Transfusion Support of Thrombotic Thrombocytopenic Purpura (TTP)

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Learning Objectives

- Understand the TTP syndrome and its relevance to blood banking
- Be familiar with the pathogenesis and laboratory diagnosis of TTP
- Explain how therapeutic apheresis is used to treat TTP
- Describe the types of blood products required for management of patients: frequency, volume, and duration of transfusions
- Provide strategies for ensuring adequate inventory of components
- Be prepared for adverse reactions encountered in TTP
TTP: *In the beginning* …..

- Described by Eli Moschcowitz 1924
- 16 year old girl
- Anemia, fever, renal dysfunction, CNS impairment, and cardiac failure
- Died in 2 weeks
- Autopsy: hyaline microthrombi in arterioles and capillaries
  
  Heart, spleen, kidney
TTP: pathophysiology

Microthrombi in small arterioles of heart
TTP: diagnosis

PENTAD for recognition:

- microangiopathic hemolytic anemia
- thrombocytopenia
- renal failure
- mental status changes
- fever

Rule out other causes such as DIC, HTN

No diagnostic test!
TTP Characteristics

- Rare but increasing - 4 cases per million
- Females > males 4:1
- Any age from pediatric to geriatric
- Mean age 40 yo
  - 70% between ages 18-49
  - Patients often have no preceding health problems
- No geographic or seasonal patterns
- 90% mortality without treatment!
  - 10% mortality with plasma exchange
TTP Characteristics

- 90% survival
- 10% mortality rate

Mortality highest within initial 48 hours of presentation

EARLY recognition and treatment !!!

Platelet count, LDH, and degree of hemolysis are *not* predictive of survival.
TTP: diagnosis

Microangiopathic Hemolytic Anemia (MAHA)

Mechanical RBC destruction

Red Cell Fragments or schistocytes

May be associated with ↓ platelet count
TTP: diagnosis

Diverse Causes of MAHA:

- TTP
- Malignant hypertension (systolic BP > 200)
- DIC, sepsis
- HELLP syndrome (preclampsia)
- Metastatic adenocarcinoma
- Intravascular prosthetic devices: e.g. LV assist device
TTP: diagnosis

Complete Blood Count will show

- Low platelet count
  - Can be <10k
- Schistocytes
- Anemia is variable
- Plasma may be hemolyzed, dark red-brown or icteric

Peripheral blood smear with schistocytes
TTP: diagnosis

Supporting Laboratory Studies

- LDH * Lactate dehydrogenase
- Haptoglobin
- Bilirubin, indirect
- Creatinine, BUN
- PT, PTT Coagulation studies
- DAT Direct Coombs' test

RESULT

* Anemia in TTP is not immunologic
TTP is found in many clinical settings

- Primary or Idiopathic
- Secondary causes of TTP
  - Connective Tissue Disease (SLE)
  - Hormonal (menses, pregnancy, OCP's)
  - Infection
  - Diarrhea (HUS)
  - Drugs: quinine, ticlid, plavix, FK506, cyclosporin
  - Chemotherapy: cis platinum, mitomycin c
  - Transplant (BMT, solid organ)
TTP: pathophysiology

Hmmm.... what's going wrong here?
TTP: pathophysiology

- Earliest research implicated
  - Endothelial cells damage
  - Sheer stress caused by blood flow
  - Abnormalities in vWF (von Willebrand Factor)

- Resulting in abnormal aggregation of platelets causing thrombi in microvasculature
TTP: pathophysiology

vWF von Willebrand Factor important in clot initiation and platelet aggregation.

Moake, et al

- vWF multimers abnormal in relapsing TTP
  - Unusually large multimers of vWF
    - Or missing large multimers of vWF suggesting consumption during acute episode
  - Multimers may unfold under sheer stress
- Predispose to platelet aggregation
  - Ultralarge multimers have qualitatively stronger mechanical binding to platelets
TTP: unusually large vWF multimers

Multimeric patterns of plasma
ADAMTS13

- vWF protease: 150 kd single chain glycoprotein
- Rapidly breaks vWF into smaller sized multimers when released from damaged endothelial cells
- Discovered that the function of this enzyme in the plasma was deficient in TTP
TTP: vWF Protease Functional Activity before and after treatment of TTP
TTP: pathophysiology

ADAMTS13 Protease defect:
- Inherited deficiency / absence
- Acquired inhibitor
  - IgG like autoantibody which blocks protease
  - Results in an ↑ in vWF multimers
- Not specific to TTP but very characteristic
  - Severe deficiency <10% activity
  - Presence of autoimmune inhibitor
Normal Processing Activity

ULvWF

P-selectin

Weibel-Palade Body
Normal Processing Activity
TTP Pathophysiology
TTP Pathophysiology
TTP Pathophysiology
TTP: pathophysiology

- Protease defect is
  - NOT ALWAYS seen in patients presenting with TTP
- May be different pathophysiologic mechanisms
- ADAMTS13 not currently available as a rapid test
TTP

CURRENT MANAGEMENT

Emergent Treatment with Plasma

Preferred treatment is Therapeutic Plasma Exchange (TPE)
apheresis

- Means “to separate”
- The process of removing normal or abnormal blood constituents from circulating blood
  - Donation of blood
  - Treatment of disease
- “Pheresis” often used and synonym
Therapeutic Apheresis

- Therapeutic Plasma Exchange
  - Plasma separation (plasmapheresis) and replacement
  - Other nomenclature/abbreviations:
    - TPE = therapeutic plasma exchange
    - PLEX
Apheresis Machine
Anticoagulant
Anticoagulant
Anticoagulant
Anticoagulant

Product

Replacement Plasma
Figure 1-12. IBM 2997 single-stage channel and collection chamber. See text for structural and operational details. (Courtesy of Gambro BCT, Inc.)
Emergent plasma exchange (TPE)

1. Plasma Volume of the patient is removed and replaced with donor plasma from the blood bank
   - Average plasma volume is 3000mL
   - Range 2500-4000 mL
   - May be 8 to 15 units of plasma required

Plasma exchange is repeated daily
   - In some severe cases physicians may increase plasma volume exchanged
   - Or increase the frequency to 2 times a day

Treatment continues until platelet count is normal >150k for 2 days
TPE is preferred instead of simple transfusion of plasma


7 year N=102
Fresh Frozen Plasma
FP24
Thawed Plasma
Blood Bank Support of TTP

- Plasma and LOTS of it

- CALL YOU BLOOD SUPPLIER!
Blood Bank Support of TTP

- What type of plasma is used?
- FFP, FP24, or CPP (cryopoor plasma)
- Cryopoor plasma is the supernatant plasma left over from the manufacture of Cryoprecipitate
  - Contains less von Willebrand factor, multimers are smaller
  - Once considered better than FFP, it is now considered equivalent to FFP
- TTP is the only indication for CPP
Blood Bank Support of TTP

- Prepare to order type specific plasma in large quantities from blood supplier
- Plan to thaw multiple units simultaneously—can delay treatment
- May cause inventory concerns
  - Group AB and Group B TTP patients
  - Relative scarcity of these plasma ABO types
  - AB plasma needed in reserve for trauma
Blood Bank Support of TTP

What if plasma resources are limited?

Discuss with physician these options:

- If using FFP or FP24, advise use of CPP for all or some of plasma for replacement
- Use of partial replacement of removed plasma with 5% albumin from pharmacy
  - Albumin is standard replacement in other diseases treated with TPE
  - HOWEVER, albumin is not therapeutic by itself
  - 1 liter of initial replacement with albumin followed by 2 liters of plasma has been standard of care at many academic medical centers
Packed RBCs
Blood Bank Support of TTP

Red Cell Transfusions

- KEEP TYPE AND SCREEN CURRENT!
Blood Bank Support of TTP

Red Cell Transfusions

- Patients present with anemia which can be symptomatic
- Further problem is that when putting patient on apheresis machine there is another 3% hemodilution
- Apheresis personnel may also request some pRBCs
- Transfusions may be required until hemolysis due to MAHA subsides
platelets
Blood Bank Support of TTP

- AVOID PLATELET TRANSFUSION!
Blood Bank Support of TTP

Platelet Transfusions

- Avoid transfusion of platelets
- Anecdotal reports of TTP patients experiencing acute worsening and death following transfusion of platelets
- Most platelets are well tolerated
- Flag / warn staff to check with MD to be sure there is an indication
  - Central line placement, concern of head bleed
TTP: Adjunct therapies in TTP

- Steroids: dosage typically 1mg/kg/day
- Anti-platelet drugs
- Rituximab (anti B cell immune therapy)
- Plasma Infusions- for maintenance therapy and chronic TTP
- Splenectomy
Response Time by Replacement

CURRENT CLINICAL OUTCOMES

- 60-65% complete remission
- 35-40% relapse rate
  - Early relapse-days to weeks
  - Late recurrence- months

No diagnostic test to predict relapse
Adverse reactions

- TTP patients have a higher risk of allergic and other complications
- Coordinate reporting of Rxns with the apheresis unit
Allergic reactions

Reutter JC, Sanders K, et al

Incidence of Allergic Reactions with Fresh Frozen Plasma or Cryo-supernatant Plasma in the Treatment of Thrombotic Thrombocytopenic Purpura.

*Journal of Clinical Apheresis* 2001

- Retrospective Analysis of TTP patients 1982-1999
- received *all* FFP or *all* CPP (n=41)
- *not* premedicated with antihistamine (e.g. Benadryl) until after 1st rxn
Allergic reactions

RESULTS: Incidence of Allergic Reactions

- Urticaria/hives: 76% (CPP), 55% (FFP), p=0.27
- Respiratory distress: 5% (CPP), 5% (FFP)
Allergic reactions

**RESULTS:** Mean volume of donor plasma before first allergic reaction

- CPP: 9883mL
- FFP: 9348mL

p = 0.85
Allergic reactions

- Urticaria/hives are commonly seen in TTP patients
- frequency of 55%-76%
- tend to occur after 30 to 35 donor exposures
- or 9 to 10 liters of plasma
Managing allergic reactions

- If history of allergic reaction to blood
  - PRE medicate with Benadryl
- If pre-medication fails = “breakthrough” reactions
  - Benadryl drip
    - 50 mg of Benadryl diluted with .9% NaCl to 100mL
    - Infuse at 50 to 100 mL per hour during TPE
- H2 blockers may also be helpful
  - Axid 150-300mg po 1 hour pre TPE then q 6 hours
Managing allergic reactions

- For patients with severe plasma sensitivity or problematic frequent allergic reactions:

  5% albumin and plasma

- Initial half of the plasma exchange is done with 5% albumin

- The second half of the procedure is completed with plasma

- May also use this replacement combination for AB blood type
Management issues: citrate

- ACD anticoagulation for apheresis plus citrate in the plasma replacement.
- Higher incidence of citrate related symptoms
  - Paresthesias
  - N & V
  - Hypotension
  - Flatus
  - EKG changes
Challenges for TTP

- Unsure how long to treat and how close to follow up
- Currently cannot detect subclinical disease
- Cannot predict relapse
- Still have mortality rate of 10%
- ADAMTS13 (vWF protease) deficiency not pathognomonic
TTP: On the Horizon

Multicenter studies:

- NIH Transfusion Medicine/ Hemostasis Clinical Research Network
  - 16 Academic Centers with a clinical coordinating center
  - STAR Study now enrolling
  - TPE and rituximab versus TPE alone
- Risk factors of TTP: Northwestern University (SERFTTP)
  - NIH funded multicenter study
  - Epidemiology, risk factors (drugs), and pathophysiology