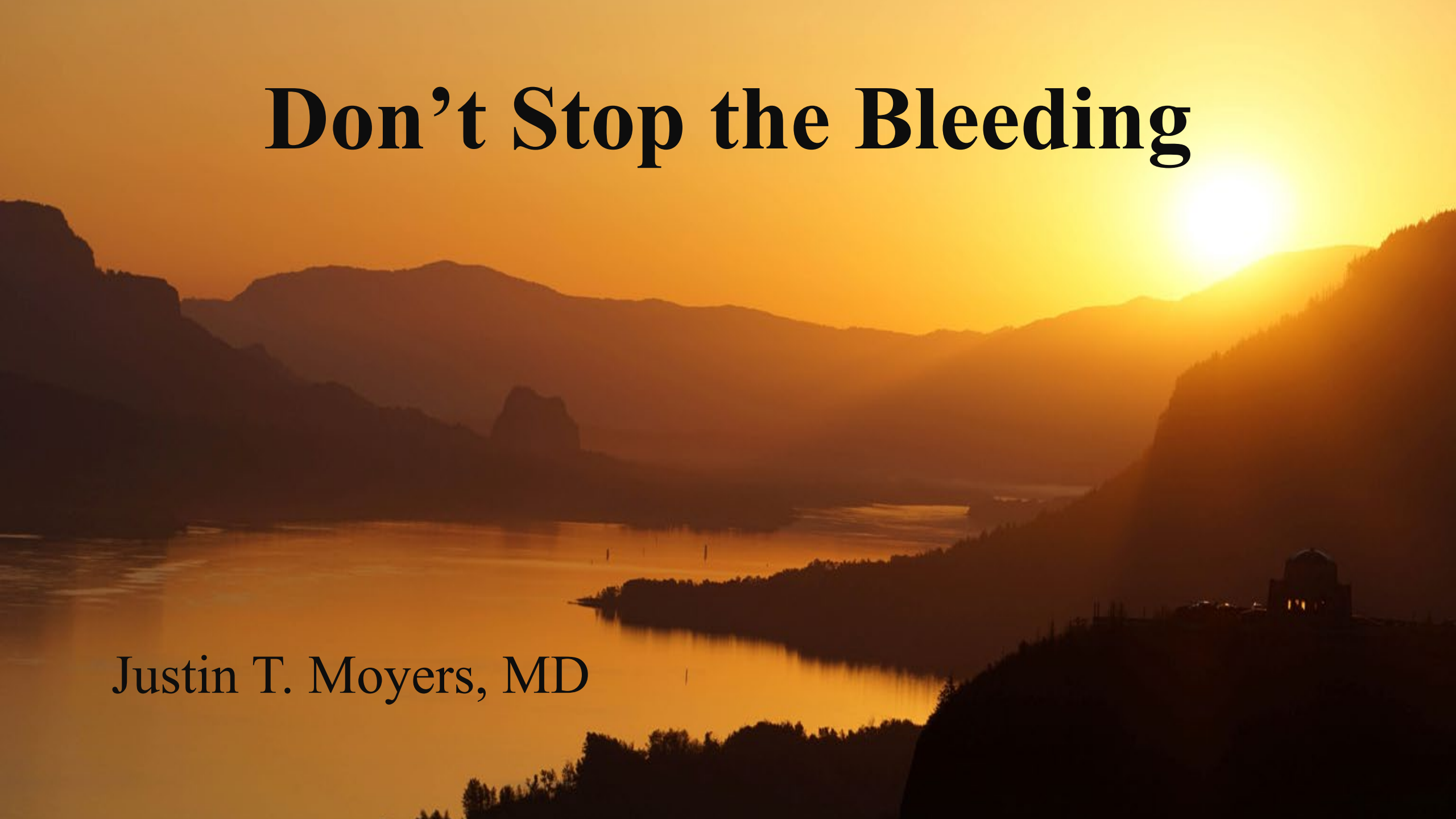
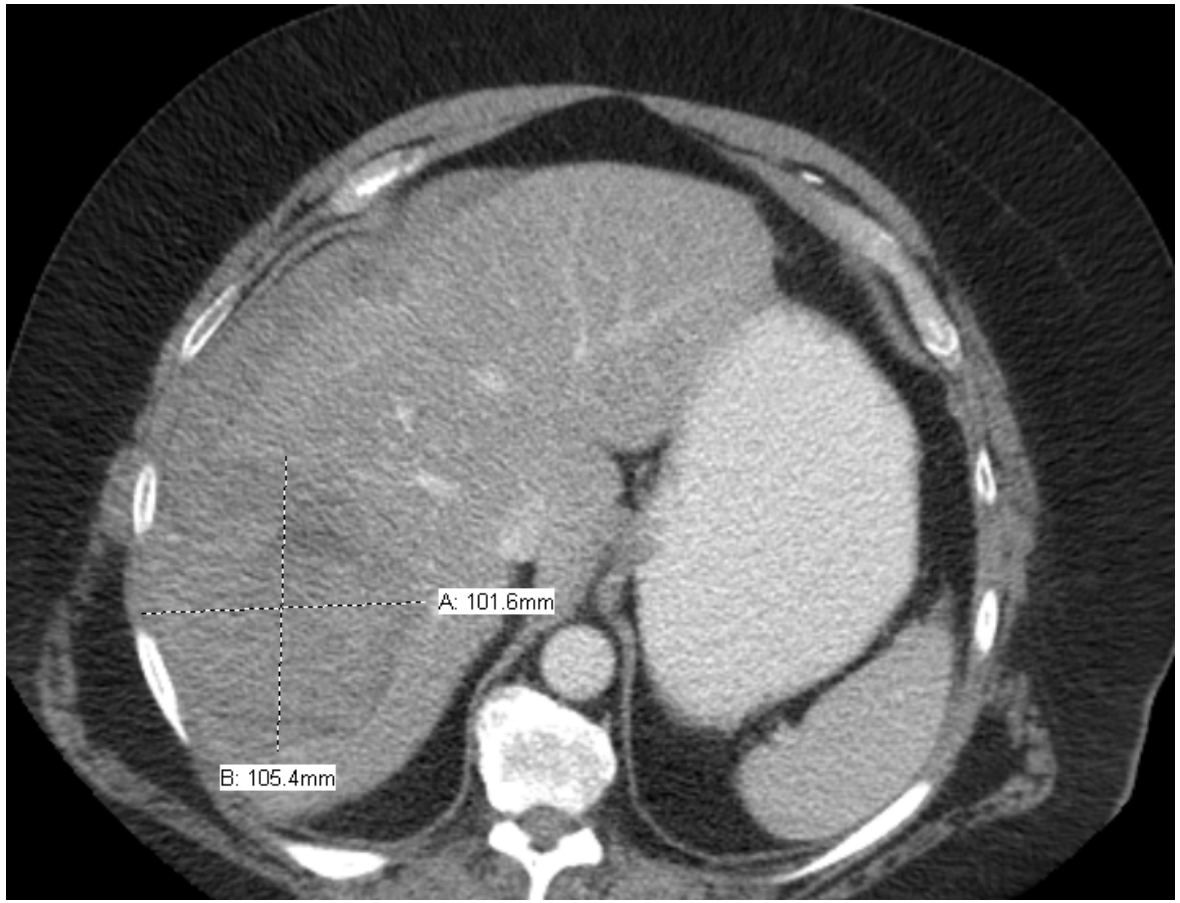
Don’t Stop the Bleeding



Justin T. Moyers, MD

Chief Complaint: Hepatic Hematoma

- 58 year old man
- Presented to Outside Hospital for **abdominal pain** found to have spontaneous **hepatic hematoma** (10x9cm) with suspected rupture



Chief Complaint: Hepatic Hematoma

- Taking **Warfarin** for recent DVT with INR of 2.8
- Given 5mg of **Vitamin K** IV and 15,000U at 100U/kg of **Factor Eight Inhibitor Bypassing Activity** (FEIBA) infused over 1 hour at 250 U/min

Chief Complaint: Hepatic Hematoma

Admitted to the ICU

Medical History

PMH:

DVT

HTN

PSH:

Appendectomy

Hernia

Tonsillectomy

Family History:

Father- Liver Cancer

Allergies: None Known

Medications:

Ascorbic Acid 500 mg

Lisinopril 20 mg daily

Vitamin D-3 1,000 Units daily

Warfarin (7.5 mg Tu & Th; 5 mg other days)

Social:

Current Smoker since 15y/o 1 ppd

Denies IVDU and EtOH use

Married with six kids

Works as a chef

Physical Exam:

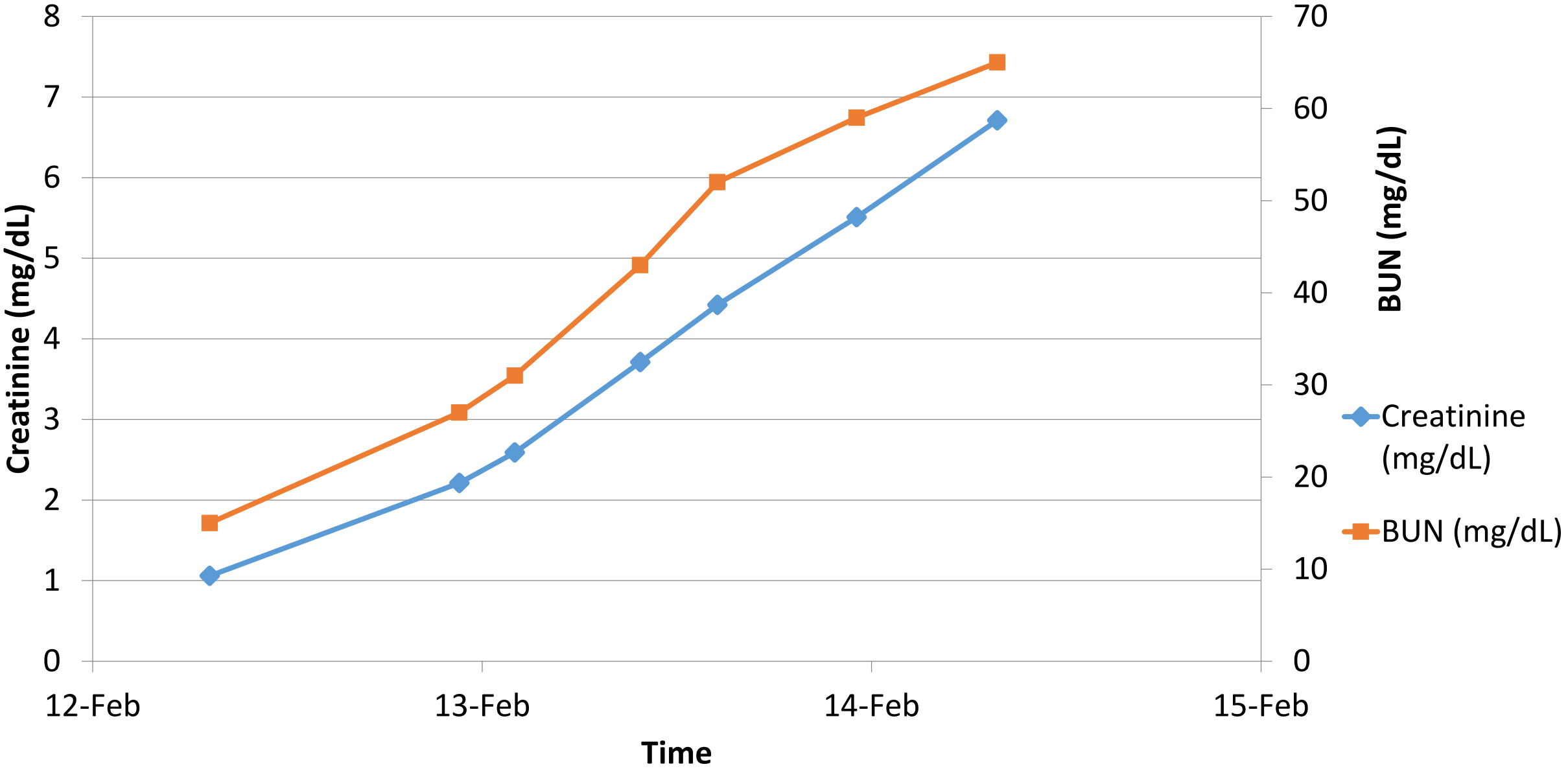
BP: 130/87	HR: 67	RR: 16	SpO2: 97% on Room Air
Height= 5’9”	Weight= 147kg	BMI=48kg/m^2	

Gen: **Mild distress.** Non-toxic appearance. Lying comfortably in bed.
Pulm: Lungs clear to auscultation
CV: Regular Rate and Rhythm, Normal S1 and S2, No S3 or S4, No murmur
Abd: **Obese,** Normal Active BS, **mild right upper quadrant tenderness, mild tenderness of right flank,** no guarding/rigidity/ rebound/distension
Lymph nodes: No cervical or supraclavicular nodes
Skin: No rash
Neuro: Alert and coherent.

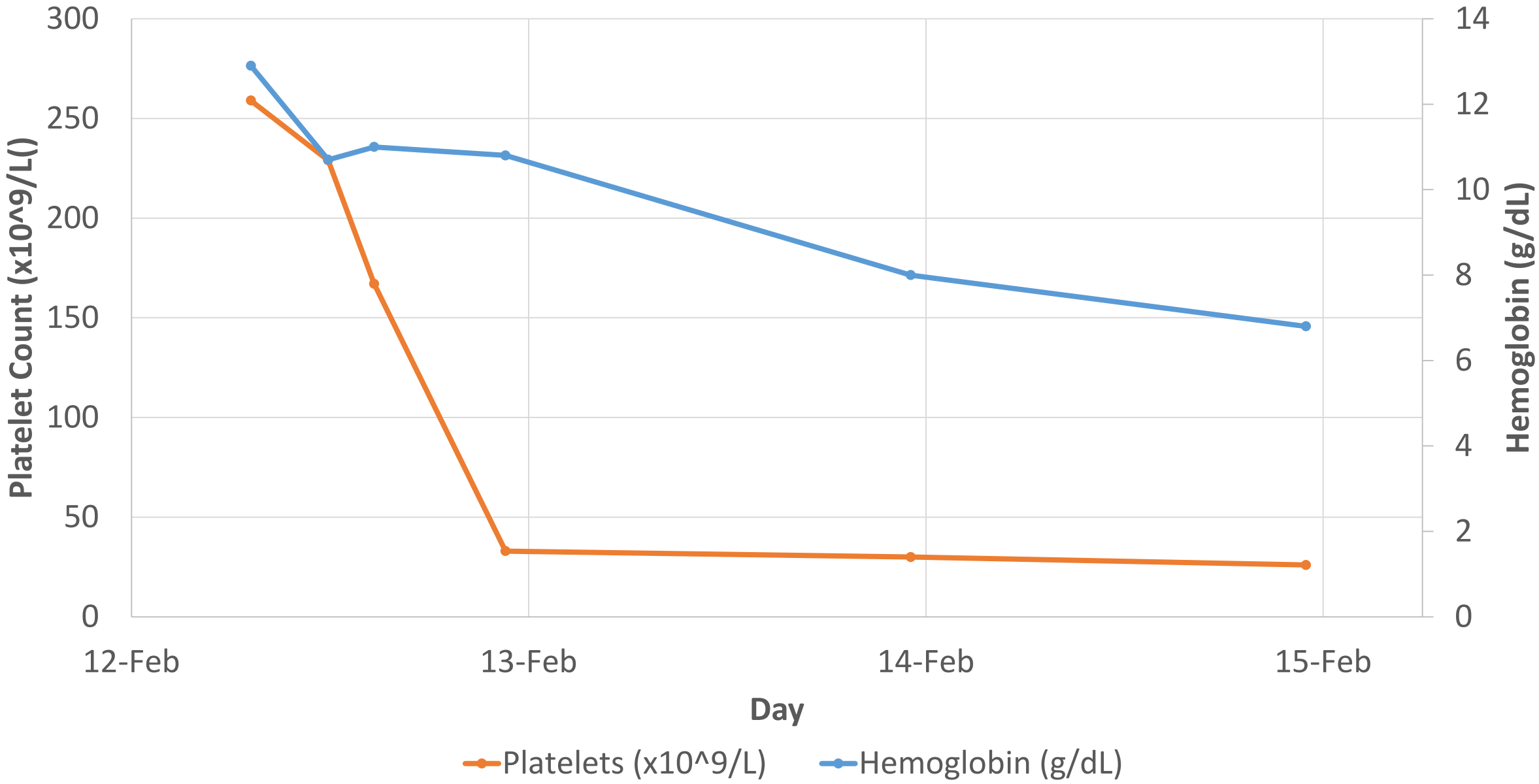
ICU Course: Day 2

- Remained normotensive without drops in blood counts overnight
- Urine output ceased

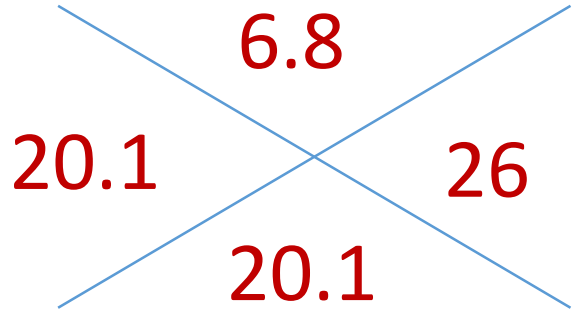
Renal Function Over Time



Blood Counts Over Time



Laboratory Studies on ICU Day 3

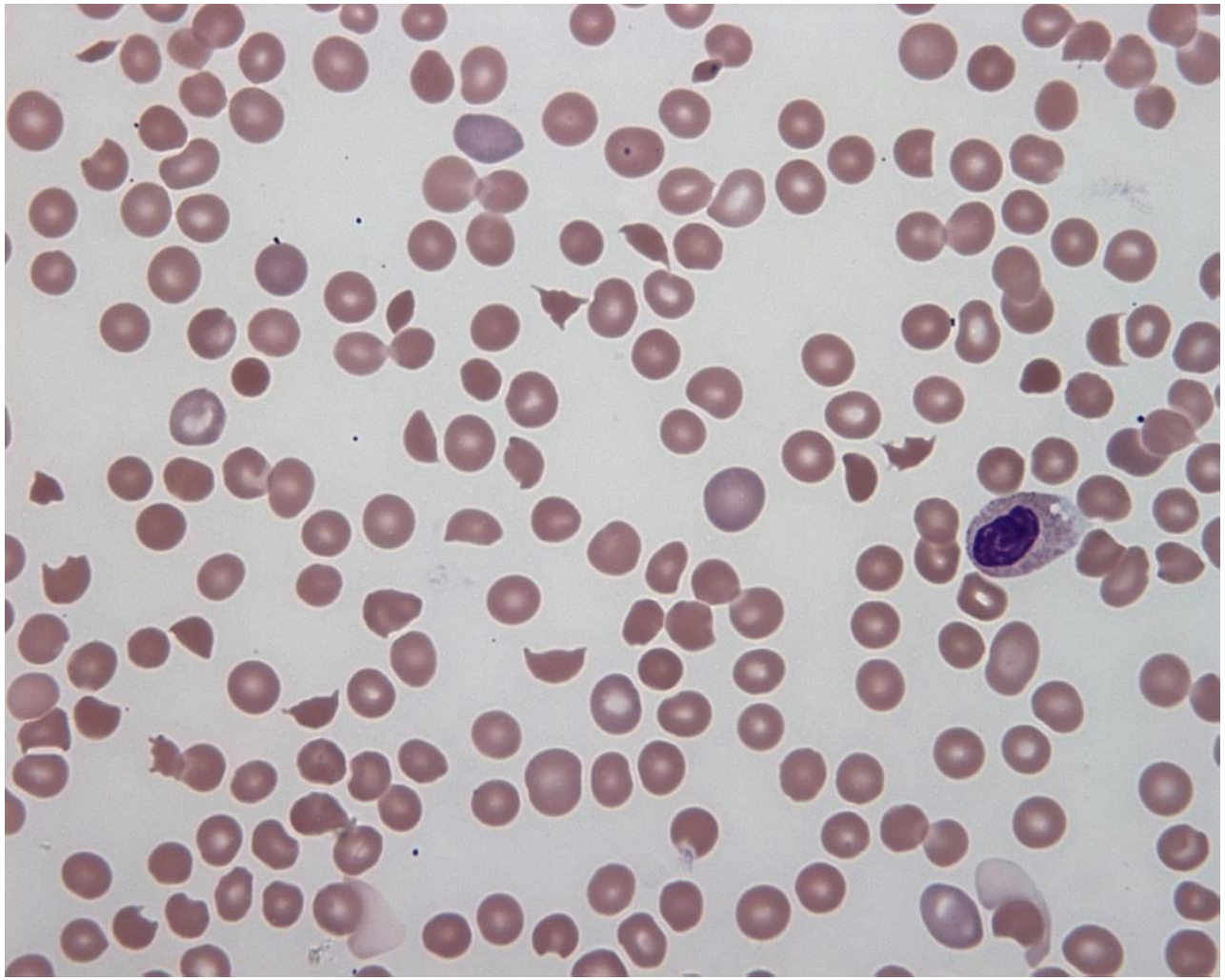


137	106	**59**	153
6.0	22	**5.51**	

Alk Phos= 61 (32-110 IU/L)
ALT= 582 (6-42 IU/L)
AST= 517 (11-39 IU/L)
Total Bilirubin= 1.8 (0.2-1.2 mg/dL)
Retic Count= 2.4%
LDH= 2618 (100-210 IU/L)
Haptoglobin= <30 (67-214 mg/dL)

C3= 110 (96-185 mg/dL)
C4= 44 (18-53 mg/dL)
Indirect Coomb's Test= Negative
Coomb's Test (DAT)= Negative
Protime= 16.0 s (11.8-14.6 s)
INR= 1.3
Prothrombin Time= 36.5 s (22-35 s)
Fibrinogen= 445 (200-400 mg/dL)

Peripheral Smear



Significant schistocytes (helmet cells)
Moderate spherocytes
Moderate anistocytosis
Thrombocytopenia

***Representative Slide (emedicine.Medscape.com/article/779218-work-up)

Case Summary:

58 year old man with recent DVT on warfarin presenting with abdominal and shoulder pain found to have hepatic hematoma given FEIBA to control bleeding.

Over the course of two days, developed **microangiopathic hemolytic anemia, thrombocytopenia,** and **acute renal failure** requiring **hemodialysis**

MAHA with Thrombocytopenia Differential

- Disseminated Intravascular Coagulation
- HELLP Syndrome and Pregnancy
- Heparin-Induced Thrombocytopenia
- Paroxysmal Nocturnal Hemoglobinuria
- Malignant Hypertension
- Antiphospholipid Antibody Syndrome
- Kasabach-Merritt Syndrome
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

MAHA with Thrombocytopenia Differential

- **Disseminated Intravascular Coagulation**
- HELLP Syndrome and Pregnancy
- Heparin-Induced Thrombocytopenia
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- Malignant Hypertension
- Antiphospholipid Antibody Syndrome
- Kasabach-Merritt Syndrome
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

- Normal fibrinogen
- No new DVT on venous doppler

1. British Journal of Haematology, 145, 24–33

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- **HELLP Syndrome and Pregnancy** ←
- Heparin-Induced Thrombocytopenia
- Paroxysmal Nocturnal Hemoglobinuria
- Malignant Hypertension
- Antiphospholipid Antibody Syndrome
- Kasabach-Merritt Syndrome
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- **Heparin-Induced Thrombocytopenia** ← •Never received heparin
- Paroxysmal Nocturnal Hemoglobinuria
- Malignant Hypertension
- Antiphospholipid Antibody Syndrome
- Kasabach-Merritt Syndrome
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- **Paroxysmal Nocturnal Hemoglobinuria** ← Peripheral blood flow cytometry did not support PNH diagnosis
- Malignant Hypertension
- Antiphospholipid Antibody Syndrome
- Kasabach-Merritt Syndrome
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- ~~Paroxysmal Nocturnal Hemoglobinuria~~
- **Malignant Hypertension** ← •Normotensive
- Antiphospholipid Antibody Syndrome
- Kasabach-Merritt Syndrome
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

1. Hypertension. 2005;45:246-251

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- ~~Paroxysmal Nocturnal Hemoglobinuria~~
- ~~Malignant Hypertension~~
- **Antiphospholipid Antibody Syndrome**
- Kasabach-Merritt Syndrome
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

3 Antibodies Negative:

- Cardiolipin Ab Negative
- Beta-2 Glycoprotein Negative
- Lupus anticoagulant negative

1. British Journal of Haematology, 2012, 157, 47–58

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- ~~Paroxysmal Nocturnal Hemoglobinuria~~
- ~~Malignant Hypertension~~
- ~~Antiphospholipid Antibody Syndrome~~
- **Kasabach-Merritt Syndrome**
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

- Not seen in adults
- Fibrinogen normal throughout

1. Korean J Gastroenterol Vol. 67 No. 4, 220-223
2. British Journal of Haematology, 2001, 112, 851-862

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- ~~Paroxysmal Nocturnal Hemoglobinuria~~
- ~~Malignant Hypertension~~
- ~~Antiphospholipid Antibody Syndrome~~
- ~~Kasabach-Merritt Syndrome~~
- **Thrombotic Thrombocytopenic Purpura** ←
- **Hemolytic Uremic Syndrome** ←

Begun on:

- Plasma Exchange
- Prednisone

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- ~~Paroxysmal Nocturnal Hemoglobinuria~~
- ~~Malignant Hypertension~~
- ~~Antiphospholipid Antibody Syndrome~~
- ~~Adult Kasabach-Merritt Syndrome~~
- **Thrombotic Thrombocytopenic Purpura** ←
- Hemolytic Uremic Syndrome

ADAMTS-13:
74% activity
(>20% activity)
= Negative

1. Blood. 2002 Aug 1;100(3):778-85.

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- ~~Paroxysmal Nocturnal Hemoglobinuria~~
- ~~Malignant Hypertension~~
- ~~Antiphospholipid Antibody Syndrome~~
- ~~Kasabach-Merritt Syndrome~~
- ~~Thrombotic Thrombocytopenic Purpura~~
- **Hemolytic Uremic Syndrome** ←

Hemolytic Uremic Syndrome (St+ HUS)

- Preceding Diarrheal illness
- **Thrombotic microangiopathy: (1)**
  - Nonimmune Hemolytic Anemia
  - Thrombocytopenia
  - Renal impairment
- Incidence of 1-2 cases per 100,000 **(2)**
- Most are secondary to Infection (including 90% in children)
  - **Enterohemorrhagic Escherichia Coli** (EHEC)
    - Shiga-like toxin (Stx) producing strains O157:H7, O111:H8, O103:H2, O123, O26, or others
  - Streptococcus pneumonia

1. Br J Haematol. 2012 Aug;158(3):323-35
2. N Engl J Med 2009;361:1676-87

MAHA with Thrombocytopenia Differential

- ~~Disseminated Intravascular Coagulation~~
- ~~HELLP Syndrome and Pregnancy~~
- ~~Heparin-Induced Thrombocytopenia~~
- ~~Paroxysmal Nocturnal Hemoglobinuria~~
- ~~Malignant Hypertension~~
- ~~Antiphospholipid Antibody Syndrome~~
- ~~Kasabach-Merritt Syndrome~~
- ~~Thrombotic Thrombocytopenic Purpura~~
- **Hemolytic Uremic Syndrome** ←

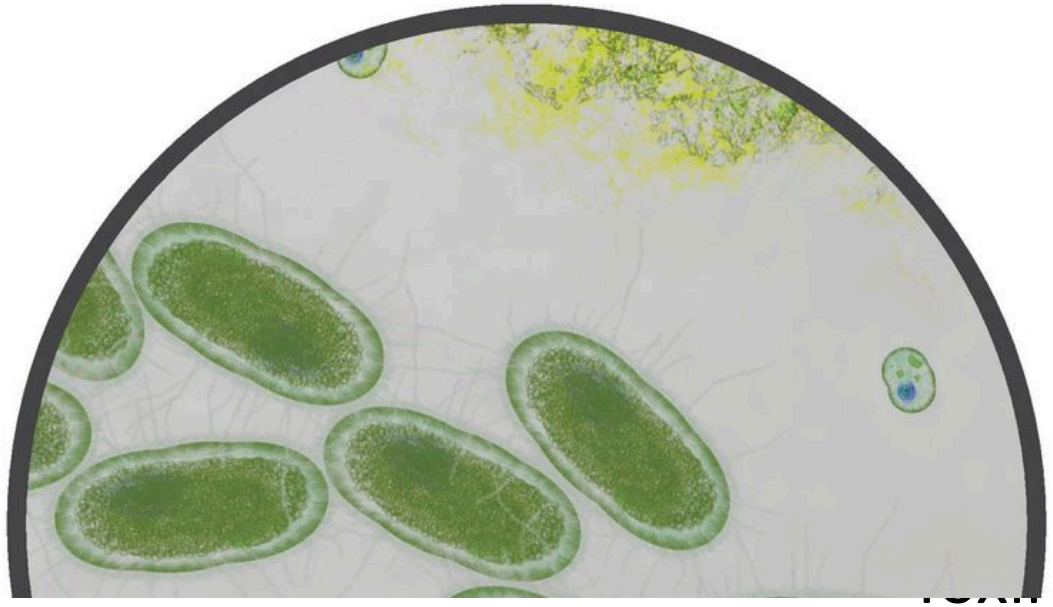
Not Typical HUS:

- No history of diarrheal illness
- Negative Stool Culture for EHEC species
- Negative for Shiga-Like Toxins 1 & 2

MAHA with Thrombocytopenia Differential

- ~~Diss~~
- ~~HEL~~
- ~~Hep~~
- ~~Parc~~
- ~~Mal~~
- ~~Anti~~
- ~~Kasa~~
- ~~Thro~~
- **Hem**

YOU CAN'T SPELL "CHIPOTLE" WITHOUT "E. COLI"



rheal

lture for

a-Like

Atypical Hemolytic Uremic Syndrome (aHUS)

- Approximately 10% of cases of HUS are classified as atypical (not caused by Shiga-toxin producing bacteria or streptococci) **(1)**
- Incidence of 2 per million (among all ages) **(2)**
- Disease of complement pathway dysregulation **(3)**

1. N Engl J Med 2009;361:1676-87
2. Orphanet J Rare Dis. 2011; 6:60
3. Blood 2006 108:1267-1279

Potential Etiologies:

- Less than 20% of cases of aHUS are familial
  - Poor prognosis with rate of ESRD in 50% and death in an additional 25%
- Genetic mutations have been implicated in many sporadic cases
- The rest are a sporadic form with triggers identified as:
  - HIV infection
  - Cancer
  - Organ transplantation
  - Pregnancy
  - Anticancer drugs
  - Immunotherapeutic agents
  - Antiplatelet agents (ticlopidine and clopidogrel)

1. N Engl J Med 2009;361:1676-87
2. Blood 2006; 108:1267-1279

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  - Pregnancy
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  - Immunotherapeutic agents
  - Antiplatelet agents (ticlopidine and clopidogrel)
- **FEIBA?**

1. N Engl J Med 2009;361:1676-87
2. Blood 2006; 108:1267-1279

What is FEIBA?

- **F**actor **E**ight **I**nhibitor **B**y-passing **A**ctivity or
  - Anti-Inhibitor Coagulant Complex or
  - “activated” prothrombin-complex concentrate (aPCC)
- Developed as an alternative to Factor VIII infusions for Hemophiliacs who developed antibodies against Factor VIII and IX
- Contains activated **Factor VII** and inactivated **Factors II, IX, and X**
- Achieved hemostasis significantly better control of bleeding than control (non-activated prothrombin-complex concentrate= Prothromblex Immuno) in RCT using dose of 50U/kg **(1)**
- Found to be safe and efficacious for acquired inhibitors in another uncontrolled trial**(2)**

1. NEJM. 1981; 305: 717-21
2. Blood, 1983; 6: 36-40

FEIBA

- Thrombotic complications have been seen (DVT, MI, CVA) **(1,2)**
- In addition, disseminated intravascular coagulation, a thrombotic microangiopathy, is a known complication **(1, 3)**
- Although not reported with FEIBA, a single case report noted aHUS as complication with K-Centra (An inactivated four factor prothrombotic complex concentrate) **(4)**

1. NEJM. 1981; 305: 717-21
2. FEIBA [package insert]. Westlake Village, CA: Baxter Healthcare Inc; 2013.
3. Thromb. Res. 1981;22(1-2):177-84.
4. Case Rep Nephrol Urol 2013; 3:139-146

FEIBA for Control of Warfarin-Induced Bleeding?

Methods: Protocol for use of FEIBA for emergent reversal of warfarin-related coagulopathy.

Fixed Dose: IV Vitamin K regardless of INR

+

INR<5.0= 500 Units of FEIBA

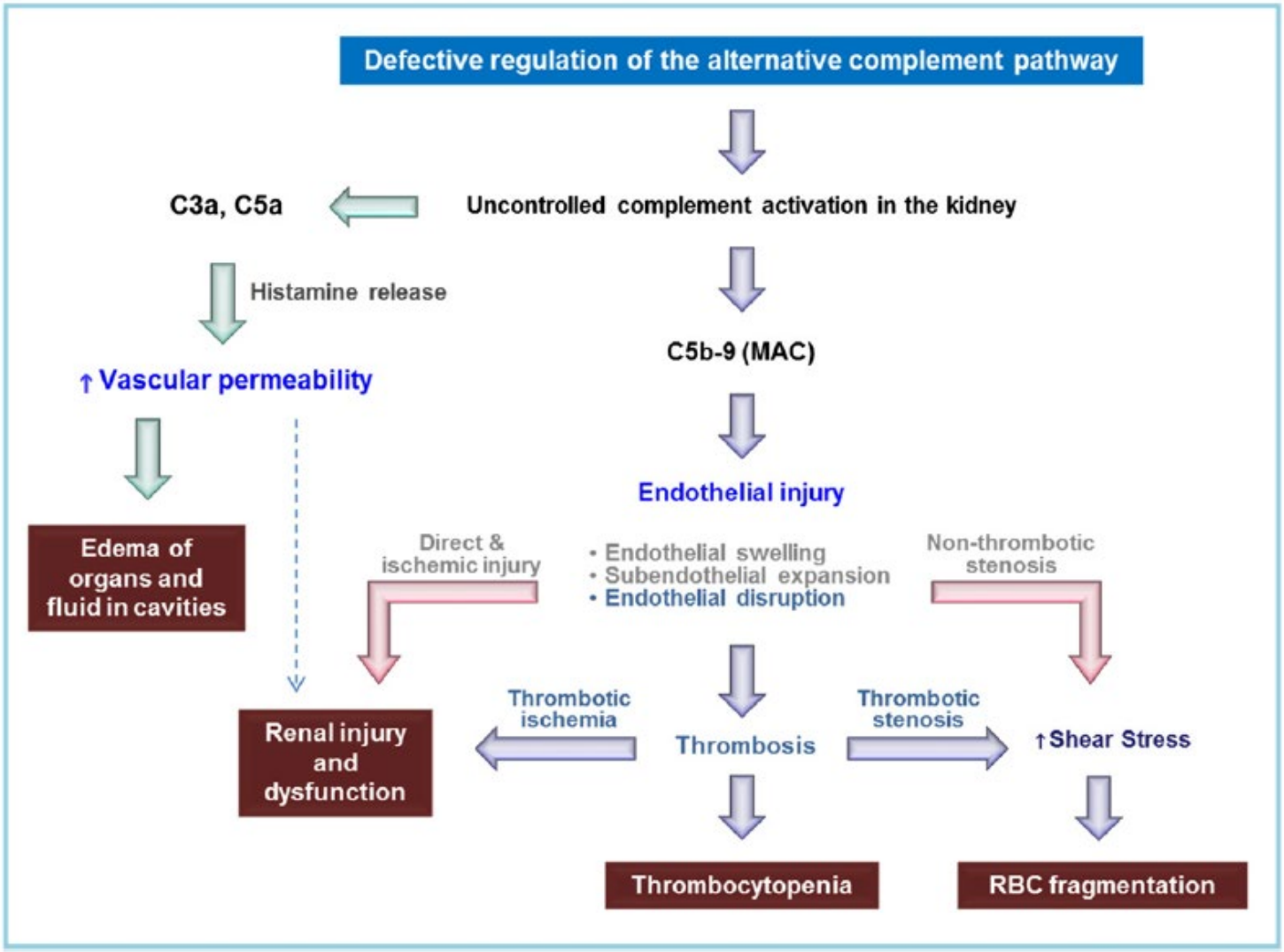
INR > 5.0= 1000 Units of FEIBA given

Infused at rate of 1-2U/min

Results: 16 patients were treated on protocol (most for intracranial hemorrhage) for mean pre-treatment INR of 3.56 and post-treatment INR of 1.16. Two patients required additional dose. No thromboses associated with use.

1. Am J Emerg Med. 2013 Aug;31(8):1251-4.

Atypical HUS Pathogenesis



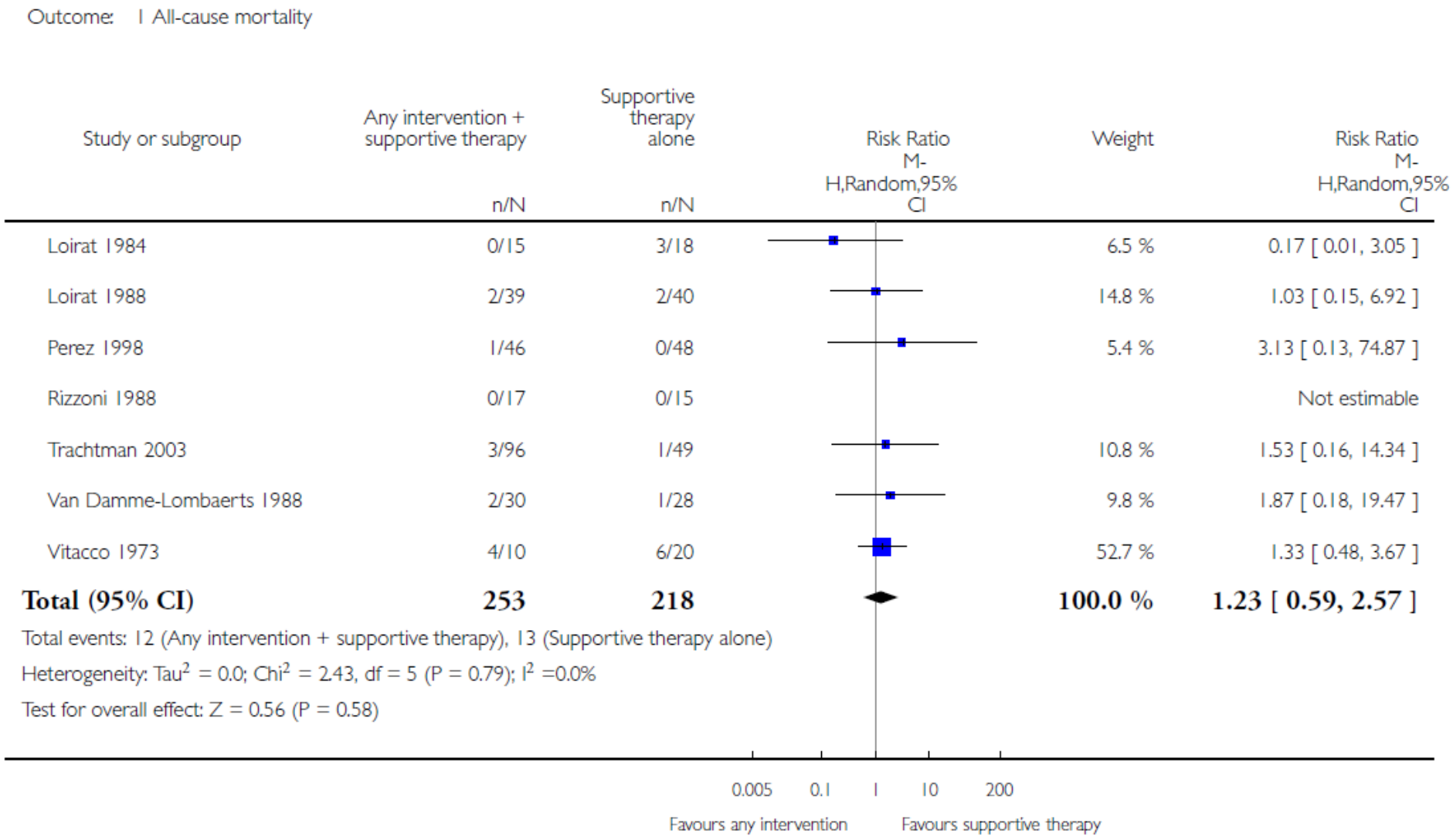
1. Transfusion Medicine Reviews 29 (2014) 187-197

Atypical HUS Treatment

- Within 24 hours of diagnosis, plasma based therapies with FFP infusion or plasma exchange is recommended
- Based on hypothesis that complement regulation abnormalities are the most likely etiology
- Duration should extend until response is achieved by normalization of platelet count and serum LDH

1. N Engl J Med 2009;361:1676-87

Meta-Analysis of Thrombotic Microangiopathies



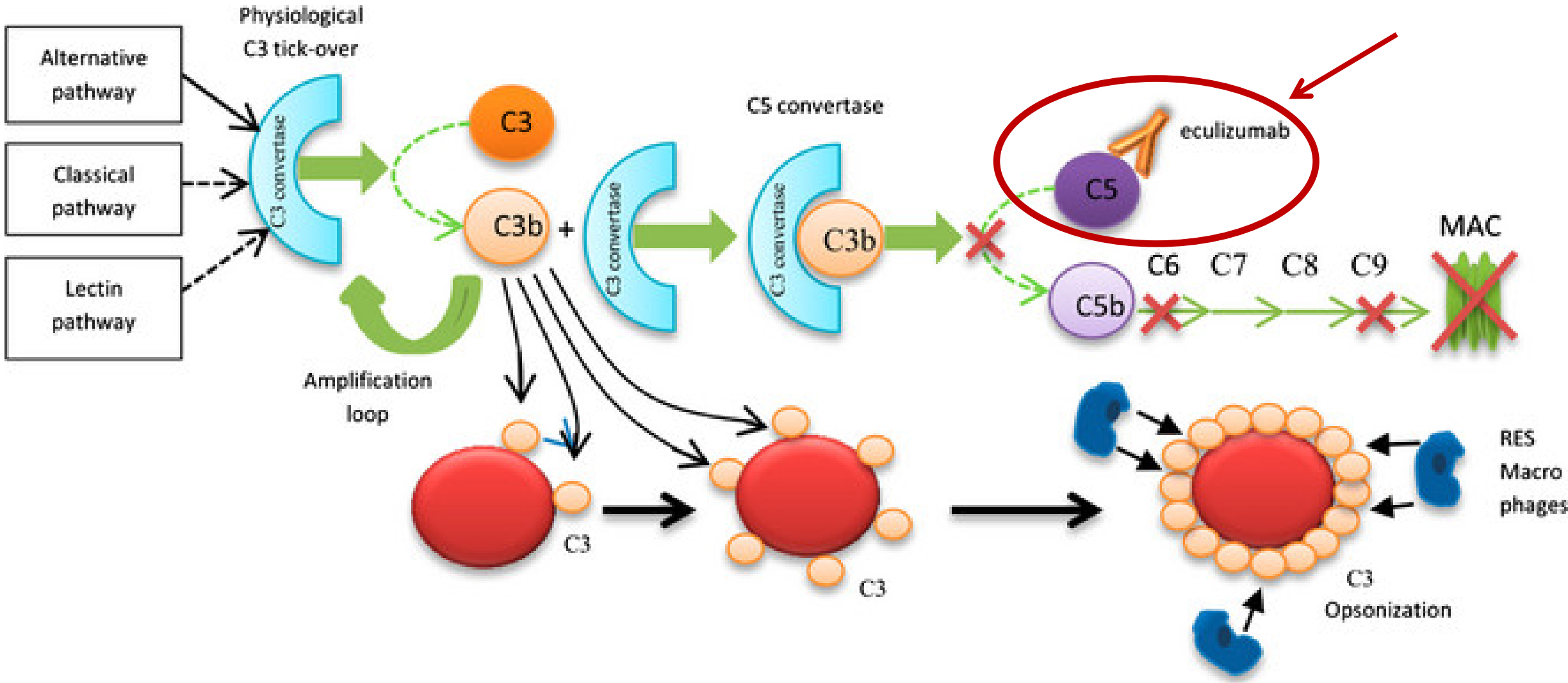
1. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD003595.

Eculizumab

- First in class humanized monoclonal antibody that blocks complement activity high affinity binding to Complement C5 **(1)**
- Marketed as Soliris by Alexion Pharmaceticals
- Prevents cleavage of C5→C5a + C5b
  - Blocks production of proinflammatory and prothrombotic C5a production **(2)**
  - Blocks formation of complex C5b-9 / MAC
- Has been used as first-line agent for atypical HUS **(3)**

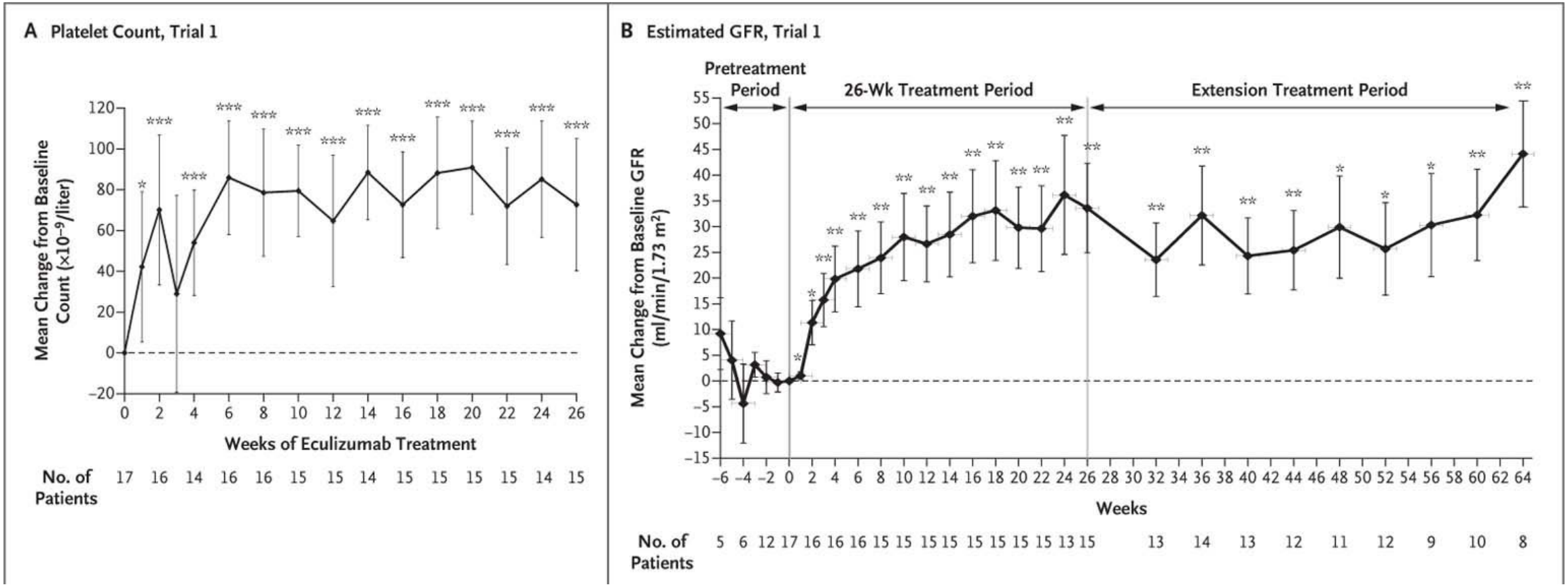
1. N Engl J Med 2013;368:2169-81.
2. Pediatr Nephrol (2008) 23:1957–1972
3. Case Rep Nephrol Urol 2013;3:139–146

Eculizumab



1. Eur J Haematol. 2015;95(3):190-8.

Eculizumab



1. N Engl J Med 2013;368:2169-81.

ICU Course: Day 4

- Plasma exchange and prednisone were discontinued
- Hemodialysis continued
- Weekly infusion of **eculizumab** started for **atypical HUS**

Hospital Course:

- Received 4 weekly doses of eculizumab
- His renal function slowly began to improve
- Cessation of MAHA occurred first within week of eculizumab treatment
- Graduated from dialysis within two months

Follow-up:

2 years post-hospitalization:

Doing well with Stage III CKD off HD presently and without recurrent aHUS!

Summary:

- Atypical HUS is **Shiga-toxin negative** illness characterized a triad of **microangiopathic hemolytic anemia, thrombocytopenia,** and **renal failure**

- Treatment includes plasma-based therapies and now **eculizumab**

- **Atypical HUS** should be added as a rare complication of **FEIBA** administration

Thanks!

Supplemental Slides

1. Did he receive a high FEIBA Dose?
2. Extra lab studies
3. Remind me of TTP
4. Inheritance pattern of familial forms of disease
5. Common warfarin complication? What caused hematoma/biopsy?
6. What is Thrombotic Microangiopathy?
7. What is mechanism of shigatoxin in D+ HUS?
8. Are you sure he didn't have an aHUS trigger you listed?
9. Where does FEIBA Act?
10. Coagulation cascade and complement interaction
11. Eculizumab Indications

1. FEIBA Dose

<u>FEIBA for Anticoagulation Reversal:</u>

Warfarin:

-500 or 1000Units of FEIBA + Vitamin K stratified based on INR **(1-2)**

DOACs:

Dabigatran- 50U/kg FEIBA **(3)**

Rivaroxaban or Dabigatran- 50U/kg **(4)**

<u>Our Patient:</u>

Received 15,000 Units at 100U/kg

-Upper range of Hemophilia dosing

1. Am J Emerg Med. 2013 Aug;31(8):1251-4.
2. Int J Emerg Med. 2009 Nov 26;2(4):217-25
3. *Thrombosis and Haemostasis*. 2012;108(2):217–224
4. Circulation. 2011 Oct 4;124(14):1573-9.

2. Extra Lab Studies

Ferritin= 452
CK= 231 (23-270 IU/L)
Heterozygote for Factor V Leidin
Negative Strep Pneumo Urinary Antigen
UA- 3+protein, 3+ blood, 5-10 WBC, 2-5 RBC, 1+ Squam, Bacteria trace
Urine Na=50
Urine Cr= 93.1

VAS Lower Extremity Duplex 2/12:
Abnormal exam demonstrating right lower extremity DVT: - of chronic appearance in the proximal femoral, mid femoral, distal femoral, popliteal, and posterior tibial vein segment(s). Non-occlusive deep venous thrombus in the right proximal femoral, mid femoral, distal femoral, popliteal, and posterior tibial vein vein(s). There was evidence of deep system valvular incompetence (chronic venous insufficiency) of the right lower extremity. Occlusive deep venous thrombus in the left soleal sinus and gastrocnemius vein(s).

Abdominal Ultrasound:
10 cm heterogeneous mass lesion in the right lobe of the liver concerning for possible malignancy. Recommend contrast-enhanced abdomen and pelvis CT for further evaluation of this finding.

Renal Duplex 2/13:
Bilateral renal duplex study revealed no evidence of renal arterial occlusion or hemodynamically significant stenosis. Normal kidney anatomy, size and parenchymal perfusion.

3. Thrombotic Thrombocytopenic Purpura (TTP)

Classic "Pentad":

-Microangiopathic Hemolytic Anemia (MAHA)

-Thrombocytopenia (consumptive process)

-Renal Insufficiency (due to deposits in renal vasculature)

-Fever

-Neurologic Symptoms (AMS, Seizures, paresthesias, aphasia

Pathophysiology:

Associated with severe deficiency of ADAMTS13 activity due to autoantibodies against the protease

4. aHUS Causes

Table 1. Classification of Atypical Hemolytic–Uremic Syndrome.*

Form of Disease	Complement Abnormalities
Familial	Mutations in *CFH*, 40–45%; in *CFI*, 5–10%; in *C3*, 8–10%; in *MCP*, 7–15%; in *THBD*, 9%; and in *CFB*, 1–2%.
Sporadic	
Idiopathic	Mutations in *CFH*, 15–20%; in *CFI*, 3–6%; in *C3*, 4–6%; in *MCP*, 6–10%; in *THBD*, 2%; and in *CFB*, 2 cases; anti-CFH antibodies: 6–10%
Pregnancy-associated	Mutations in *CFH*, 20%; in *CFI*, 15%
HELLP syndrome	Mutations in *CFH*, 10%; in *CFI*, 20%; and in *MCP*, 10%
Drugs	Rare *CFH* mutations (mostly unknown)
Organ transplantation	Mutations in *CFH*, 15%; in *CFI*, 16%
Human immunodeficiency virus infection	Unknown†
Cancer	Unknown†

* HELLP denotes hemolytic anemia, elevated liver enzymes, and low platelet count.
† There are no published data on the frequency of complement gene mutations or anti-CFH autoantibodies in patients with this condition.

Noris M, Remuzzi G. N Engl J Med 2009;361:1676-1687

4b. aHUS Causes

Table 2. Genetic Abnormalities and Clinical Outcome in Patients with Atypical Hemolytic–Uremic Syndrome.*

Gene	Protein Affected	Main Effect	Frequency	Response to Short-Term Plasma Therapy†	Long-Term Outcome‡	Outcome of Kidney Transplantation
			%			
CFH	Factor H	No binding to endothelium	20–30	Rate of remission: 60% (dose and timing dependent)	Rate of death or ESRD: 70–80%	Rate of recurrence: 80–90%§
CFHR1/3	Factor HR1, R3	Anti–factor H antibodies	6	Rate of remission: 70–80% (plasma exchange combined with immunosuppression)	Rate of ESRD: 30–40%	Rate of recurrence: 20%¶
MCP	Membrane cofactor protein	No surface expression	10–15	No definitive indication for therapy	Rate of death or ESRD: <20%	Rate of recurrence: 15–20%¶
CFI	Factor I	Low level or low cofactor activity	4–10	Rate of remission: 30–40%	Rate of death or ESRD: 60–70%	Rate of recurrence: 70–80%§
CFB	Factor B	C3 convertase stabilization	1–2	Rate of remission: 30%	Rate of death or ESRD: 70%	Recurrence in one case
C3	Complement C3	Resistance to C3b inactivation	5–10	Rate of remission: 40–50%	Rate of death or ESRD: 60%	Rate of recurrence: 40–50%
THBD	Thrombomodulin	Reduced C3b inactivation	5	Rate of remission: 60%	Rate of death or ESRD: 60%	Recurrence in one case

* ESRD denotes end-stage renal disease.
† Remission was defined as either complete remission or partial remission (i.e., hematologic remission with renal sequelae).
‡ The long-term outcome was defined as the outcome 5 to 10 years after onset.
§ Patients in this category were eligible for combined liver and kidney transplantation.
¶ Patients in this category were eligible for single kidney transplantation.

Genetic Abnormalities and Clinical Outcome in Patients with Atypical Hemolytic–Uremic Syndrome

Noris M, Remuzzi G. N Engl J Med 2009;361:1676-1687

5. What caused hematoma? Common warfarin complication?

Hematoma Causes:

Spontaneous from warfarin use?

-One review only identified 6 case reports in world literature **(1,2)**

-One retrospective study of 184 patients with hemorrhagic complications with VKA noted 3/184 had splenic/liver hematomas **(3)**

1. World J Gastroenterol. 2013 Oct 14; 19(38): 6494–6499.
2. Hepatogastroenterology. 1993 Aug;40(4):402-6.
3. Rozhl Chir. 2010 Feb;89(2):124-9.

5b. Liver Lesion Biopsy

2 Months after admission for aHUS, underwent IR-guided biopsy of liver lesion:

-Blood and fibrin deposition consistent with **hemangioma**

6. Thrombotic Microangiopathy

7. What is mechanism of shiga toxin in D+ HUS?

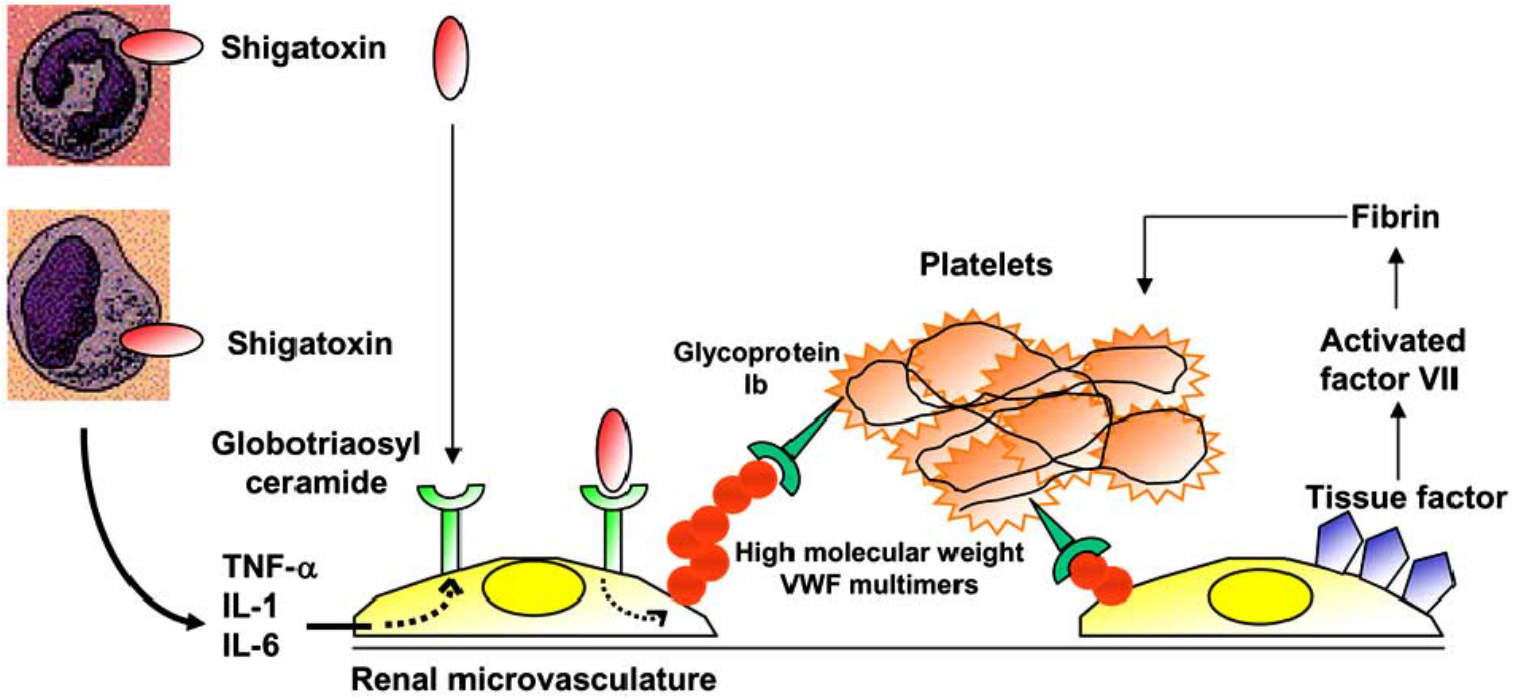
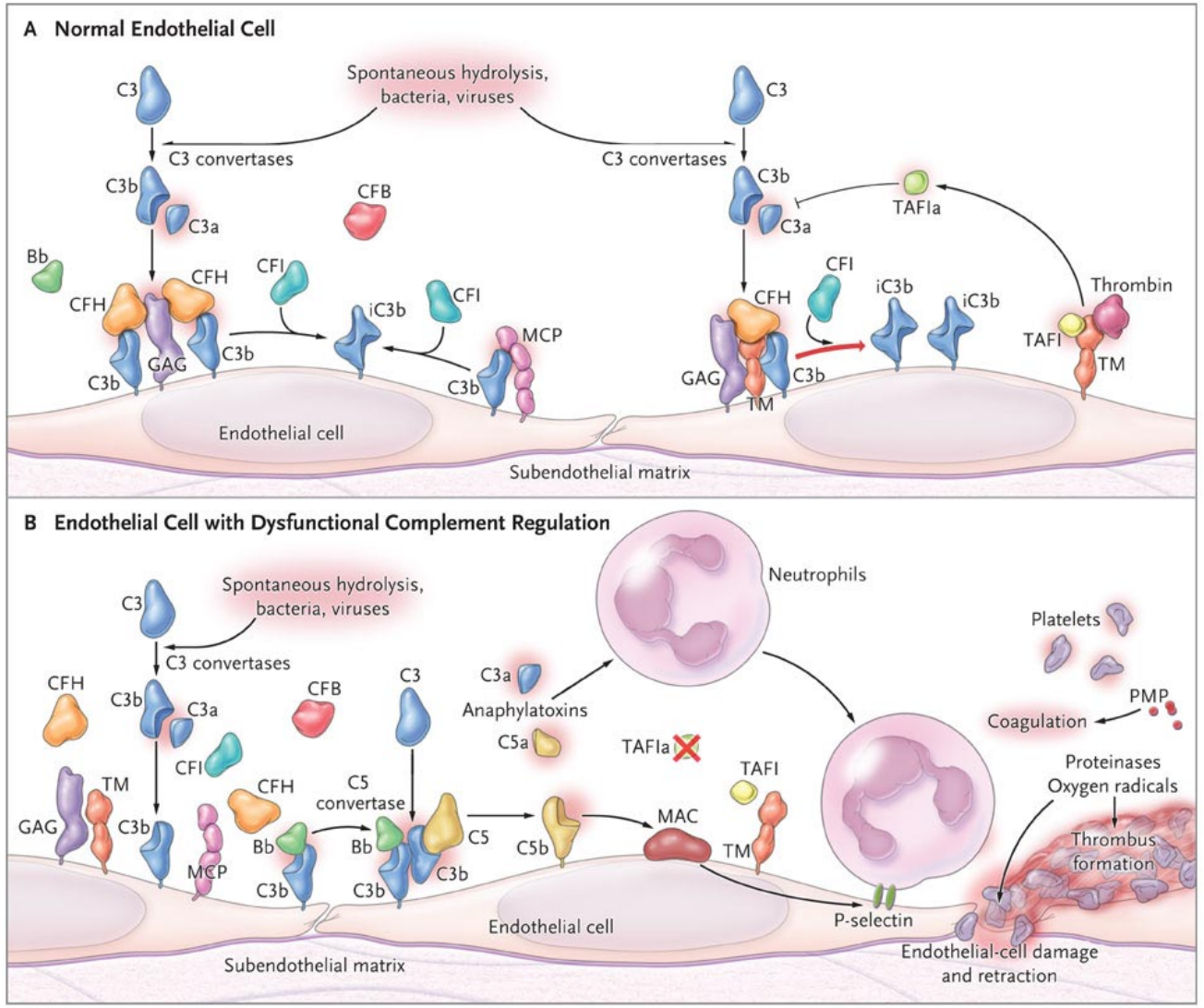


Fig. (4). Pathophysiological mechanisms leading to microthrombi formation in diarrhea-associated HUS. Shigatoxins are transported in blood flow by neutrophils, platelets and monocytes, and bind their receptors (globotriaosyl ceramide) at the surface of renal endothelial cells. IL-1, IL-6 and TNF-α up-regulate expression of shigatoxins receptors on endothelial cells surface. After internalization, they interfere with protein traduction machinery and thereby induce endothelial cell apoptosis. Damaged cells express surface high molecular weight VWF, which initiates platelet clumping through interaction with glycoprotein Ib. Shigatoxins also induce tissue factor expression on endothelial cells, leading to factor VII activation and fibrin formation. VWF: von Willebrand factor.

1. Drug Targets, 2009, Vol 9, No.1, pp36-50.

8. Are you sure he didn't have an aHUS trigger you listed?



Model for the Mechanisms Leading from Impaired Regulation of the Alternative Pathway to Thrombotic Microangiopathy

Noris M, Remuzzi G. N Engl J Med 2009;361:1676-1687

8b. Are you sure he didn't have an aHUS trigger you listed?

The rest are a sporadic form with triggers identified as:

HIV infection – **HIV test negative**

Cancer – **Following hospitalization Lung nodule and Liver mass biopsied and non-cancerous**

Organ Transplantation- **Did not have**

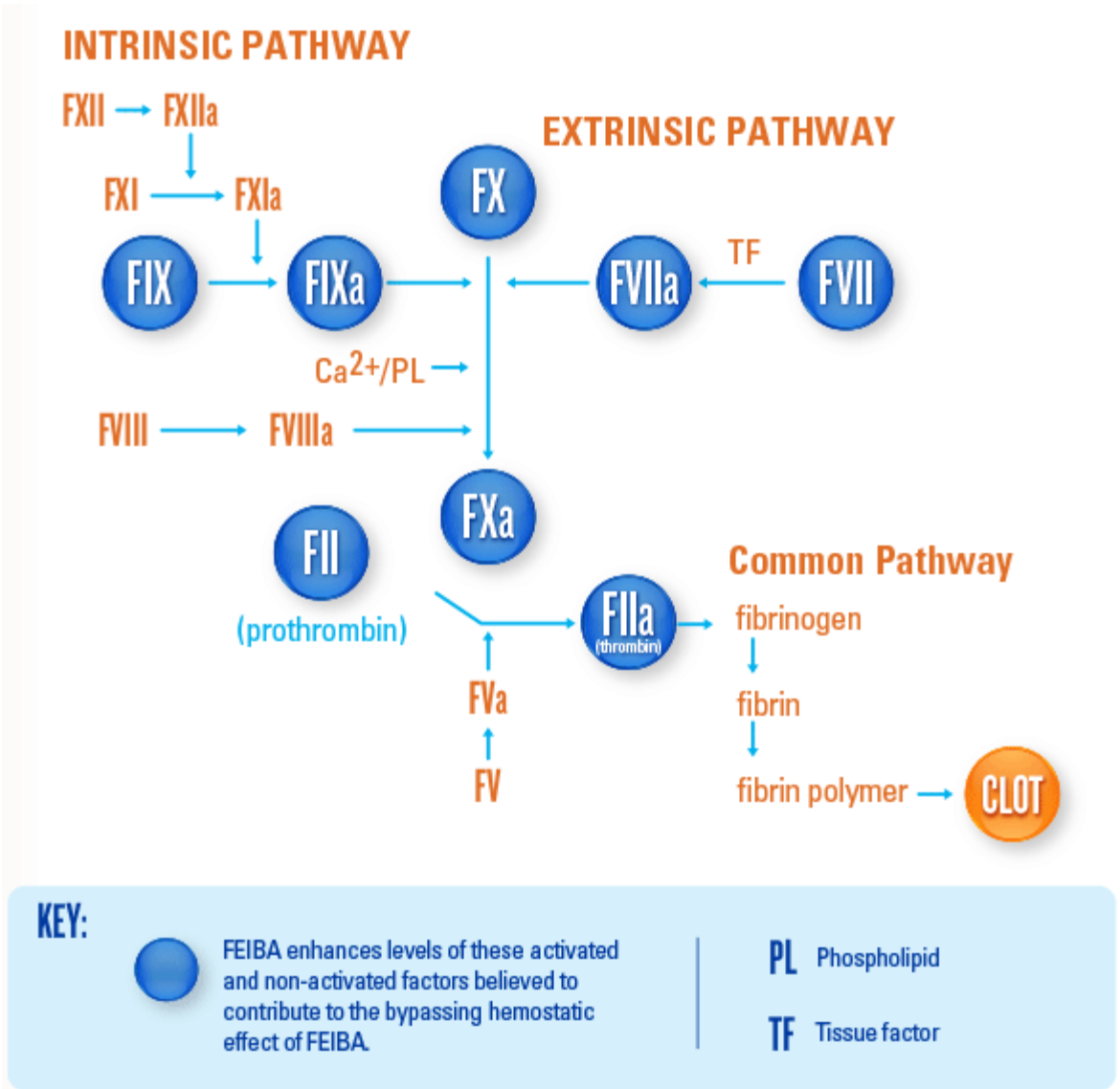
Pregnancy- **Not pregnant**

Anticancer drugs – **Not on chemotherapy**

Immunotherapeutic Agents- **Not immunosuppressed**

Antiplatelet Agents (ticlopidine and clopidogrel)**-Not on these**

9. Where does FEIBA Act?



10. Coagulation Cascade and Complement Interaction

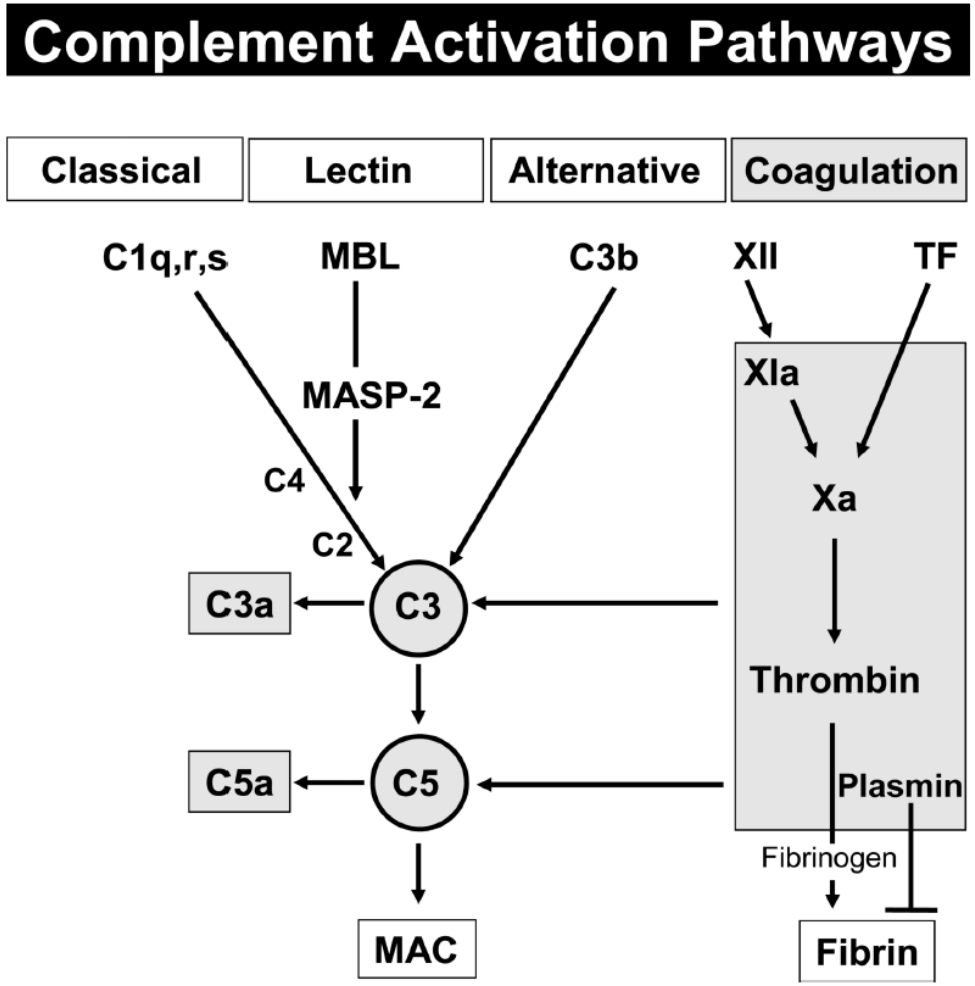


Fig. 2.
Complement activation pathways (*MAC* membrane attack complex; *MBL* mannose binding lectin; *MASP-2* mannose associated serine protease-2; *TF* tissue factor.

Activation of the coagulation cascade through **thrombin, XIa** and **Xa** has been shown to activate the complement pathway

1. Adv Exp Med Biol. 2008 ; 632: 71–79.

11. Additional Eculizumab Indications

- Initially FDA-approved for paroxymal nocturnal hemoglobinuria (PNH) **(1)**
- Studies recruiting trials for Neuromyelitis Optica **(2)**
- For the prevention of Renal Transplant Rejection **(3)**
- Refractory Generalized Myasthenia Gravis **(4)**

1. *Nature Biotechnology* **25**, 1256 - 1264 (2007)
2. Alexion Pharmaceuticals. In ClinicalTrials.gov [internet]. Bethesda (MD). National Library of Medicine (US). [Jan 1, 2015] Available from: https://clinicaltrials.gov/ct2/show/record/NCT02003144?term=eculizumab&rank=2: NCT02003144
3. Lonze, Bonnie E. In ClinicalTrials.gov [internet]. Bethesda (MD). National Library of Medicine (US). [Dec 9, 2009] Available from: https://clinicaltrials.gov/ct2/show/study/NCT01029587?term=eculizumab&rank=11: NCT01029587
4. Wang, Jing. In ClinicalTrials.gov [internet]. Bethesda (MD). National Library of Medicine (US). [Nov 11, 2014] Available from: https://clinicaltrials.gov/ct2/show/NCT02301624?term=eculizumab&rank=18: NCT02301624.