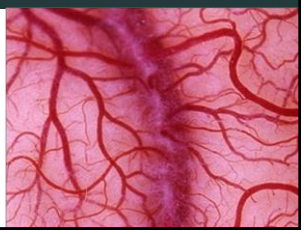
TTP, HUS, AND DIC:
Thrombotic Microangiopathies with a Side of Alphabet Soup

Lee Ellen Brunson, MHS, MLS(ASCP)CM
LSU Health Shreveport
Department of Medical Laboratory Science

1

Objectives

1. Discuss causes of thrombotic microangiopathies.
2. Distinguish TTP, HUS, and DIC based on clinical and laboratory features.
3. Describe treatments for the disorders presented.



2

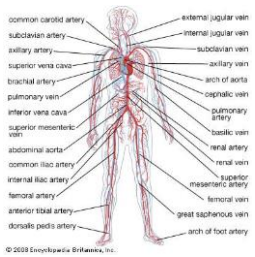
Thrombotic Microangiopathies (TMA)

- Rare yet life-threatening disorders characterized by the presence of a microangiopathic hemolytic anemia, thrombocytopenia, as well as microvascular thrombosis and ischemic tissue injury
- Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) are some of the most common.
  - DIC is a syndrome with numerous potential causes that may initially appear very similar to TTP or HUS.
  - TTP and HUS were initially considered to be similar and overlapping disorders but are now accepted as two distinct entities with very different causes.
- Considered to be hematologic emergencies that require prompt treatment

3

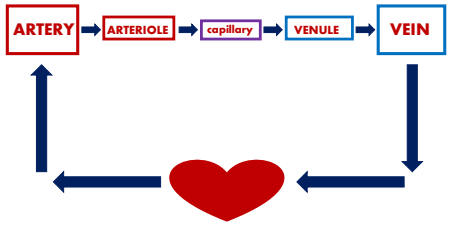
Circulatory system

System of organs that includes, the heart, blood vessels, and blood which is circulated continuously throughout the entire human body



4

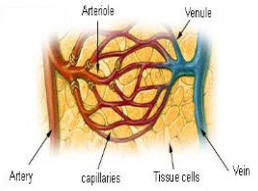
The Vascular System



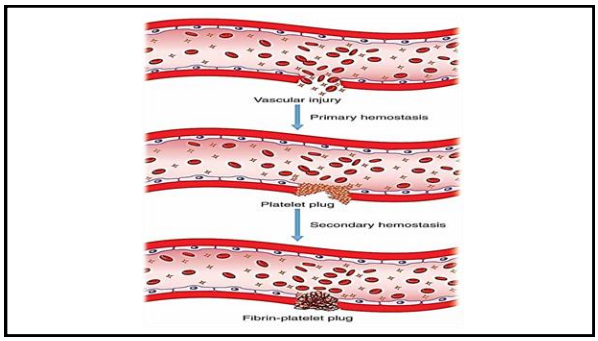
5

Microvasculature

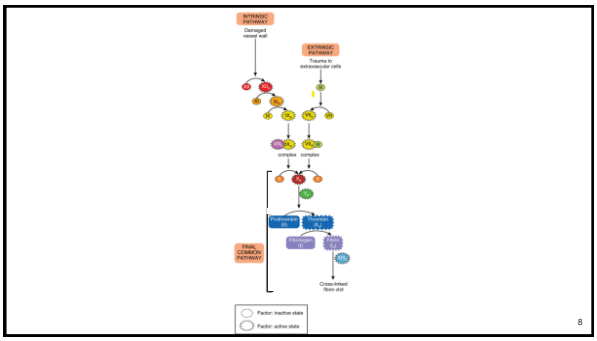
- The portion of the circulatory system composed of the smallest vessels, such arterioles, venules, and capillaries
- Most easily occluded



6



7



8

Disseminated Intravascular Coagulation (DIC)

- Widespread, uncontrolled, simultaneous formation and lysis of fibrin within the blood vessels
- Systemic activation of coagulation
- **Consumptive coagulopathy** results in deficiency of hemostatic components.
- Fibrinolysis over-activated in response to inappropriate clotting, leads to bleeding.

9

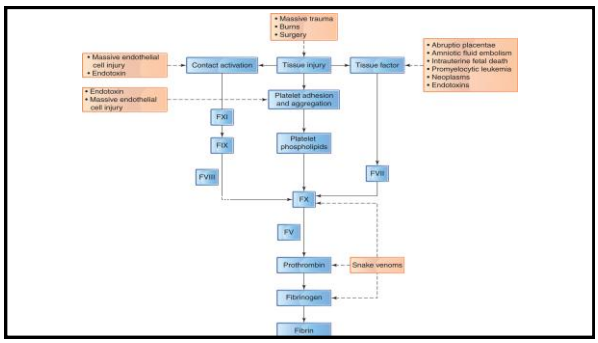
9

Disseminated Intravascular Coagulation (DIC)

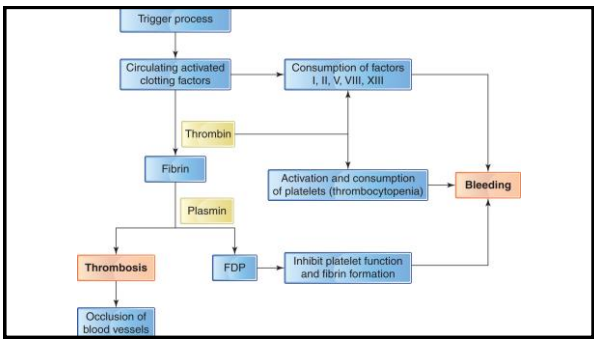
- Syndrome, not a disease
- Occurs in ~1 in 1000 hospitalized patients
- Several mechanisms are triggers of DIC
  1. Release of Tissue Factor (TF), activation of FVII
  2. Endothelial cell damage, contact factor activation & TF release
  3. Direct activation of FX, FII or fibrinogen
- Most common activators of DIC:
  - **M**alignancy
  - **O**B complications
  - **S**epsis
  - **T**rauma

10

10

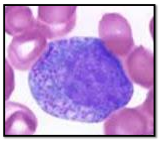


11



12

DIC – Triggering Mechanisms

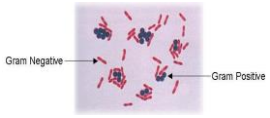


1. Release of TF, activation of FVII
   - Amniotic fluid embolism
   - Premature separation of placenta
   - Intrauterine fetal death
   - AML-M3 → promyelocytic leukemia (contents of primary granules in immature WBC)
   - Trauma

13

13

DIC – Triggering Mechanisms



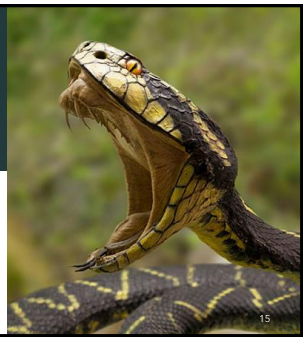
2. Endothelial cell damage, TF release, contact factor activation
   - Gram negative septicemia
   - Gram positive septicemia
   - Septic miscarriage
   - Severe burns

14

14

DIC – Triggering Mechanisms

3. Direct activation of FX, FII or fibrinogen
   - Snake bites
   - Certain malignancies



15

15

Thrombin goes rogue!

- Thrombin normally acts at the site of injury to convert fibrinogen to sticky fibrin during clot formation
- In DIC, the actions of thrombin are not localized, resulting in widespread:
  - Platelet activation and aggregation
  - Depletion of multiple coagulation factors
  - Fibrinolysis
- Normal thrombin inhibitory pathways fail.

16

16

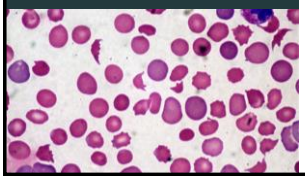
Clinical manifestations of DIC

- Can be acute or chronic; hemorrhage or thrombosis
- Hemorrhaging from at least 3 separate sites
  - Bleeding from GI, GU, and respiratory tracts
  - Oozing from surgical or puncture sites
  - Epistaxis, bruising, intracranial bleeding
- Small fibrin strands obstruct microvasculature
  - Hemolytic anemia
  - Widespread organ dysfunction or failure
  - Thromboembolism
  - Hypotension, shock, coma
- Mortality rate 50-60%

17

17

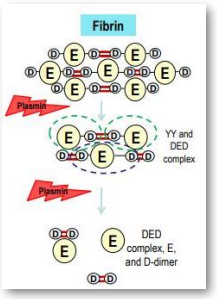
Lab findings in DIC



Thrombocytopenia
PT – prolonged
APTT – prolonged
TT – prolonged
Fibrinogen – decreased
FDPs/FSPs – increased
D-dimers - increased
RBCs may be fragmented by fibrin strands (schistocytes)

18

18



19

Treatment for DIC

- First treat/remove underlying cause or stimulus
  - Antibiotic for infection
  - Resolve or treat OB complication
- *Treatment should be initiated with caution*
- Patient given supportive treatment:
  - RBC to maintain blood volume
  - Transfusion of fresh frozen plasma (FFP), cryoprecipitate, specific factor concentrates, platelets to restore hemostatic function

20

20

TTP and HUS

- Damage to endothelial cells triggers widespread PLT aggregation
- Activation of PLT without activation of coagulation cascade
- Platelet consumptive disorders: lead to thrombocytopenia, bruising, bleeding, organ damage or failure, death
- May cause widespread organ dysfunction as microthrombi (composed primarily of PLT aggregates) lodge in small vessels

21

21

"Classic pentad" of symptoms

1. **F**ever
2. Microangiopathic Hemolytic **A**nemia (MAHA): hematuria, jaundice
3. **T**hrombocytopenia: bleeding and bruising
4. **R**enal Failure: decreased urine output from thrombi in kidneys
5. **N**eurological Deficits: bizarre behavior from thrombi in brain

22

22

TTP

- Triggered by presence of ultralarge von Willebrand factor (VWF) multimers in plasma
- ADAMTS-13 enzyme normally cleaves VWF prior to release into plasma
- Large VWF multimers can directly agglutinate PLTs
- Inherited – Deficiency or dysfunction
- Acquired – Autoantibodies cause deficiency
- TTP more often associated with **neurological symptoms** and more severe thrombocytopenia, **multiple organs affected**

23

23

HUS

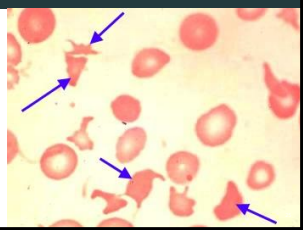
- More likely to be seen as outbreaks rather than individual cases
- Acquired HUS usually seen in children, strongly associated with ingestion of *E. coli O157:H7*
- Bloody diarrhea, fever, **renal failure** that may lead to organ failure
- Inherited form not associated with bacteria; no bloody diarrhea; chronic episodes
- Renal involvement more severe than in TTP.
  - Renal insufficiency
  - Renal dialysis
  - Possibly lifelong
- ADAMTS-13 **normal**

24

24

Lab findings: TTP and HUS

- Thrombocytopenia
- Schistocytes
- LDH, serum bilirubin, and reticulocyte counts are elevated.
- PT/APTT: normal
- Proteinuria and hematuria may be present.
- ADAMTS13?
  - Decreased in TTP
  - Normal in HUS



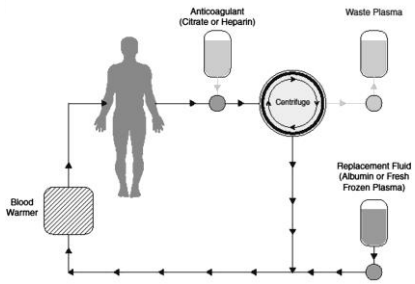
25

Treatment of TTP and HUS

- Therapeutic plasma exchange (TPE) should be initiated even if ADAMTS-13 results are not yet available
  - "Access" port removes whole blood
  - Whole blood is centrifuged
  - Plasma discarded, cells back to body via "return" port
  - Donor plasma transfused along with cells
- Has decreased mortality rate from 90% to 15%

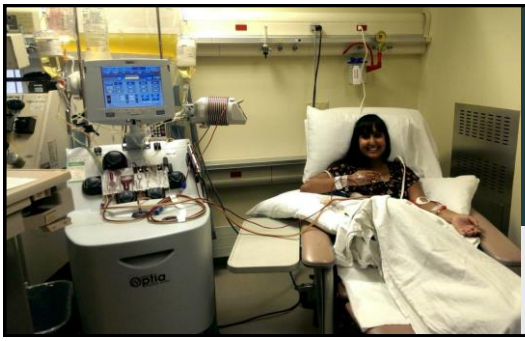
26

26



27

27



28

28

29

29

Treatment of TTP and HUS, cont.

- For TTP:
  - TPE replenishes functional ADAMTS-13 and removes autoantibody to the enzyme.
  - Patients may also be administered steroids to decrease autoantibody production
- For HUS: TPE may help to remove toxin that is causing damage to endothelial cells.

30

30

An Infamous Outbreak

- January, 1993: pediatric gastroenterologist notified the Washington State Department of Health of an increase in ER visits for bloody diarrhea and HUS in Seattle-area children
- Source of illness was traced back to *E. coli* 0157:H7 that had contaminated hamburger patties sold at area Jack in the Box restaurants
- Scope of the outbreak widened in subsequent weeks to California, Idaho, and Nevada
- 73 Jack in the Box locations ultimately linked to the outbreak
  - Over 700 people sickened
  - 171 hospitalizations
  - 4 deaths

31

How did this happen?

- Jack in the Box "Monster Burger" promotion overwhelmed restaurants
- Parent company of Jack in the Box (Foodmaker) blamed the supplier of the hamburger meat (Vons Companies)
- Five slaughterhouses in U.S. and one in Canada were highly implicated as causes of contamination, but no exact source was ever pinpointed
- Despite being warned by local health departments, Jack in the Box disregarded Washington state laws requiring burgers to be cooked to 155°F because it made the meat too tough; instead adhered to the federal standard of 140°F

32

Brianne Kinner

- Nine-year-old admitted to hospital after eating hamburger from a Richmond, WA Jack in the Box
- Developed HUS, causing edema and jaundice
- All organs began to fail; she began to bleed from all orifices
- Required months of dialysis
- Slipped into a coma for 40 days, doctors removed her large intestine, placed her on ECMO
- Regained consciousness and began to improve
- After three strokes and thousands of seizures, had to relearn how to even the easiest tasks
- Left the hospital after 6 months, suffering with brain damage, diabetes, and asthma

33

Silver Linings

- *E. coli* O157:H7 upgraded as a reportable disease at all state health departments
- FDA increased recommended internal cooking temperature to 155°F
- USDA introduced safe food-handling labels for packaged raw meat and poultry at supermarkets
- USDA introduced testing for *E. coli* O157:H7 in ground meat
- National Cattlemen's Beef Association created a task force to fund research into reduction of *E. coli* O157:H7 in cattle and slaughterhouses
- Jack in the Box set new safety standards across the fast-food industry by overhauling and restructuring their operations around food safety priorities

34

References

- McKenzie, Shirlyn B., Clinical Laboratory Hematology, 4th ed. Pearson, 2019.
- Arnold, D., Patriquin, C., & Nazy, I., Thrombotic microangiopathies: a general approach to diagnosis and management. *CMAJ* 2017 January 30; 189:E153-9. https://doi.org/10.1503/cmaj.160142
- Bell BP, Goldoft M, Griffin PM, et al. A multistate outbreak of Escherichia coli O157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers. The Washington experience. *JAMA*. 1994;272(17):1349-1353.

35

Thank you!

Lee Ellen Brunson, MHS, MLS(ASCP)CM

LeeEllen.Brunson@lsuhs.edu

(318)813-2913

36