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TITLE: Therapeutic Plasma Exchange in TTP

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Hello, my name is Edward Yoon. I am one of the Clinical Pathology chief residents at Beth Israel Deaconess Medical Center in Boston. Welcome to this Pearl of Laboratory Medicine on "Therapeutic Plasma Exchange in TTP."

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For this presentation, we will first introduce the pertinent definitions and terminology as they pertain to this topic. This will be followed by a discussion of the pathophysiology of TTP, which will be critical to the understanding of its treatment options. Finally, we will discuss the specific role of therapeutic plasma exchange in the treatment of TTP, as well as some of the specific aspects for this treatment modality.

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TTP, or thrombotic thrombocytopenic purpura, which is the main focus of this presentation, is a rare, life-threatening condition in which the ultimate pathology stems from ischemic end-organ damage due to the formation of microvascular thrombi, that is, a thrombotic microangiopathy. For this discussion, the focus will be on idiopathic TTP, which is the most commonly encountered form. Although important, secondary and congenital forms of thrombotic microangiopathy are beyond the scope of this presentation.

Apheresis is a complex medical treatment modality that might be best described as extracorporeal therapy with an automated cell-separator in which a patient's blood is removed and continuously physically separated into its various components. The eventual goal of this separation is to remove pathogenic substances from whichever blood component is affected

while simultaneously returning replacement fluids and non-pathogenic blood components to the patient.

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This schematic illustration demonstrates the basic tenets of apheresis that were just discussed. A patient's efferent and afferent vascular access is obtained either through venous central access catheters or through venous peripheral access with large-bore needles able to withstand relatively high pressures and flow-rates. The whole blood that is initially removed from the patient is separated in the apheresis machine, commonly through continuous centrifugation, which separates out blood components such as red blood cells, buffy coat layer, and plasma based on relative density. The machine can be programmed to remove a specific component, such as the plasma layer. When the remaining components are returned to the patient, replacement fluids are added to the return line, depending on the specific indication. Calcium can also be added to the return line to offset the effects of the citrate anticoagulant used throughout the process.

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In the setting of TTP, the apheresis procedure aims to remove a patient's native plasma, which contains pathogenic components. Native plasma is exchanged for a replacement fluid such as 5% albumin, donor plasma, or a combination of both. The amount that is exchanged per procedure is typically expressed in multiples of the patient's total plasma volume. A rough, simple calculation of a patient's plasma volume, expressed in liters, is outlined as follows: 0.07 multiplied by the patient's weight, in kilograms, multiplied by the difference between 1 and the patient's hematocrit, expressed as a decimal.

The American Society for Apheresis (ASFA) periodically releases guidelines on various potential indications for apheresis. Their systematic and evidence-based reviews of current literature and practices culminate in the assignment of ASFA categories that define the role of apheresis for a given condition, as well as grades of recommendation based on the quality of existing evidence. As an example, TTP is designated as ASFA category I with grade 1A recommendation in the most recent 2016 guidelines, meaning that apheresis is accepted as first-line therapy for TTP with high-quality evidence in the literature to support its use.

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The pathophysiology of TTP stems from a deficiency of the ADAMTS13 metalloprotease enzyme, which has the normal in-vivo function of cleaving unusually-large von-Willebrand factor multimers into smaller circulating forms. In TTP, autoantibodies with specificity for ADAMTS13 can be formed, which inhibit its enzymatic activity and lead to a functional deficiency. Severe ADAMTS13 deficiency with less than 10% activity and the presence of inhibiting antibodies can be demonstrated by laboratory assays in the majority of TTP cases.

The ultimate consequence of ADAMTS13 deficiency is the widespread formation of microvascular thrombi. This deficiency leads to an increased amount of circulating unusually-large von-Willebrand multimers, which physically interact with platelets and endothelial cells in high-shear flow environments such as the arterial microvasculature. This interaction leads to local activation of pro-thrombotic physiology and the formation of platelet and von-Willebrand factor-rich thrombi. Ischemic end-organ damage then ensues, manifesting in widespread locations such as the cerebral and renal microvasculature.

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This schematic illustration demonstrates the differences between normal microvascular physiology and that of TTP. Under normal circumstances ADAMTS13 cleaves von-Willebrand factor into smaller functional fragments. Platelets are able to pass through the microvasculature without abnormal activation. In TTP, however, autoantibodies interfere with the normal action of ADAMTS13 and lead to a functional deficiency. The unusually-large von-Willebrand factor multimers remain non-cleaved, which interact with the local endothelium and passing platelets. These interactions in the high-shear flow microvascular environment activate a pro-thrombotic state, leading to occlusive thrombus formation rich in both platelets and von-Willebrand factor.

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The classic teaching is that patients with TTP present with a pentad of features stemming from the thrombotic microangiopathy, including: thrombocytopenia, microangiopathic hemolytic anemia, neurologic changes, renal dysfunction, and fever. In reality, this entire pentad is rarely encountered, and other signs or symptoms such as abdominal pain may be prominent. Therefore TTP remains largely a clinical diagnosis based on the available information and a clinician's index of suspicion. In the absence of other plausible causes, thrombocytopenia and microangiopathic hemolytic anemia may be enough to render the provisional diagnosis of TTP until proven otherwise.

Observable laboratory abnormalities in TTP reflect the underlying pathophysiology and its hematologic consequences. Thrombocytopenia results from the active consumption of platelets by thrombosis. In addition to end-organ ischemia, there is also a microangiopathic hemolytic anemia caused by physical shearing of passing red blood cells by the microvascular thrombi, resulting in the broken red blood cell fragments known as schistocytes visible in a peripheral smear. The intravascular hemolytic anemia that ensues also leads to an increased total and indirect bilirubin, increased lactate dehydrogenase (LDH), and decreased haptoglobin. Tissue ischemia may also contribute to the increased LDH. Finally, as previously discussed, ADAMTS13 activity is typically markedly decreased with demonstrable inhibitor antibodies that can be titered.

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Therapeutic plasma exchange has been established as proven first-line therapy for TTP, with an ASFA category I indication as previously mentioned. It has been shown to significantly reduce overall mortality from >90% when untreated to <10% with proper management. Once a clinical diagnosis has been made, plasma exchange should be initiated as soon as possible, as patients with TTP can deteriorate rapidly and abruptly. Exchanges are typically performed using multiple donor plasma units such as FFP or FP24. It should be noted here that ADAMTS13-related testing is complex and is usually performed by larger reference laboratories. Turnaround times on such results may be on the order of days, and therefore treatment for TTP should not be delayed while awaiting these results. It is advisable, however, to secure a blood sample for ADAMTS13 testing prior to infusion of donor plasma.

The physiology of a therapeutic plasma exchange involves the simultaneous repletion of uninhibited, functional ADAMTS13 enzyme from the donor plasma as well as the removal of inhibitor antibodies from the patient's circulation. Both effectively act to halt the propagation of further microvascular thrombi and tissue ischemia.

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The typical apheresis treatment regimen for TTP consists of repeated, daily plasma exchanges. These usually process between 1 to 1.5 plasma volumes per procedure. An example calculation of a single plasma volume is shown here for a 70kg male with a hematocrit of 45%, which amounts to approximately 2.7 liters of plasma. This translates to replacement with approximately 8 units of donor plasma, assuming a volume of 350mL per unit. If circumstances preclude timely initiation of plasma exchanges, donor plasma infusions should be started at a dose around 30 mL/kg with the minimum goal of functional ADAMTS13 repletion. Plasma exchange is ultimately still the definitive therapy, and therefore plasma infusions should only be a temporizing measure.

Monitoring patients for a response to treatment involves daily measurement of pertinent laboratory parameters. An improving platelet count is the most important indicator of treatment response, and a general goal is to have platelets sustained at >150,000 /µL for at least two to three days. Many institutions also monitor for normalizing LDH levels as an indicator of decreased hemolysis and tissue ischemia. Along with improving clinical signs and symptoms, these laboratory values help inform clinicians as to whether or not daily plasma exchanges can be safely discontinued. The utility of tapering plasma exchanges, such as every-other-day procedures following clinical and laboratory evidence of response, has not been firmly established. Nonetheless, this approach has been adopted by many clinicians.

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Additional treatment options may be necessary in cases of TTP that are refractory to daily plasma exchanges, or in cases of exacerbation or relapse. Corticosteroids are often administered as initial adjunctive therapy, typically at a dose of 1 mg/kg/day. The chimeric anti-

CD20 antibody rituximab, which was mostly used for refractory disease, has gained some traction among clinicians as initial adjunctive therapy. This is typically administered 18-24 hours before the next scheduled plasma exchange, since the procedure will remove a large proportion of the circulating rituximab if administered without a sufficient time interval.

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Some special considerations regarding blood components are worth mentioning. Red blood cells should be transfused judiciously if deemed medically necessary, and platelet transfusions are generally contraindicated in TTP due to the risk of active consumption and exacerbating thromboses. Platelet transfusions may be cautiously considered in life-threatening situations such as intracranial hemorrhage.

Cryoprecipitate-poor plasma, also called Cryosupernatant, is donor plasma from which the fraction of cryoprecipitate has been removed. Cryosupernatant has been touted as a comparable, if not superior replacement fluid over regular donor plasma for plasma exchange in TTP, since in theory it contains less von-Willebrand factor and therefore less unusually-large multimers. This would result in a decreased risk of further thromboses. However, several randomized trials have suggested no appreciable differences in outcomes between the uses of Cryosupernatant versus regular donor plasma for plasma exchanges.

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Some practical considerations regarding therapeutic plasma exchange for TTP are also worth mentioning. Limited availability of apheresis services, especially in smaller community or primary care settings, may preclude prompt initiation of plasma exchanges and may require transfer to another facility. Issues with vascular access in the patient, whether central or peripheral, will likewise delay treatment. Finally the size and limited transportability of the apheresis machines themselves may restrict the physical settings in which plasma exchange can be safely performed, for instance in an overcrowded emergency department. In any event, expeditious efforts should be made to initiate plasma exchanges, with temporizing plasma infusions administered as needed.

Potential adverse events may also be encountered during the treatment course. Allergic reactions to donor plasma, as with any other blood component, are very common and can vary in severity from isolated urticaria to frank anaphylaxis. In patients who suffer from intractable allergic reactions to donor plasma, premedication and a regimen of 5% albumin for the initial half of the plasma exchange followed by donor plasma units for the latter half may be preferable. This approach has been demonstrated as a safe alternative to using donor plasma exclusively with comparable response and relapse rates. In addition to allergic reactions, patients should be monitored for evidence of any other transfusion reactions to blood products, as well as negative reactions to supplemental treatments such as corticosteroids and managed

appropriately. Finally, potential complications of vascular access should be considered, particularly in patients with long-term central access catheters which may be prone to infection.

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In summary, TTP is a complex disease. The clinical diagnosis is made alongside pertinent laboratory data. Therapeutic plasma exchange is an apheresis-based treatment modality that is first-line for TTP, with ample evidence to support its use. Finally, clinical decision-making is critical throughout the treatment course for TTP.

Slide 14: References

Slide 15: Disclosures

Slide 16: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on “Therapeutic Plasma Exchange in TTP.”