CLINICAL PRACTICE

Thrombotic Thrombocytopenic Purpura

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 40-year-old obese black woman has had weakness and epigastric pain for several weeks and diarrhea and vomiting for four days. She does not appear acutely ill; physical examination is normal except for abdominal tenderness. Her hematocrit is 25 percent. Her white-cell count and differential count are normal. The platelet count is 10,000 per cubic millimeter. The peripheral-blood smear shows occasional fragmented and polychromatophilic red cells. The serum creatinine level is 1.1 mg per deciliter (97.2 μmol per liter), bilirubin 2.5 mg per deciliter (42.8 μmol per liter), and lactate dehydrogenase 722 U per liter (normal, <250). How should this case be managed?

THE CLINICAL PROBLEM

Prompt recognition of thrombotic thrombocytopenic purpura is important because the disease responds well to plasma-exchange treatment[1] but is associated with a high mortality rate when untreated. In the era before effective treatment with plasma exchange, 90 percent of patients with thrombotic thrombocytopenic purpura died from systemic microvascular thrombosis that caused cerebral and myocardial infarctions and renal failure.[2] However, recognition of thrombotic thrombocytopenic purpura can be difficult because of the variety of presentations and lack of specific diagnostic criteria. The only consistent abnormalities are microangiopathic hemolytic anemia, characterized by red-cell fragmentation,[3] and thrombocytopenia, features that can also occur in other conditions.

Before the availability of effective therapy, the diagnosis of thrombotic thrombocytopenic purpura was based on the progressive appearance of the following pentad of clinical features: microangiopathic hemolytic anemia, thrombocytopenia, neurologic and renal abnormalities, and fever.[2] However, recognition of the efficacy of plasma-exchange therapy meant that less stringent diagnostic criteria were required to allow a more rapid initiation of treatment. In a randomized trial demonstrating the efficacy of plasma-exchange therapy,[1] only microangiopathic hemolytic anemia and thrombocytopenia, without an apparent alternative cause, were required for the diagnosis of thrombotic thrombocytopenic purpura; the frequency of neurologic and renal abnormalities and fever was less than in previous reports.[2] This change in diagnostic criteria has resulted in an increase by a factor of seven in the number of patients treated for thrombotic thrombocytopenic purpura.[4] Nonetheless, the disease remains uncommon, with the annual incidence in the United States estimated at 4 to 11 cases per million people.[5]

Thrombotic thrombocytopenic purpura occurs primarily in adults. Children with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure were originally said to have the hemolytic–uremic syndrome.[6] Childhood hemolytic–uremic syndrome, typically preceded by abdominal pain and diarrhea, was recog-

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nized in 1983 as a complication of infection caused by bacteria that produce Shiga toxins, such as *Escherichia coli* O157:H7.[7] Currently, 91 percent of children with typical hemolytic–uremic syndrome survive with supportive care, without plasma-exchange treatment.[8,9]

These observations suggested that thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome were two discrete syndromes,[10] an interpretation supported by reports describing severe deficiency (<5 percent activity) of a von Willebrand factor–cleaving protease, termed "ADAMTS 13" (an acronym for a disintegrin and metalloprotease with thrombospondin-1–like domains), in patients with a diagnosis of thrombotic thrombocytopenic purpura but not in patients with a diagnosis of the hemolytic–uremic syndrome.[11,12] ADAMTS 13 cleaves the large von Willebrand factor multimers that are synthesized and secreted by endothelial cells. When ADAMTS 13 is not present, the resulting abnormally large von Willebrand factor multimers in plasma have a greater ability to react with platelets and cause the disseminated platelet thrombi characteristic of thrombotic thrombocytopenic purpura.[10]

However, thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome are not distinct syndromes; their essential diagnostic criteria — microangiopathic hemolytic anemia and thrombocytopenia — are the same. Although neurologic abnormalities are commonly considered characteristic of thrombotic thrombocytopenic purpura and renal failure characteristic of the hemolytic–uremic syndrome,[13] patients with these syndromes may have neither abnormality or both.[14] Yet the name of the syndrome — thrombotic thrombocytopenic purpura or the hemolytic–uremic syndrome — has assumed clinical importance because of suggestions that plasma-exchange treatment may be appropriate for thrombotic thrombocytopenic purpura but not for the hemolytic–uremic syndrome.[13]

In this article, the term "thrombotic thrombocytopenic purpura" is used to describe microangiopathic hemolytic anemia and thrombocytopenia occurring in adults without an apparent alternative cause, with or without neurologic or renal abnormalities, and regardless of the cause or associated condition. This terminology is consistent with that used in recent reviews.[15,16] Since these diagnostic criteria were the same as those used in the trial documenting the efficacy of plasma-exchange therapy, the diagnosis of thrombotic thrombocytopenic purpura should prompt consideration of such treatment.[1,17]

Children in whom microangiopathic hemolytic anemia, thrombocytopenia, and renal failure develop, typically after diarrhea, are described as having the hemolytic–uremic syndrome; plasma exchange is not standard treatment for these children.[8,9,16] Thrombotic microangiopathy is a term describing the pathological morphology of thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome, but this abnormality can also be present in other conditions such as malignant hypertension and autoimmune disorders.[18]

This article focuses on acquired thrombotic thrombocytopenic purpura. Congenital disorders, thrombotic thrombocytopenic purpura caused by mutations in the *ADAMTS 13* gene,[19] and the hemolytic–uremic syndrome caused by complement dysregulation due to mutations in the genes for factor H and membrane cofactor protein[20] are rare.

STRATEGIES AND EVIDENCE

EVALUATION

The most common symptoms at presentation are nonspecific and include abdominal pain, nausea, vomiting, and weakness. The diversity of the clinical features is related to the presence of microvascular thrombi in many organs (Fig. 1). Approximately half of patients with thrombotic thrombocytopenic purpura have severe neurologic abnormalities at presentation or during the course of the disease, such as seizures and fluctuating focal deficits.[14] However, many patients may have no or only minor neurologic abnormalities, such as transient confusion.[14,21,22] Fever is uncommon. A temperature above 102°F (38.9°C) and chills suggest infection rather than thrombotic thrombocytopenic purpura. Although thrombotic thrombocytopenic purpura is often described as acute, one fourth of patients have symptoms for several weeks before diagnosis.[14] The importance of considering the possibility of thrombotic thrombocytopenic purpura is emphasized by the frequent misdiagnosis of the symptoms as gastroenteritis, sepsis, or transient cerebral ischemia, for example.

The key diagnostic clues are from the laboratory evaluation. The presence of both anemia and thrombocytopenia (in the absence of leukopenia)

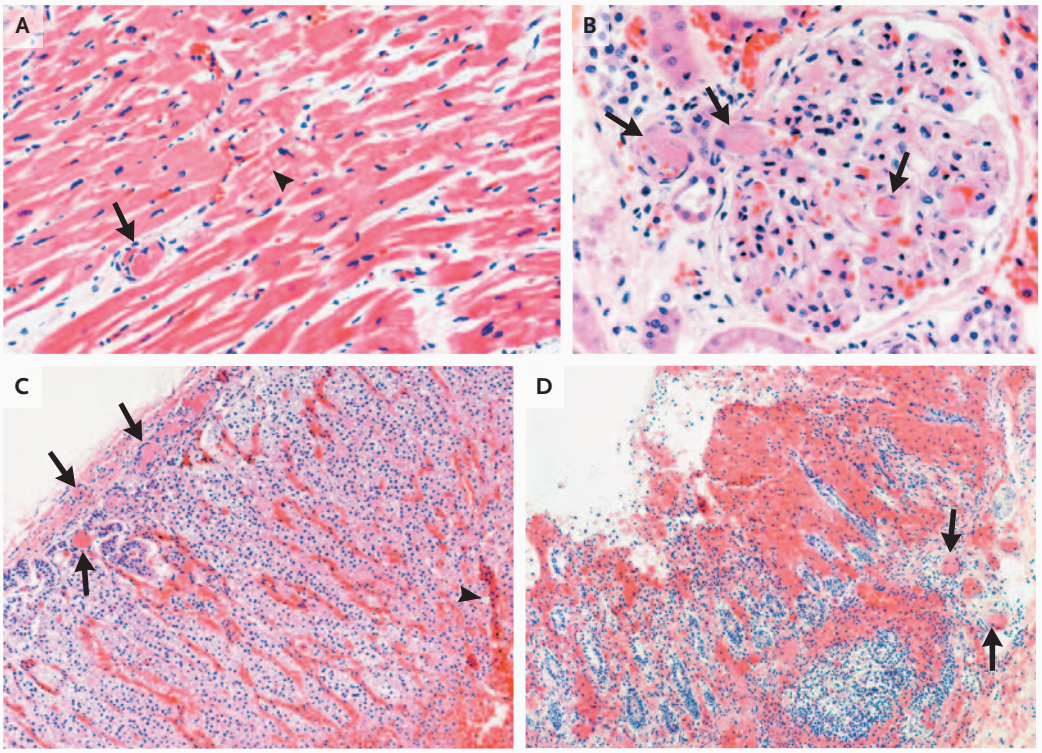

Figure 1. Tissue Specimens Obtained at Autopsy from a Patient with Abnormalities Characteristic of Thrombotic Thrombocytopenic Purpura.

The initial presentation of the patient was similar to that of the woman described in the vignette. A specimen from the heart (Panel A) shows multiple intramyocardial microthrombi (arrow), hemorrhage, and early ischemic changes, with scattered foci of contraction-band necrosis (arrowhead). A specimen from the kidney (Panel B) shows characteristic microthrombi in an afferent arteriole, the glomerular hilum, and glomerular capillaries (arrows), with vascular congestion and parenchymal hemorrhage in the surrounding interstitium. A tissue specimen from the adrenal gland (Panel C) shows characteristic subcapsular microthrombi (arrows), with congestion of cortical arterioles and medullary parenchymal hemorrhage (arrowhead). A specimen from the cecum (Panel D) shows submucosal microthrombi (arrows) and hemorrhagic mucosal ulceration and necrosis. Microthrombi were also present in the pancreas, thyroid gland, and other organs. (Photographs and interpretation by Patrick Stangeby.)

suggests the diagnosis. The following evidence of microangiopathic hemolytic anemia provides support (but is not specific) for the diagnosis: fragmented red cells (schistocytes) and polychromatophilic red cells (reticulocytes) on the peripheral-blood smear (Fig. 2), increased serum levels of lactate dehydrogenase and indirect-reacting bilirubin, and a negative direct Coombs' test. Examination of the blood smear is critical. Observation of two or more schistocytes in a microscopic field with a magnification of 100 suggests microangiopathic hemolysis,[23] although in some cases, schistocytes are less frequent. Many patients have normal serum creatinine levels; transient high levels may occur in one third of patients, and acute renal failure occurs infrequently.[14]

It is critical to rule out other potential causes of the presenting signs and symptoms, including sepsis, disseminated cancer, and malignant hypertension.[3,14,24] Laboratory evidence of disseminated intravascular coagulation suggests the presence of sepsis or disseminated cancer. Rarely, disseminated intravascular coagulation may be present in patients with thrombotic thrombocytopenic purpura, presumably the result of tissue ischemia (Fig. 1). Evaluation of women during pregnancy is especially difficult. Although pregnancy is associated with thrombotic thrombocytopenic purpura, especially near term or post partum,[25,26] signs characteristic of thrombotic thrombocytopenic purpura may also occur in patients with severe preeclampsia, eclampsia, and the HELLP

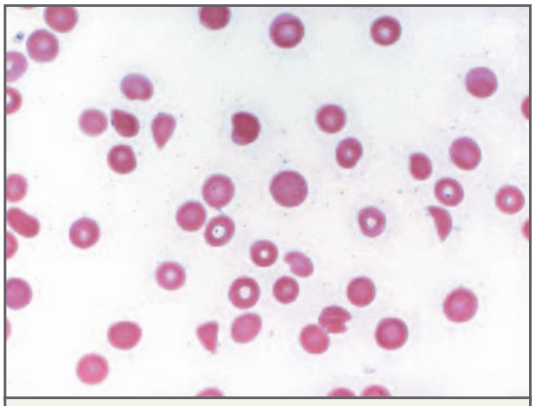

Figure 2. Peripheral-Blood Smear Showing Abnormalities Characteristic of Thrombotic Thrombocytopenic Purpura.
This smear from the patient described in Figure 1 shows fragmented red cells (schistocytes), polychromatophilic red cells (reticulocytes), and a lack of platelets, consistent with the presence of microangiopathic hemolysis.

syndrome (hemolysis, elevated liver-enzyme levels, and a low platelet count).[27]

The circumstances of the presentation are important. Patients in critical care units commonly have anemia and thrombocytopenia, and thrombotic thrombocytopenic purpura is unlikely in these patients even if fragmented red cells are present. Thrombotic thrombocytopenic purpura is rare in children; among adults it occurs predominantly in women.[5] Black race[5] and obesity[14] are associated with an increased risk of thrombotic thrombocytopenic purpura. Assessment is also warranted for conditions known to be associated with thrombotic thrombocytopenic purpura. These conditions are relevant in classifying thrombotic thrombocytopenic purpura and guiding therapy (Table 1),[14-16,28] although patients may have features of more than one of these clinical categories.

The value of measurements of ADAMTS 13 activity and inhibitors remains uncertain.[14,22] There are discrepancies among assay techniques, and in vitro measurements may not always correlate with in vivo activity.[29] In nine cohort studies, the frequency of severe ADAMTS 13 deficiency among patients with idiopathic thrombotic thrombocytopenic purpura was 33 to 100 percent.[29] Clinical manifestations of severe ADAMTS 13 deficiency, either congenital[26] or acquired,[21,30] are heterogeneous. They range from no or minimal symptoms and signs to progressive multiorgan failure (Fig. 1),[14,22] suggesting that many factors contribute to acute episodes.[31] Severe ADAMTS 13 deficiency may also occur in disorders other than thrombotic thrombocytopenic purpura,[14,32] whereas patients with normal levels of ADAMTS 13 activity may have the characteristic features and clinical course of thrombotic thrombocytopenic purpura.[14,33]

Even after a diagnosis of thrombotic thrombocytopenic purpura is made, continuing evaluation is important. In the Oklahoma Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome (TTP–HUS) Registry, 10 percent of patients with an initial diagnosis of idiopathic thrombotic thrombocytopenic purpura were subsequently found to have sepsis or systemic cancer.[24]

MANAGEMENT

Plasma-Exchange Treatment

For adults, plasma exchange is the only treatment for which there are firm data on its effectiveness.[1] The clinical trial that documented the efficacy of plasma exchange included 102 patients randomly assigned at the time of diagnosis to receive either daily plasma exchange (exchanging 1.0 to 1.5 times the predicted plasma volume of the patient) or plasma infusion (30 ml per kilogram of body weight for one day, then 15 ml per kilogram per day).[1] This trial demonstrated significantly improved survival at six months among patients receiving plasma exchange as compared with patients receiving plasma infusion (40 of 51 [78 percent] vs. 32 of 51 [63 percent], $P=0.04$).[1] Twelve of the 51 patients assigned to plasma infusion were subsequently treated with plasma exchange because of clinical deterioration. Initial response rates were also higher with plasma exchange; within seven days after randomization, 24 patients treated with plasma exchange (47 percent) had a normal platelet count (i.e., >150,000 per cubic millimeter) and no new neurologic events, as compared with 13 patients in the plasma-infusion group (25 percent, $P=0.02$). Twenty-four patients with renal failure who were not eligible for the trial (because they would have been unable to tolerate plasma infusion) were treated with plasma exchange; 20 (83 percent) survived.[17] Plasma infusion remains appropriate for patients with thrombotic thrombocytopenic purpura when there may be a delay until plasma exchange is available (Fig. 3).

Before effective therapy was available, most survivors of thrombotic thrombocytopenic pur-

Table 1. Clinical Categories of the Acquired Thrombotic Thrombocytopenic Purpura (TTP) Syndromes.*

Category	Cause or Associated Conditions	Risk Factors	Clinical Features†	Treatment	Clinical Course
Idiopathic TTP	Severe deficiency of ADAMTS 13 activity is present in many but not all patients. Relapses may be triggered by pregnancy and inflammatory conditions (e.g., infection, surgery, and pancreatitis).	Black race, female sex, obesity	One third with no neurologic abnormalities; fever uncommon; acute renal failure rare	Plasma exchange is required, and immunosuppressive treatment is appropriate.	Eighty percent of patients recover. In patients with a severe deficiency of ADAMTS 13 activity, the relapse rate is 50%.
Pregnancy	In addition to being pregnant, patients may have a severe deficiency of ADAMTS 13 activity.	Near-term or postpartum period	May be indistinguishable from severe preeclampsia, eclampsia, and the HELLP syndrome	Plasma exchange is required, and immunosuppressive treatment may be appropriate.	Relapse may occur, but most subsequent pregnancies are unaffected.
Autoimmune disorders	Acute flares of systemic lupus erythematosus, antiphospholipid antibody syndrome, or scleroderma may be indistinguishable from TTP. Patients may have a severe deficiency of ADAMTS 13 activity.	Predominantly female sex; young adulthood and middle-age	Severe manifestations of the primary autoimmune disorders, usually including renal failure	Immunosuppressive treatment is required, and plasma exchange may be appropriate.	The course is chronic, and the mortality rate is high.
Prodrome of bloody diarrhea	Patients have hemorrhagic enterocolitis caused by Shiga toxin–producing bacteria, typically *Escherichia coli* O157:H7.	Female sex in adults and white race in both children and adults	"Typical" HUS in children; in adults, renal failure and severe neurologic abnormalities common	Children are treated with supportive care. Plasma exchange may be appropriate for adults. Immunosuppressive treatment is unnecessary.	Death or end-stage renal disease occurs in 12% of children. Mortality rate in adults is 45%. Relapse may not occur.
Acute, immune-mediated drug toxicity	Quinine is the most common cause. Quinine-induced TTP is caused by quinine-dependent antibodies to multiple tissues. Ticlopidine, clopidogrel, and other drugs have been implicated.	With quinine, older age, white race, and female sex	With quinine, sudden onset of systemic symptoms with acute renal failure; possible fever, diarrhea, liver adverse effects, and neutropenia	Plasma exchange may be appropriate. Immunosuppressive treatment is unnecessary.	With quinine, mortality rate is 15% and chronic renal failure is common. Relapse occurs only with reexposure to the drug.
Cumulative, dose-dependent drug toxicity	Cancer chemotherapy with mitomycin, gemcitabine, and possibly other agents has been implicated, as have immunosuppressive agents (e.g., cyclosporine and tacrolimus).	Drug dose and duration	Insidious onset and a progressive course after etiologic agent is discontinued; renal failure common	The benefit of plasma exchange or any other treatment, other than stopping the drug, is uncertain.	Mortality is high because of the underlying condition. Chronic renal failure is common.
Hematopoietic stem-cell transplantation	Allogeneic transplantation may be a precursor of TTP-like syndromes. The incidence is variable because diagnostic criteria are uncertain.	High-risk procedures (e.g., unrelated donor, HLA mismatch, active disease); presence of acute graft-versus-host disease; sepsis	Thrombotic microangiopathy usually limited to the kidney	The benefit of plasma exchange is unlikely.	Mortality is high because there are multiple complications.

* HELLP denotes hemolysis, elevated liver enzymes, and low platelets, and HUS hemolytic–uremic syndrome.
† The clinical features are in addition to thrombocytopenia and microangiopathic hemolytic anemia.

pura were children,[2] which may reflect their inherent resistance to thrombosis, as suggested by observations that venous and arterial thromboses are rare in children,[34] rather than different etiologic factors. For example, among patients whose illness follows *E. coli* O157:H7 infection, the mortality rate among adults (45 percent)[35] is five times as high as that among children.[9]

The effectiveness of plasma exchange has been attributed to the removal of ADAMTS 13 autoantibodies and replacement of ADAMTS 13 activity.[10,22] However, plasma exchange also seems to be effective for patients who do not have a severe deficiency of ADAMTS 13 activity.[14] In a cohort of patients with idiopathic thrombotic thrombocytopenic purpura, plasma-exchange treatment resulted in a normal platelet count in 24 of 32 patients who did not have a severe deficiency of ADAMTS 13 activity (75 percent), as compared with 14 of 16 patients who had a severe deficiency (88 percent).[14]

Although a case series suggested that cryosupernatant plasma, which is deficient in von Willebrand factor, may be superior to fresh-frozen plasma as a replacement product in plasma exchange,[36] a small, randomized trial failed to confirm this. Among 27 patients treated at the time of initial diagnosis with either cryosupernatant plasma or fresh-frozen plasma, there was no significant difference in the time to response (5.5 and 6.0 days, respectively) or in survival (79 percent and 77 percent).[37] Therefore, fresh-frozen plasma is an appropriate replacement product.[38]

On the basis of observational data, daily plasma exchange should be continued until the platelet count is normal (Fig. 3).[13,39] Lactate dehydrogenase levels, which reflect tissue ischemia as well as hemolysis,[40] are also a marker of response to treatment.

Risks of plasma exchange should be recognized.[41] In a nine-year cohort study of 206 consecutive patients treated for thrombotic thrombocytopenic purpura, 5 (2 percent) died of complications attributed to the plasma-exchange treatment (3 from hemorrhage related to the insertion of a central venous catheter and 2 from catheter-related sepsis).[41] Fifty-three other patients (26 percent) had major complications attributed to plasma-exchange treatment, including systemic infection, venous thrombosis, and hypotension requiring dopamine.[41] However, given the poor prognosis of untreated thrombotic thrombocytopenic purpura, the benefits of therapy outweigh the risks.

Immunosuppressive Agents

In patients who have idiopathic thrombotic thrombocytopenic purpura, exacerbations when plasma exchange is stopped, or a relapse after a remission is achieved (conditions suggestive of acquired deficiency of ADAMTS 13 activity[10,14,22,29]), glucocorticoid therapy is often prescribed in addition to plasma exchange (e.g., 1 to 2 mg of prednisone per kilogram daily until remission is achieved; or 1 g of methylprednisolone per day for three days[13] administered intravenously) (Fig. 3). The rationale is that plasma exchange will have only a temporary effect on the presumed autoimmune basis of the disease and additional immunosuppressive treatment may cause a more durable response.[13] The use of glucocorticoids in such patients is based on clinical experience and case series,[42] although other case series have reported similar outcomes without the use of glucocorticoids.[1] For patients who require additional treatment to have a remission, small case series have suggested a benefit with more intensive immunosuppressive therapy with rituximab, cyclophosphamide, vincristine, or cyclosporine.[13,21,28,30,43,44] Clinical trials are lacking to guide the use of immunosuppressive agents.

Remission and the Risk of Relapse

Relapses are rare in patients with thrombotic thrombocytopenic purpura, except in those with a severe deficiency of ADAMTS 13 activity; half of such patients may have a relapse, most within a year.[22] Long-term follow-up data suggest a diminished frequency of relapses over time, though a relapse can occur years after the initial episode.[22] Small case series have suggested lower rates of relapse after splenectomy[45] or the use of rituximab,[32] but it is unclear whether these observations reflect the efficacy of these therapies or the natural history of disease. The current recommended approach to patients in remission is only to ensure prompt medical attention, including a complete blood count, in the event of any systemic symptoms that may suggest relapse, such as abdominal pain, nausea, vomiting, or diarrhea.

Because many patients with thrombotic thrombocytopenic purpura are young women and because of the association of thrombotic thrombocytopenic purpura with pregnancy,[25] the risk of

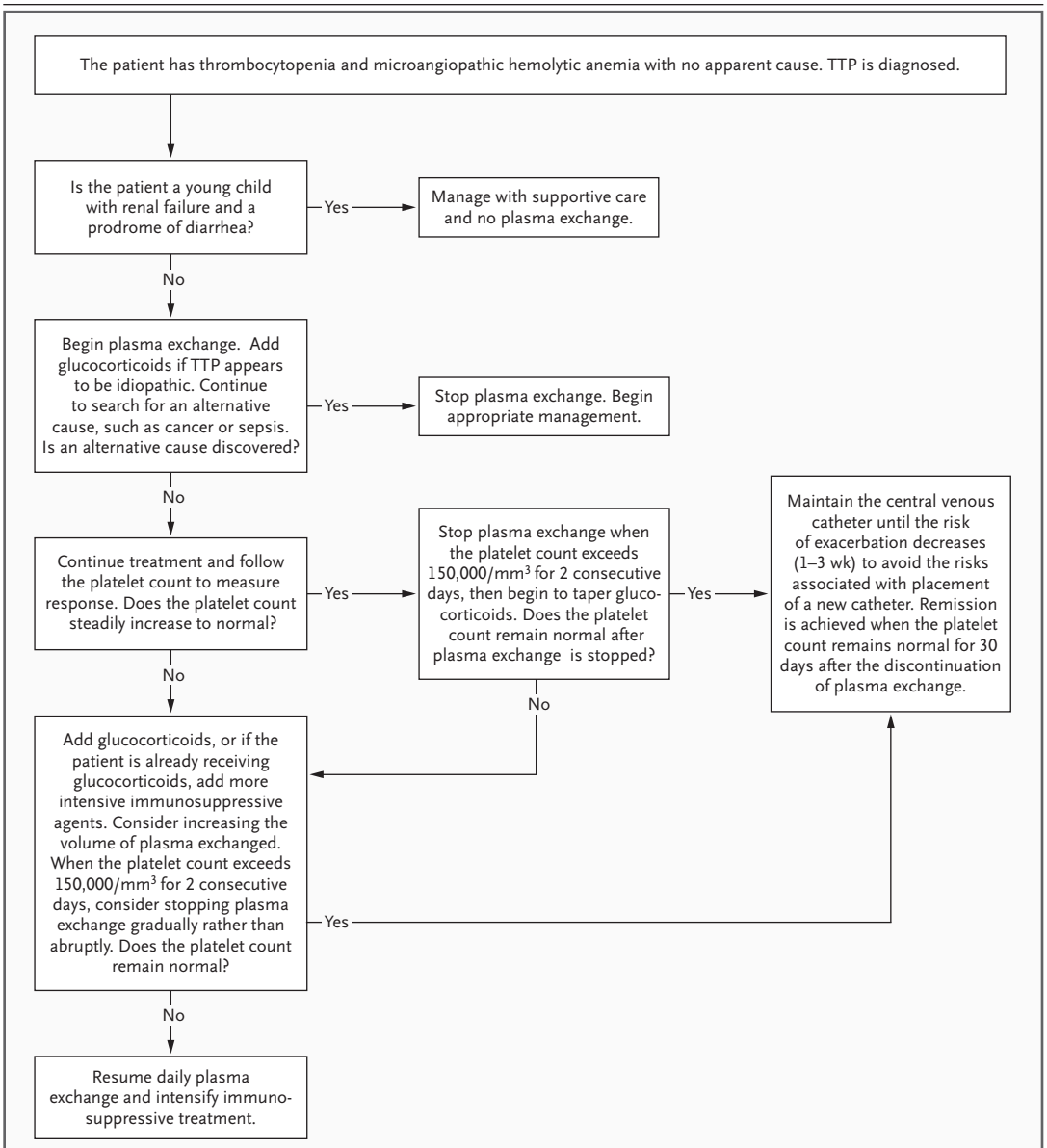

Figure 3. A Plan for the Management of an Initial Episode of Clinically Diagnosed Thrombotic Thrombocytopenic Purpura (TTP).

Recurrent thrombocytopenia within 30 days after the discontinuation of plasma-exchange treatment indicates an exacerbation of a continuing episode of TTP. Data defining remission have been previously described.[24] A plasma-exchange procedure typically requires several hours and costs $1,500 to $3,000.

relapse with a future pregnancy is an important concern. Although many case reports and small case series have described recurrences of thrombotic thrombocytopenic purpura in pregnant women who had a previous episode of thrombotic thrombocytopenic purpura,[46] a follow-up study involving 30 pregnancies among 19 women who had recovered from thrombotic thrombocytopenic purpura (including women whose initial episode was idiopathic, pregnancy associated, or preceded by bloody diarrhea) revealed that most subsequent pregnancies were unaffected.[46] Thrombotic thrombocytopenic purpura was diagnosed during one pregnancy in each of five women; all five women and two of the infants survived.

AREAS OF UNCERTAINTY

It may be difficult to distinguish thrombotic thrombocytopenic purpura from other conditions with similar manifestations. Plasma exchange is recommended for patients who meet the diagnostic criteria for thrombotic thrombocytopenic purpura and have no alternative explanation for the findings, but its efficacy for some categories of patients (e.g., those who have undergone allogeneic hematopoietic stem-cell transplantation[47,48]) is uncertain or unlikely (Table 1). In adults who have thrombotic thrombocytopenic purpura after a prodrome of bloody diarrhea or acute, immune-mediated drug toxicity, evidence of any benefit of plasma-exchange treatment is limited to case series.[35,49]

Although plasma exchange is usually continued until the platelet count returns to normal, the optimal duration of therapy is unknown. Once a patient is in remission, the efficacy of any treatment to prevent relapses is uncertain.

GUIDELINES

The American Association of Blood Banks, the American Society for Apheresis, and the British Committee for Standards in Haematology recommend daily plasma exchange with replacement of 1.0 to 1.5 times the predicted plasma volume of the patient as standard therapy for thrombotic thrombocytopenic purpura.[13,50] The British guidelines recommend that plasma-exchange therapy be continued for a minimum of two days after the platelet count returns to normal (>150,000 per cubic millimeter), and they also recommend the use of glucocorticoids for all patients with thrombotic thrombocytopenic purpura.[13]

CONCLUSIONS AND RECOMMENDATIONS

Because thrombotic thrombocytopenic purpura is uncommon, a high index of suspicion is required for rapid diagnosis and prompt initiation of plasma-exchange treatment. The unexplained occurrence of thrombocytopenia and anemia should prompt immediate consideration of the diagnosis and evaluation of a peripheral-blood smear for evidence of microangiopathic hemolytic anemia.

Other conditions (e.g., malignant hypertension, severe preeclampsia, sepsis, and disseminated cancer) that are likely to cause the same clinical findings as thrombotic thrombocytopenic purpura should be ruled out. In a patient with these findings, such as the woman described in the vignette, plasma-exchange treatment is warranted.

I would also prescribe glucocorticoids for patients who have idiopathic thrombotic thrombocytopenic purpura, whose condition worsens when plasma exchange is stopped, or who have a relapse after remission, although the use of this therapy is not supported by data from randomized trials. Measurement of ADAMTS 13 activity is not necessary for decisions about diagnosis and initial management, although a severe deficiency indicates an increased risk of relapse.

No potential conflict of interest relevant to this article was reported.

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