# HUS-TTP...SOS!

Complete plasma volume exchange treatment utilizing fresh frozen plasma.

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# Objectives

- Presentation of patient case.
- Describe etiology and pathology of disease(s).
- Explain treatment utilizing fresh frozen plasma in total volume plasma exchange.
- Describe additional and/or alternative treatments for patients who do not respond to plasma exchange or experience relapsed TTP.

# Case Study: Patient History

- 45 year-old woman admitted to ED reporting onset of diarrhea and abdominal pain x 3 days.
- Patient had just returned from cruise to the Bahamas with her daughter.
- We shall call her Bahama Mama

- Began experiencing bloody diarrhea, nausea, abdominal pain, fevers, fatigue and dizziness during the return portion of the cruise.
- Patient reports being healthy typically, no history of chronic illness or prior surgeries.

# Case Study: Day 0

- **Lab Results**

| Hematology | Patient | Normal Range |
|---|---|---|
| RBC | 5.07 M/uL (H) | 3.8-5.2 M/uL |
| HGB | 16.5 g/dL (H) | 12.0-16.0 g/dL |
| HCT | 48.9% (H) | 36.0-46.0% |
| PLT | 310 K/uL | 150-450 K/uL |
| WBC | **28.4 K/uL (*H)** | 4.5-11 K/uL |
| WBC Differential | 70% Seg, 2% Band,<br>20% Lymph, 7% Mono | |

# Case Study: Day 0

- Lab Results Continued

| Electrolytes | Patient | Normal Range |
|---|---|---|
| Sodium | 133 mmol/L (L) | 135-145 mmol/L |
| Potassium | 3.4 mmol/L (L) | 3.6-5.0 mmol/L |
| Chloride | 103 mmol/L | 98-110 mmol/L |
| Carbon Dioxide | 18 mEq/L (L) | 21-29 mEq/L |
| Calcium | 8.7 mg/dL | 8.6-10.1 mg/dL |
| Magnesium | 1.4 mEq/L | 1.4-2.2 mEq/L |

| Hepatic/Pancreatic | Patient | Normal Range |
|---|---|---|
| Amylase | 41 units/L | 15-125 units/L |
| Lipase | 10 units/L | 0-66 units/L |
| Alk Phos | 65 units/L | 40-120 units/L |
| ALT | 15 units/L | 1-35 units/L |
| AST | 21 units/L | 1-35 units/L |
| Total Bili | 0.9 mg/dL | 0-1.0 mg/dL |

| Renal | Patient | Normal Range |
|---|---|---|
| BUN | 7 mg/dL | 4-23 mg/dL |
| Creatinine | 0.7 mg/dL | 0.7-1.4 mg/dL |

# Case Study: Day 0

- Lab Results Continued

| Immunology/Bacteriology/Serology | Patient | Normal Range |
|---|---|---|
| C diff PCR | Negative | Negative |
| Norovirus 1 | Not detected | Negative |
| Norovirus 2 | Not detected | Negative |
| Culture Feces | **Escherichia coli 0157:H7*** | |
| Shiga Toxin | **Positive E. coli Shiga toxin 2** Negative E. coli Shiga toxin 1 | Negative |
| Campy screen | Negative | Negative |

* Escherichia Coli 0157:H7 PCR confirmation testing performed by Missouri Department of Health & Senior Services.

# Diagnosis, Treatment, Discharge

- Diagnosis: Acute infectious colitis with stool positive for Shiga toxin producing E. coli.
- Treatment: Received a dose of Levaquin and Flagyl, antibiotics were immediately stopped due to the association of fluoroquinolones with increased risk of toxin production by E. coli 0157:H7.
- Treatment: Patient was treated supportively with IV fluids and pain medication.
- Discharge: By hospital day 2, patient was able to tolerate a bland diet, her CBC and renal function tests remained stable, and diarrhea had slowed and became nonbloody.
- Discharge: Patient was given instructions to follow up with any evidence of worsening diarrhea, return of blood in stools, fevers, or change in urination.

# Case study: Day 9

- Following discharge, the patient's condition continued to worsen. She developed severe headaches prompting her to follow up with her primary care physician.

| Test | Day 0 | Day 9 | Normal |
|---|---|---|---|
| Hgb | 16.5 g/dL (H) | 6.2 g/dL (L) | 12.0-16.0 g/dL |
| Plt | 310 K/uL | 116 K/uL (L) | 150-450 K/uL |
| BUN | 7 mg/dL | 35 mg/dL (H) | 4-23 mg/dL |
| Creatinine | 0.7 mg/dL | 1.2 mg/dL | 0.7-1.4 mg/dL |
| ALT | 15 units/L | 100 units/L (H) | 1-35 units/L |
| AST | 21 units/L | 62 units/L (H) | 1-35 units/L |
| UA Protein | Not tested | 200 mg/dL (H) | Negative |
| Lactate Dehydrogenase | Not tested | 745 units/L (H) | 100-230 units/L |
| PT | Not tested | 12.5 seconds | 12-14.8 seconds |
| PTT | Not tested | 25 seconds | 24-34 seconds |

*Schistocytes, Acanthocytes, Teardrop cells, and Elliptocyte were all noted in the manual differential performed on Day 9.

# Review of Symptoms

1. Anemia
2. Mild thrombocytopenia
3. Increasing liver function tests
4. Mild renal function changes
5. Positive LDH
6. Headaches
7. Recent infectious diarrhea with Shiga toxin producing E. coli.

# Diagnosis

Symptoms are suggestive of…

**Hemolytic Uremic Syndrome-**
**Thrombotic thrombocytopenic purpura**

# Introduction to HUS-TTP

HUS and TTP are both systemic disorders characterized by endothelial injury accompanied by small vessel platelet-rich thrombi that cause microangiopathic hemolytic anemia, thrombocytopenia, as well as neurologic and/or renal abnormalities.

- Although these syndromes have distinct etiologies, demographics, responses to treatment, and prognoses, their features are similar in many patients.

George, 2014

# Presenting features of HUS and TTP (Classical Pentad):

1. **Microangiopathic hemolytic anemia** (defined as nonimmune hemolysis with prominent schistocytes on peripheral blood smear).
2. **Thrombocytopenia** (often with purpura but not usually severe bleeding).
3. **Acute renal insufficiency** (may be normal).
4. **Neurologic abnormalities** (may be absent).
5. **Fever** (rare).

George, 2015

# Well, which is it, HUS or TTP???

- Although some studies appear to distinguish between TTP and HUS in adults; the presenting features, pathologic changes, and initial treatment are essentially the same. Therefore patients can best be described by the comprehensive term HUS-TTP.
- The diagnoses of HUS and TTP are made clinically and require only **thrombocytopenia** and **microangiopathic hemolytic anemia** without another clinically apparent etiology.
- Treatment (plasma exchange) should be initiated even if there is some uncertainty regarding the diagnosis, as the disease follows a progressive course in which irreversible renal failure, neurologic deterioration, cardiac ischemia, and death are common outcomes if left untreated.
- Mortality rate prior to the use of plasma exchange was approximately 90%.

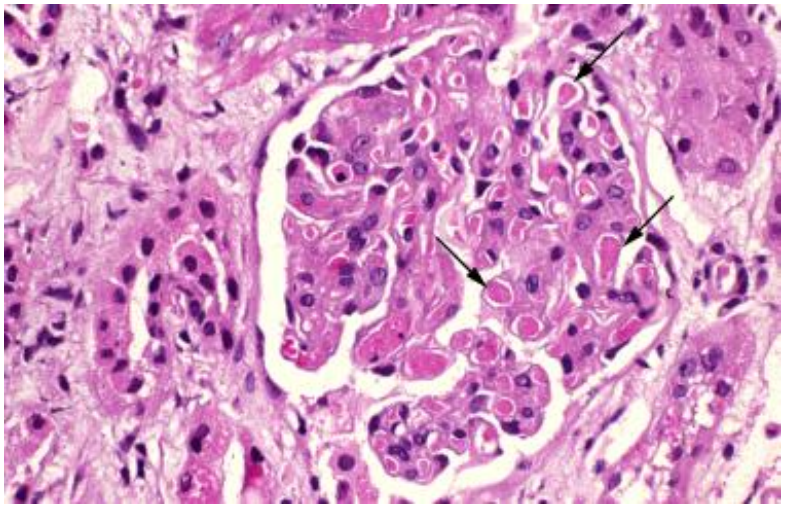
George, 2014

# Pathology

HUS-TTP is associated with thrombi composed primarily of platelets in affected organs (ie. kidney, brain, heart).

In the kidney, for example, the primary histologic changes are thrombi in the glomeruli and arterioles and subendothilial widening of the glomerular capillary wall due to the deposition of fibrin-like material. These histologic changes are consequences or manifestations of endothelial cell injury.

George, 2014



Light micrograph showing glomerular thrombi (arrows) typical of HUS.
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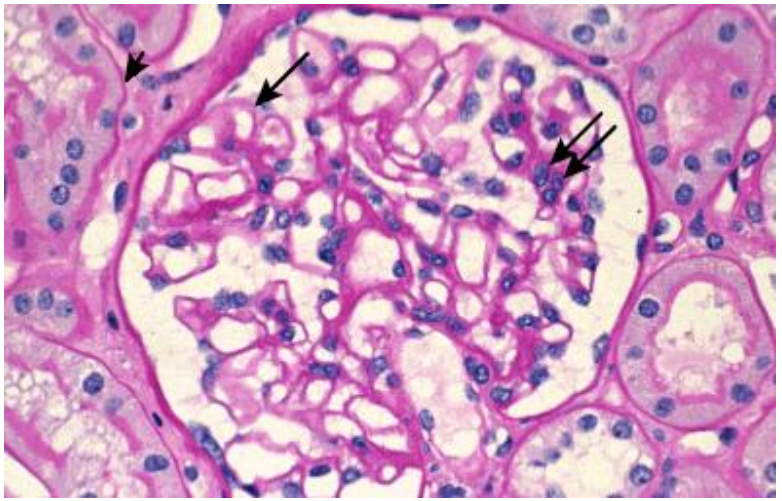

Normal glomerulus.
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# Pathogenesis

**V**on **W**illebrand **f**actor (**VWf**) is synthesized in endothelial cells and assembled in larger multimers than are present in normal plasma.

When damage to endothelial cells occurs, VWf multimers are secreted into circulation.

The large multimers, called **u**nusually **l**arge **v**on **W**illebrand **F**actor (ULVWf), are rapidly degraded in the circulation into the normal size range of VWf multimers by a protease called **A D**isintegrin **A**nd **M**etalloprotease with a **T**hrombo**S**pondin type **1** motif, member **13** (**ADAMTS13**).

A congenital or acquired deficiency of ADAMTS13 activity leads to accumulation of ULVWf multimers which bind to Plt glycoprotein 1b and the formation of disseminated fibrin-poor, VWf-rich Plt thrombi.

Results in consequent tissue ischemia.

George, 2014 and Harmening, 2009

# Causes of TTP-HUS

- Although many cases are idiopathic, a variety of underlying causes have been identified.
- TTP-HUS can occur after pregnancy, infection, pancreatitis, and surgery. These and other acute stresses can trigger an episode perhaps due to the release of inflammatory cytokines or other prothrombotic mediators, which could alter the balance between levels of VWf and ADAMTS13 activity.

George, 2014

## Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS): a classification of clinical syndromes

| |
|---|
| **Childhood TTP-HUS syndromes** |
| Typical HUS: Caused by Shiga toxin-producing *Escherichia coli* , typically *E. coli* O157:H7. Children present with abdominal pain and diarrhea, typically bloody, and acute kidney injury. Ninety percent of childhood HUS. |
| Atypical HUS: Acute kidney injury without preceding diarrhea. Some cases may be familial, caused by mutation of genes involved in complement regulation. Ten percent of childhood HUS. |
| Congenital TTP (hereditary TTP: Upshaw-Shulman syndrome): Caused by mutation (s) in the ADAMTS13 gene. |
| Acquired autoimmune TTP: Due to autoantibody inhibition of ADAMTS13 activity; rare in children. |
| **Adult TTP-HUS syndromes** |
| Acquired autoimmune TTP: Due to autoantibody inhibition of ADAMTS 13 activity. |
| Drug induced |
| Immune mediated |
| Quinine is most common cause. Among drugs suspected to be the cause of acute TTP-HUS, drug-dependent antibodies have only been documented for quinine. Other drugs may cause immune-mediated TTP-HUS, but are rare. |
| Dose-dependent toxicity |
| Cancer chemotherapy (mitomycin C, gemcitabine, possibly others) |
| Immunosuppressive agents (cyclosporine, tacrolimus, sirolimus) |
| Following bloody diarrhea caused by Shiga toxin-producing *E. coli* |
| Pregnancy or postpartum: May be indistinguishable from severe preeclampsia, eclampsia, and the HELLP syndromes. |
| Congenital TTP (hereditary TTP: Upshaw-Shulman syndrome) may present during adulthood, sometimes triggered by another condition (eg, infection, pregnancy). |
| Autoimmune disorders |
| Systemic lupus erythematosus (SLE) can mimic all features of TTP-HUS. Patients may have both TTP-HUS caused by severe ADAMTS13 deficiency and SLE. |

TTP-HUS: Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome.

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# Link to Shiga toxin-producing E. coli

- Most cases of childhood HUS and occasional cases of TTP-HUS in adults follow an episode of bloody diarrhea.
- A Shiga toxin released from E.coli (0157:H7, 0111, and 0104:H4) is felt to be etiologic in most of these patients.

Shiga toxins enter systemic circulation and are bound to polymorphonuclear leukocytes.

Shiga toxins target endothelial cells, causing vascular damage, bloody diarrhea, and (in some patients) a prothrombotic state that precedes HUS
(due to imbalance of ULVWf and ADAMTS13).

Calderwood, 2014

## Laboratory findings in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome

| |
|---|
| **Complete blood count** |
| **Anemia (microangiopathic hemolytic anemia)** |
| **Thrombocytopenia** |
| Increased reticulocyte percentage |
| White blood cell count normal to increased |
| White blood cell differential normal with no immature granulocytes |
| **Peripheral blood smear** |
| Polychromatophilic red cells (ie, reticulocytosis) |
| Fragmented red cells (schistocytes, helmet cells) |
| Nucleated red cells may be present, but are not numerous* |
| **Coagulation and immunohematologic studies** |
| Normal PT |
| Normal aPTT |
| Fibrinogen concentration normal¶ |
| Fibrin degradation products not increased¶ |
| Direct Coombs' test negative |
| **Other laboratory studies** |
| Markedly increased serum lactate dehydrogenase (LDH) |
| Increased serum indirect bilirubin |
| Markedly reduced or absent serum haptoglobin |
| Serum creatinine may be increased |

Although all of the findings listed here may be present, the diagnosis of TTP-HUS should be suspected in any patient with otherwise unexplained microangiopathic hemolytic anemia and thrombocytopenia.

TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic uremic syndrome; PT: prothrombin time; aPTT: activated partial thromboplastin time.
* The presence of many nucleated red cells suggests infiltrative disease of the marrow, such as occult metastatic cancer.
¶ Disseminated intravascular coagulation is not typically present, but may be seen when there is diffuse tissue ischemia.



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# Measurement of ADAMTS13

- Reduced ADAMTS13 is supportive of TTP-HUS diagnosis, but is not required.
- May be helpful in determining etiology (Ie. Acquired ADAMTS13 deficiency vs congenital).
- Monitoring may be helpful in predicting relapse. Patients with ADAMTS13 activity >10% at time of initial presentation rarely relapse.

Disadvantages of measuring ADAMTS13 activity in TTP-HUS patients:

1. ADAMTS13 deficiency is neither completely sensitive nor specific to diagnosis of TTP.
2. ADAMTS13 level should be obtained prior to initiation of treatment, impractical to await result to determine treatment plan as time is of the essence.
3. Reference test-may take several days before result receipt.
4. Variety of assays available, reference ranges are not completely standardized.

George 2014

# Treatment

The mainstay of treatment for most patients with TTP-HUS is plasma exchange. In the context of this syndrome refers to removal of the patient's plasma by pheresis and the replacement with donor plasma rather than another replacement fluid such as albumin.

Plasma exchange corrects disease process in 3 ways:

1. Removal of circulating autoantibody to ADAMTS13 (if present).
2. Removal of circulating ULVWf multimers.
3. Infusion of donor plasma replaces the missing ADAMTS13 protease.

Kaplan, George 2015

# Treatment continued

- Plasma exchange is initially performed daily until the plt count has normalized and hemolysis has largely ceased (as evidence by return of LDH to normal).
- Standard volume is 4 units FFP per liter of plasma removed, for most conditions, it has become standard practice to perform 1 to 1.5 plasma volume exchanges per procedure.

Estimated plasma volume (in liters) = 0.07 x weight (kg) x (1 - hematocrit)

- On average 7-16 daily exchanges are required to induce remission.
- Compared with the mortality rate of 90% prior to the use of plasma exchange, the mortality rate of patients treated with plasma exchange is 25% or less.

Fridey, Kaplan, George 2015

## Poorly responsive, Resistant, or Relapsing Disease

- 10-20% of patients will have a transient, incomplete, or no response to plasma therapy.
- In the case of Idiopathic TTP-HUS, an increasing number of reports indicate success in patients with poorly responsive disease following the use of immunosuppressive agents (eg, glucocorticoids, rituximab, cyclosporine).
- There appears to be little to no benefit to splenectomy, heparin, or antiplatelet agents.
- In the case of congenital TTP – prophylactic treatment with small volumes of FFP (10-15 mL/kg every 2-4 weeks) may be an effective maintenance therapy.

Kaplan, George 2015

# Back to our Bahama Mama…

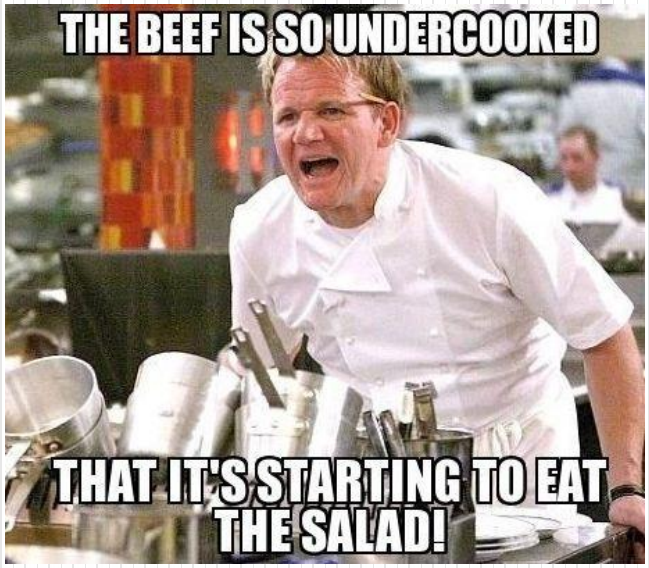
- Treatment: 4 total volume plasma exchange treatments utilizing FFP, also received 3 units LRPCs.
- Discharge: With Plt, Hgb, and LDH results all improving, patient was discharged with recommendation to do follow-up CBC and to continue with iron supplementation.

## Lab Results

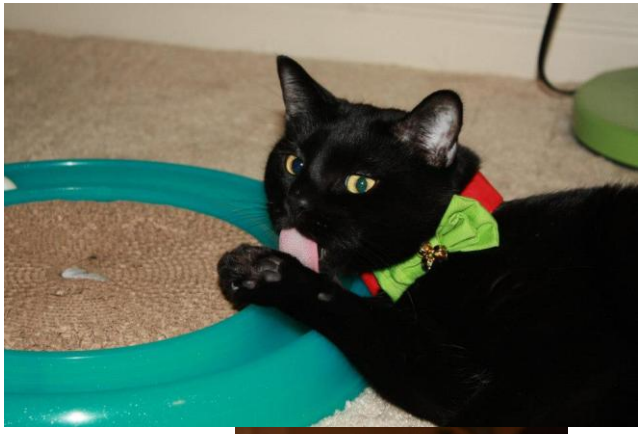
| Test | Day 9 | Post TPE #1 | Day of Discharge | 3 days post Discharge | Normal |
|---|---|---|---|---|---|
| Hgb | 6.2 g/dL (L) | 9.5 g/dL (L) | 8.8 g/dL (L) | 10.6 g/dL (L) | 12.0-16.0 g/dL |
| Plt | 116 K/uL (L) | 237 K/uL | 330 K/uL | 489 K/uL (H) | 150-450 K/uL |
| BUN | 35 mg/dL (H) | 30 mg/dL (H) | 19 mg/dL | Not tested | 4-23 mg/dL |
| Creatinine | 1.2 mg/dL | 1.0 mg/dL | 0.8 mg/dL | 0.8 mg/dL | 0.7-1.4 mg/dL |
| ALT | 100 units/L (H) | 35 units/L | 47 units/L | Not tested | 1-35 units/L |
| AST | 62 units/L (H) | 20 units/L | 23 units/L | Not tested | 1-35 units/L |
| Lactate Dehydrogenase | 745 units/L (H) | 473 units/L | 277 units/L | 288 units/L | 100-230 units/L |

# The moral of the story…

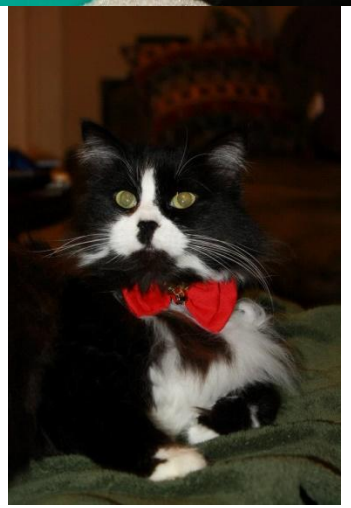
With Summer BBQs around the corner, remember to properly cook your meat to an internal temperature of in excess of 155°F to eradicate E.coli contamination!

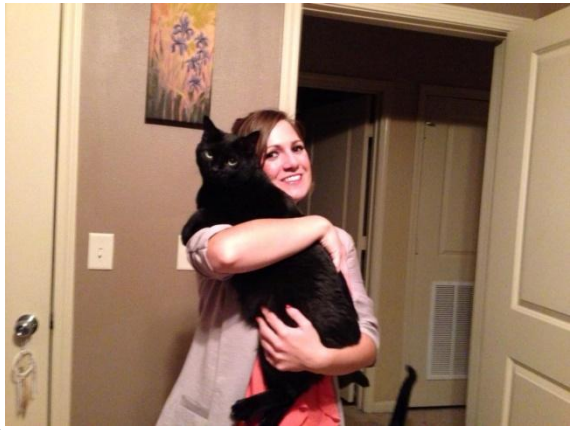


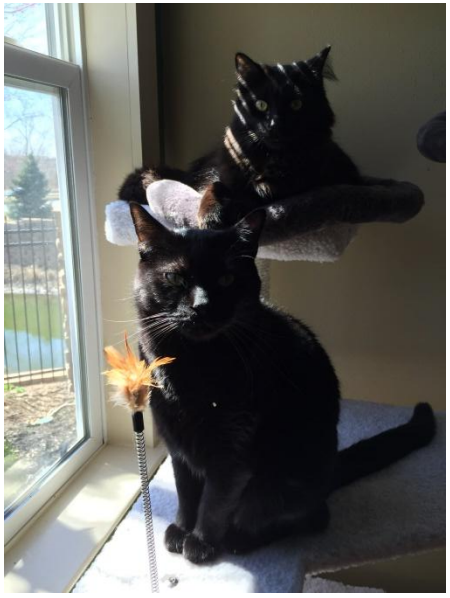

Calderwood 2014



# QUESTIONS???







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