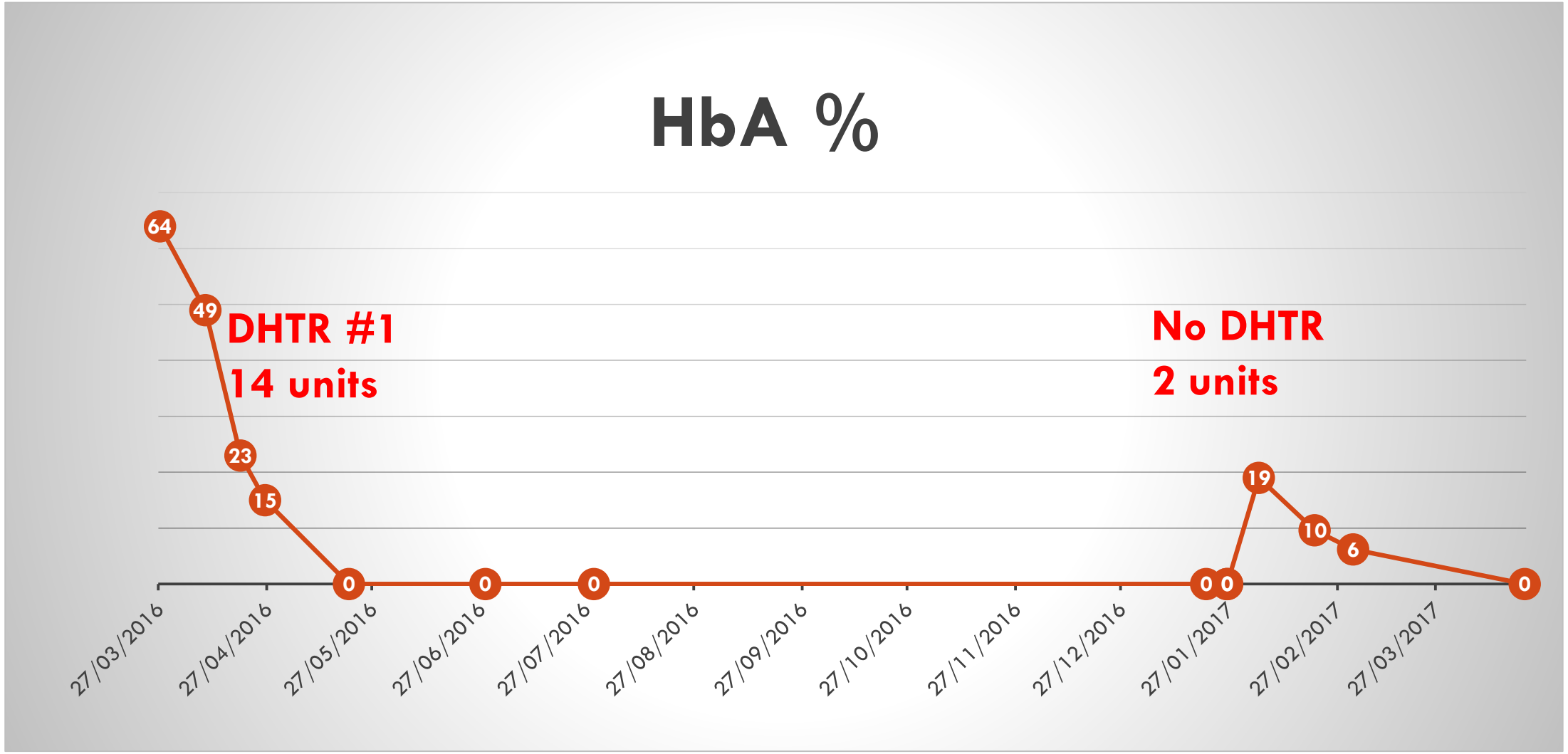
- **Bortezomib**
  - effective treatment of multiple myeloma and NHL.
  - shown to ameliorate clinical manifestations of refractory SLE
  - **Selective apoptosis occurs in monocytes and monocyte-derived DCs***
  - **Suppresses function and survival of pDC by targeting intracellular trafficking of TLRs****

*Arpinati M, et al. BMT. 2009
**Hirai M, et al Blood 2011

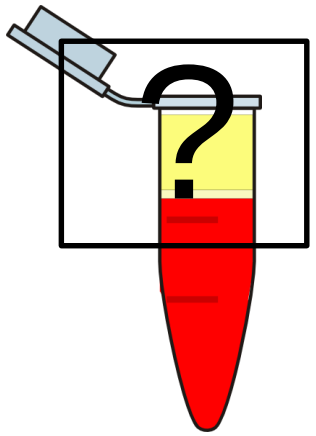
Case continued… No DHTR



Comparison of two transfusion exposures

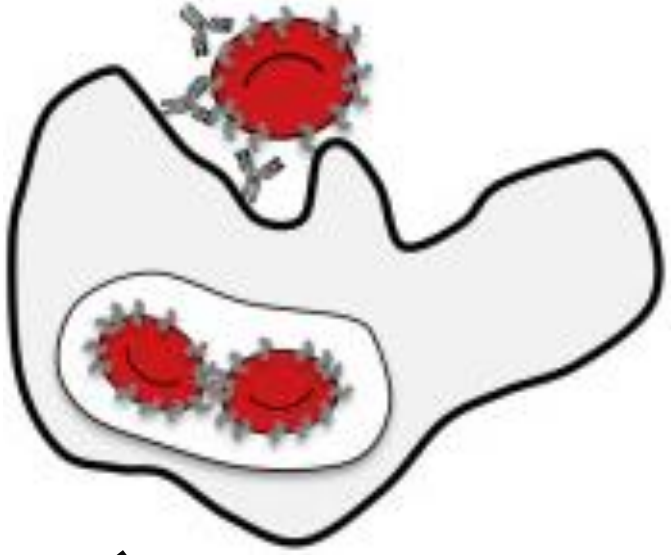


Ab-negative DHTRs: Suicidal Red Cells
Proposed mechanism



PS exposure

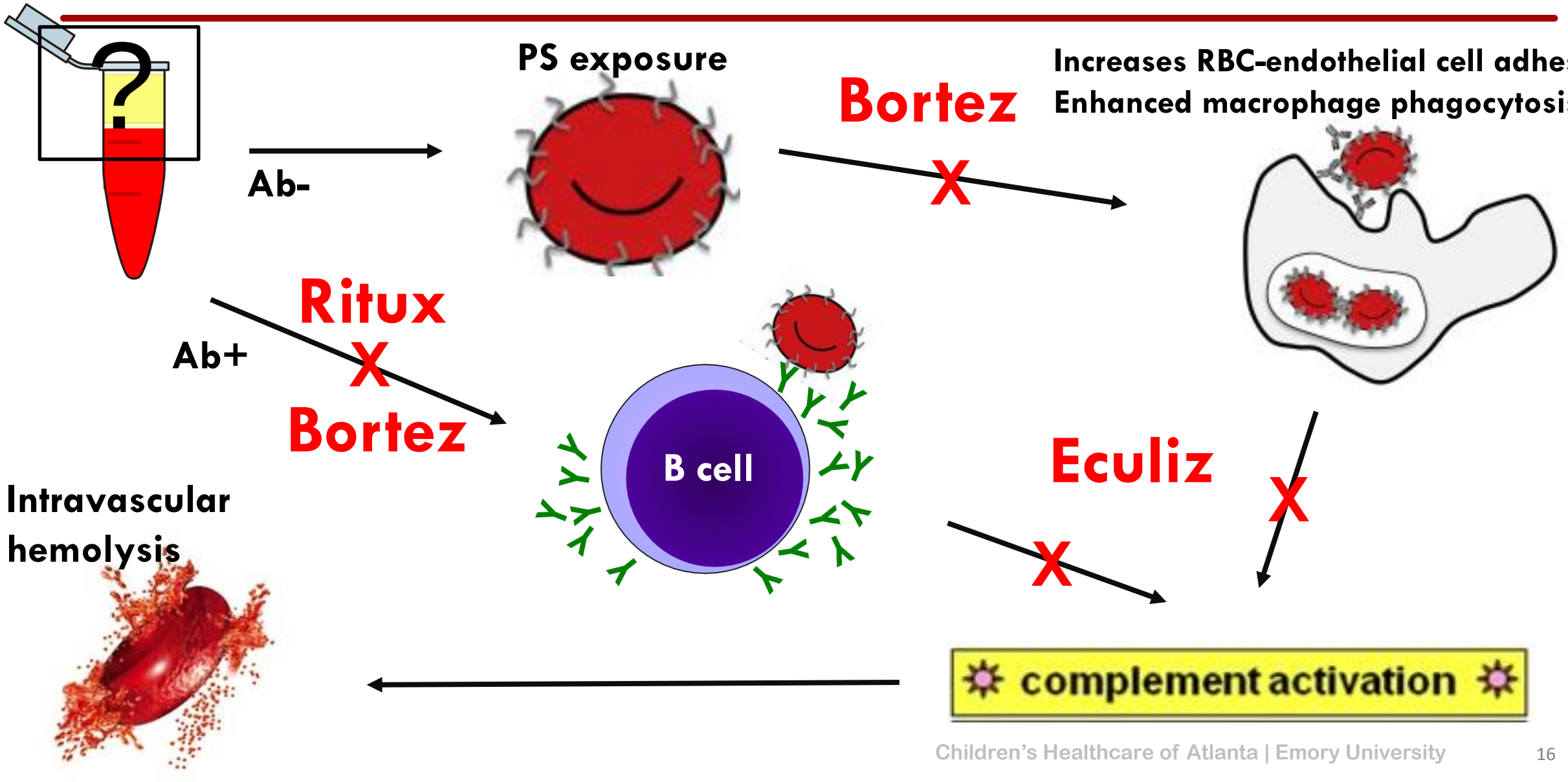
Increases RBC-endothelial cell adhesion
Enhanced macrophage phagocytosis



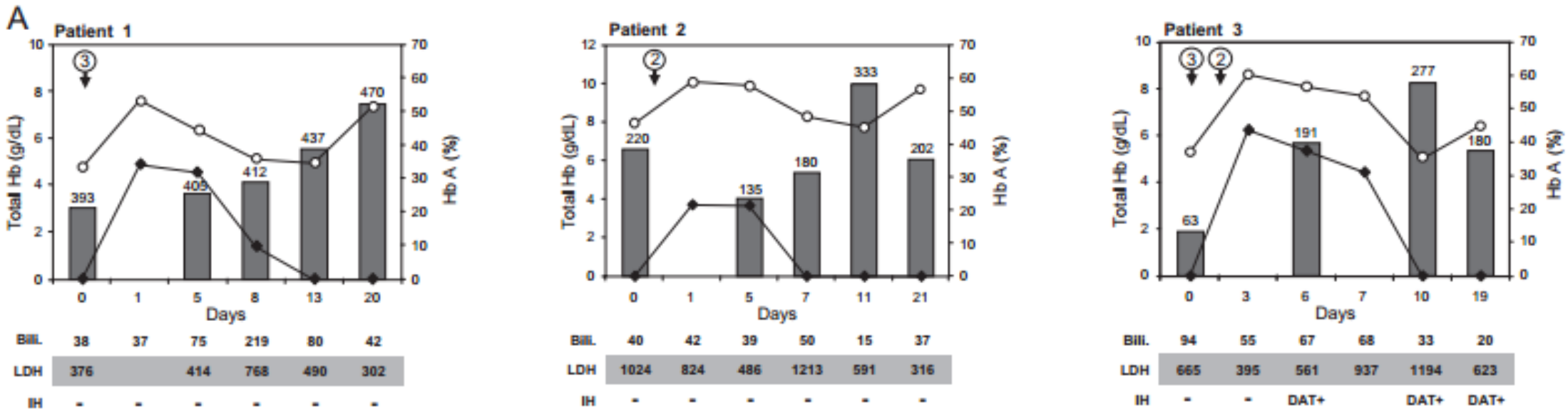
complement activation

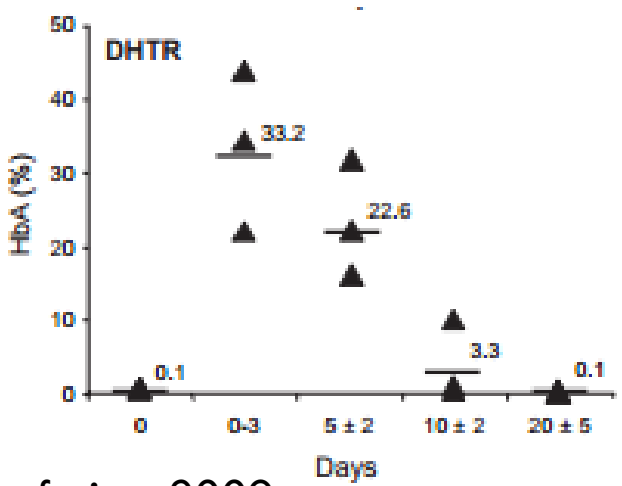
Intravascular hemolysis

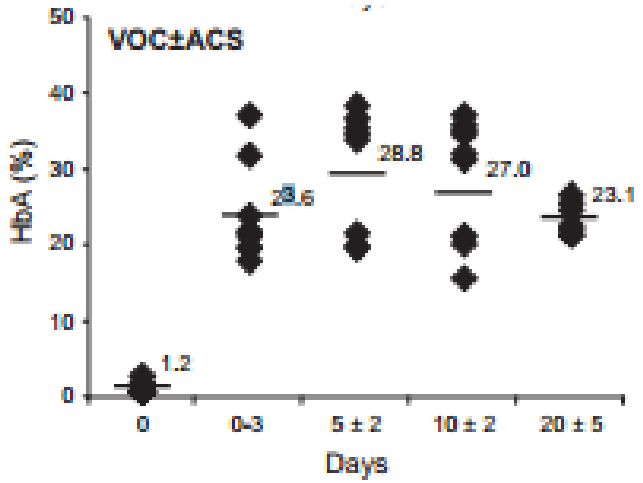
DHTRs: Proposed mechanism and potential treatments



Published Cases of Ab-negative DHTR



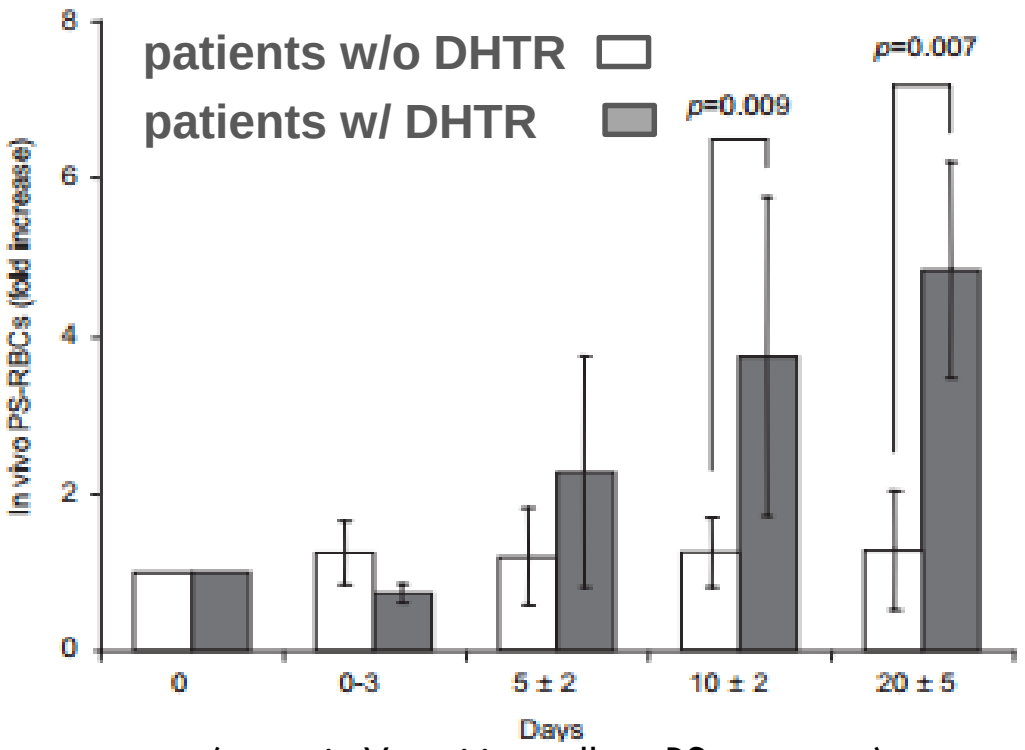




Chadebech P, et al. Transfusion. 2009

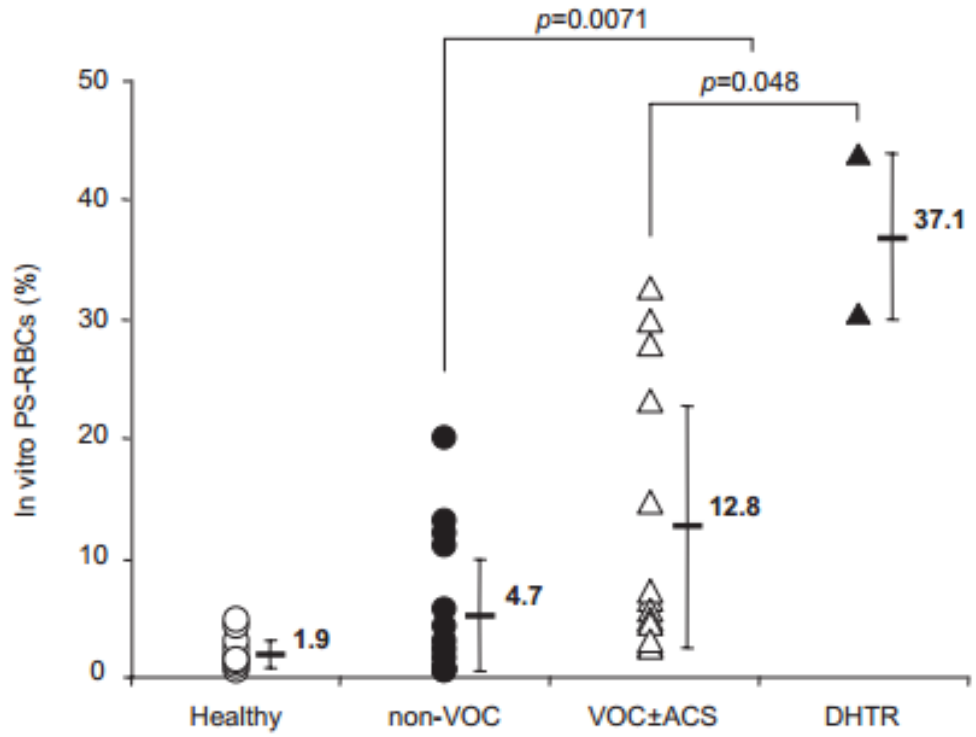
Potential mechanism for Ab-negative DHTRs:
Suicidal RBC death from PS exposure

In vivo PS-RBC % increase from pre-transfusion



(annexin V-positive cells = PS exposure)

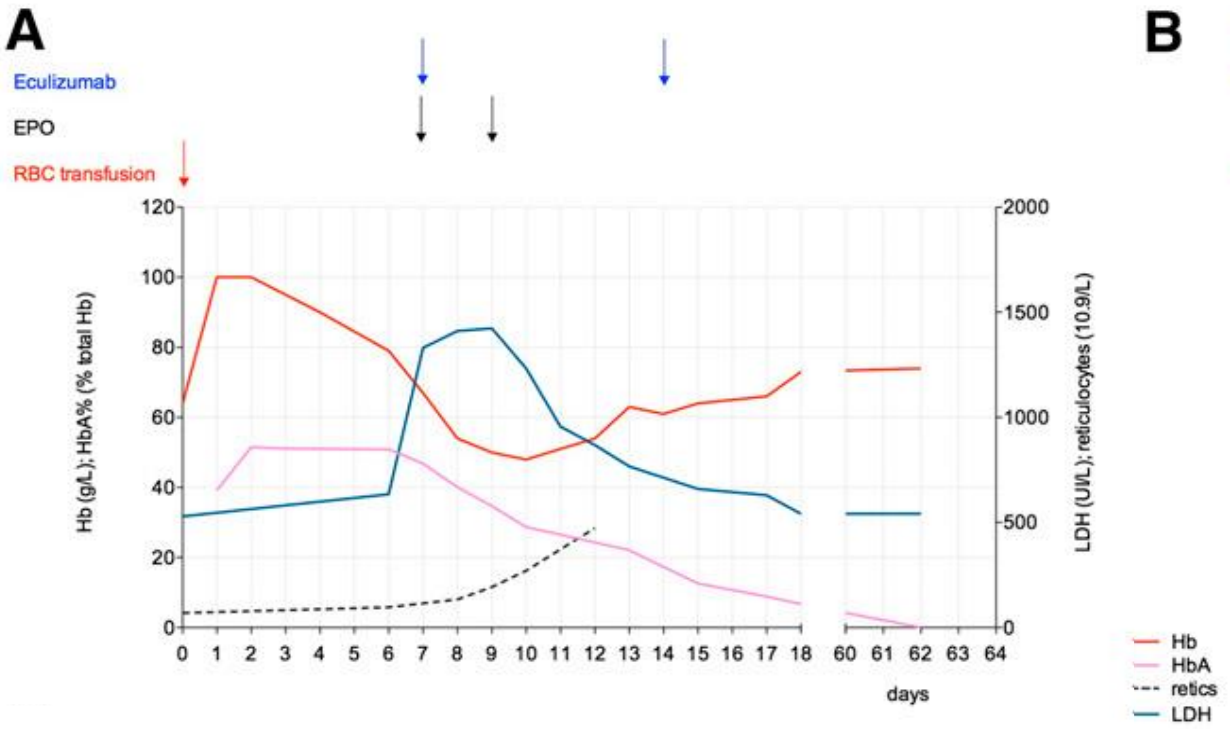
In vitro: patient plasma with donor RBCs

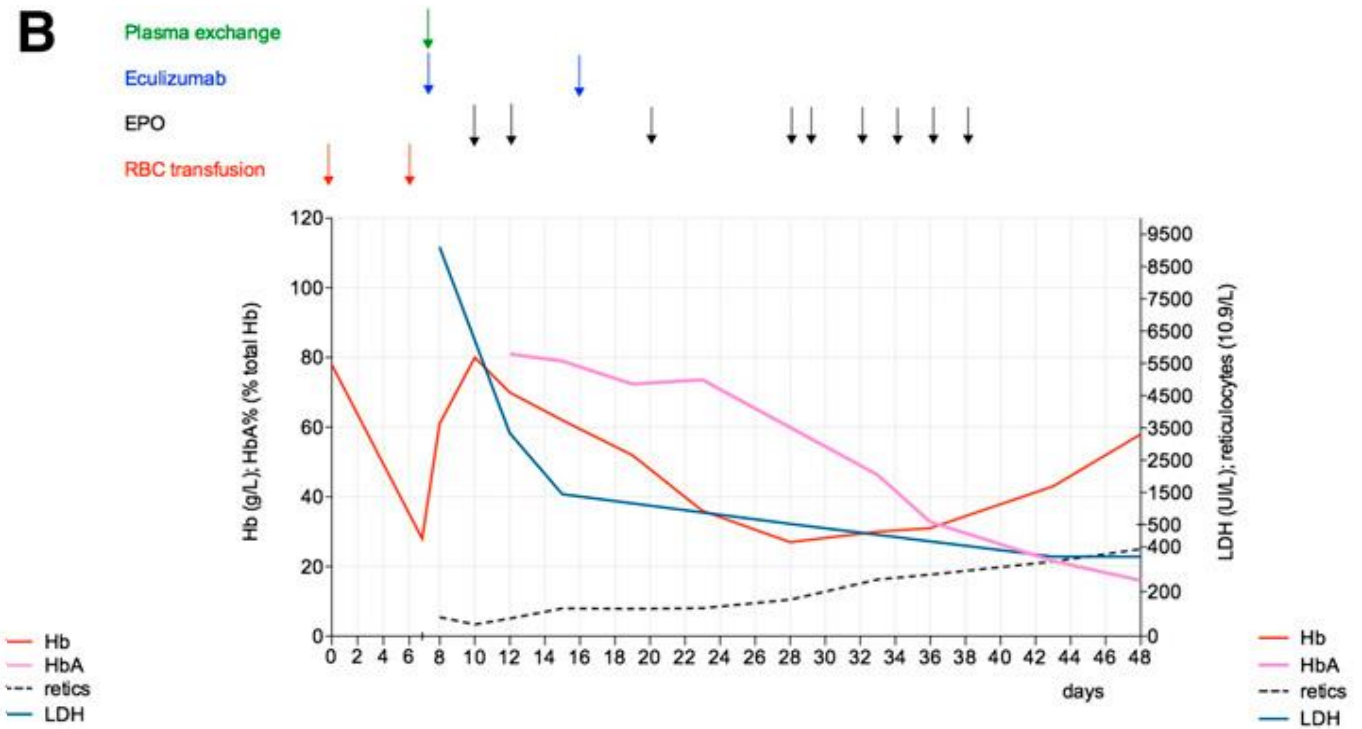


- PS exposure is a signal for eryptosis—suicidal RBC death—involving membrane shedding and leading to the physiologic clearance of apoptotic cells by **macrophages**, via specific PS receptors

Chadebech P, et al. Transfusion. 2009

Eculizumab salvage therapy for Ab-negative DHTRs in SCD patients



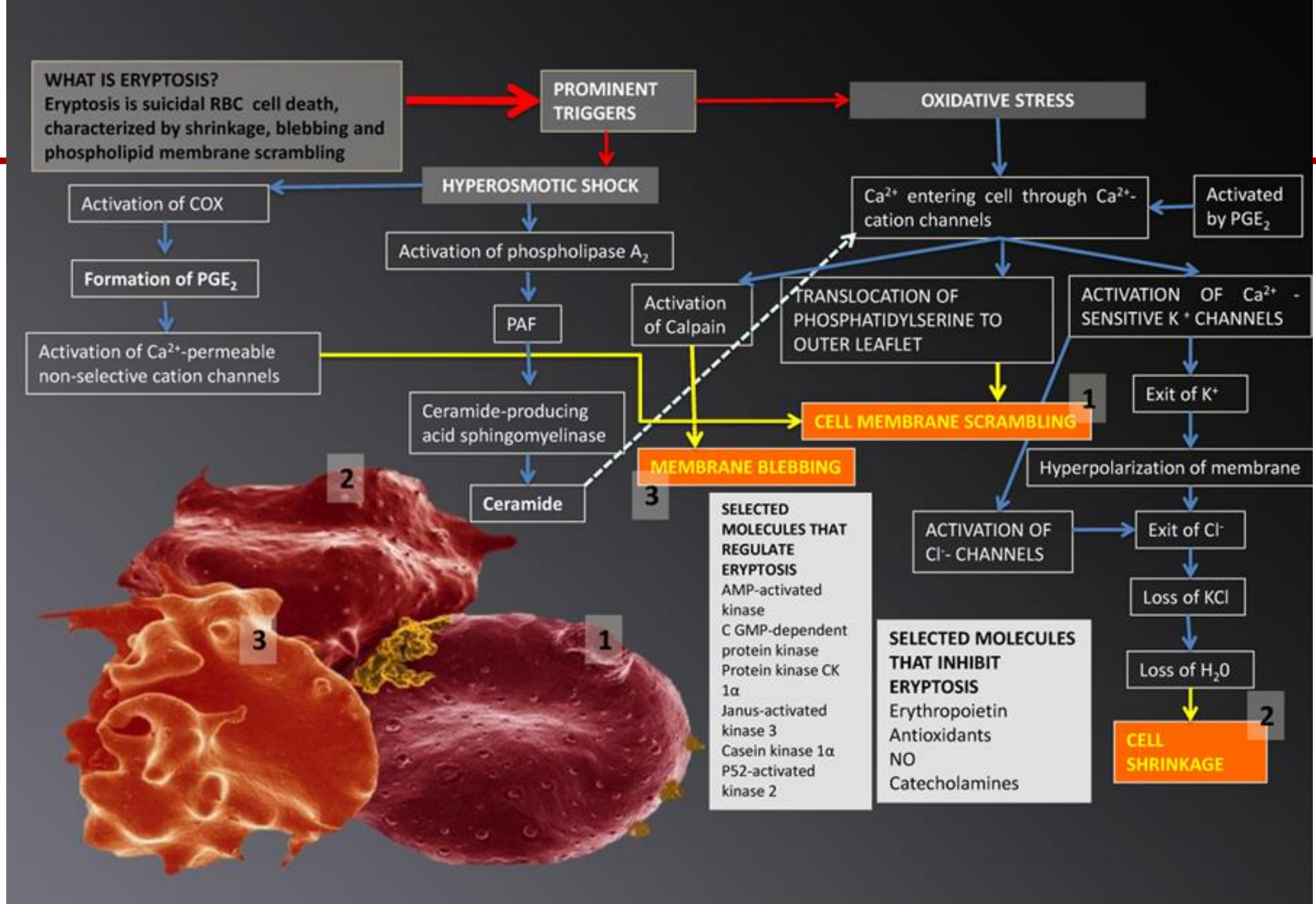


20 yr male w/ HbSS- developed severe VOC/dark urine 6 days post 6 U RBCs for acute stroke

- Dx: DHTR with negative DAT and reticulocytopenia
- **EPO and Eculizumab** given with improvement of VOC and hemoglobinuria within 24 hrs of 1st dose of Eculizumab

- 17 yr male w/ HbSS- severe ACS and dark-colored urine 7 days post 2 U RBCs to treat VOC. MSOF developed after another RBC transfusion (2 U).
- Dx: DHTR with negative DAT and reticulocytopenia
- **EPO and TPE followed by Eculizumab** given with gradual improvement over subsesequent 40 days.

Dumas G. et al. Blood 2016


WHAT IS ERYPTOSIS?
Eryptosis is suicidal RBC cell death, characterized by shrinkage, blebbing and phospholipid membrane scrambling
PROMINENT TRIGGERS
OXIDATIVE STRESS
HYPEROSMOTIC SHOCK
Activation of COX
Formation of PGE2
Activation of phospholipase A2
PAF
Activation of Ca2+-permeable non-selective cation channels
Ceramide-producing acid sphingomyelinase
Ceramide
Ca2+ entering cell through Ca2+-cation channels
Activated by PGE2
Activation of Calpain
TRANSLOCATION OF PHOSPHATIDYLSERINE TO OUTER LEAFLET
ACTIVATION OF Ca2+ - SENSITIVE K+ CHANNELS
CELL MEMBRANE SCRAMBLING
1
Exit of K+
Hyperpolarization of membrane
MEMBRANE BLEBBING
3
2
ACTIVATION OF Cl- - CHANNELS
Exit of Cl-
Loss of KCl
Loss of H20
CELL SHRINKAGE
2
SELECTED MOLECULES THAT REGULATE ERYPTOSIS
AMP-activated kinase
C GMP-dependent protein kinase
Protein kinase CK 1α
Janus-activated kinase 3
Casein kinase 1α
P52-activated kinase 2
SELECTED MOLECULES THAT INHIBIT ERYPTOSIS
Erythropoietin
Antioxidants
NO
Catecholamines
2
3
1