Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

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A question-and-answer section appears at the end of this article.

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Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are multisystemic disorders characterized by thrombocytopenia, microangiopathic hemolytic anemia, and organ ischemia due to platelet agglutination in the arterial microvasculature. Until recent years, classification of these syndromes was based primarily on clinical findings, with neurologic dysfunction being more prominent in TTP and renal dysfunction predominating in HUS. However, overlap is substantial, and precise distinction of the 2 syndromes remains somewhat arbitrary and controversial. Recent evidence suggests that deficiency of a specific plasma protease responsible for the physiologic degradation of von Willebrand factor (vWF) multimers has a causative role in a large proportion of familial and idiopathic cases of TTP. Although most cases of TTP and HUS are idiopathic, several etiologies and associations are well recognized, including infection, drugs, malignancy, chemotherapy, bone marrow transplantation (BMT), and pregnancy (Table 1).

INCIDENCE AND IMPORTANCE

Although TTP and HUS are uncommon, they are clinically important because of substantial morbidity and mortality without early recognition and treatment. The incidence of TTP in the United States has been estimated to be 3.7 cases per million people and appears to be increasing. This may be the result of enhanced physician awareness but may also reflect the increase in predisposing conditions, such as the prevalence of human immunodeficiency virus (HIV) infection, eligibility criteria for BMT (reflecting an increasing donor pool and allowable age), and widespread use of causally implicated drugs. Until the introduction of empirical plasma-based therapy in the 1970s, TTP was associated with a fatality rate greater than 90%. Current outcomes of TTP and HUS have improved significantly with the use of plasma exchange, but mortality remains unacceptably high at 10% to 20%. A significant proportion of deaths occur within 48 hours of presentation, underscoring the need for early recognition.

PATHOGENESIS

Both TTP and HUS have been hypothesized to be the result of platelet-aggregating agents in the circulation and/or endothelial cell injury. Widespread formation of platelet microthrombi results in consumptive thrombocytopenia, end-organ ischemia, and intravascular hemolysis due to fragmentation of red blood cells as they traverse partially occluded arterioles and capillaries. The characteristic occlusive hyaline thrombi have been shown to consist primarily of vWF and platelets, with little fibrinogen or fibrin and without perivascular inflammation. Serial studies of...
plasma samples from some patients with TTP have identified unusually large multimeric forms of vWF, similar to those stored in vascular endothelial cells and platelets but absent in normal plasma. These highly adhesive forms have been implicated in causing the pathologic platelet agglutination. These forms disappear as the acute episode progresses, consistent with incorporation in arteriolar microaggregates, and in some patients with relapsing TTP, they reappear during remission and are predictive of relapse.14 Two groups independently showed that such forms are physiologically cleaved to their normal size by a specific plasma protease, the vWF-cleaving protease (vWF-CP).15,16 Further work by these investigators suggests that absent or reduced activity of vWF-CP with resultant inadequate degradation of unusually large vWF multimers has a pathogenic role in a large proportion of TTP cases.4,5 An inhibiting autoantibody to the vWF-CP has been detected in most patients with acute idiopathic TTP. The inhibitor activity disappeared and vWF-CP activity returned during clinical remission in the majority of patients.4,5 No inhibiting antibody has been detected in patients with familial TTP, which appears to be the result of an inherited deficiency of vWF-CP.17 In 1 report, vWF-CP deficiency was claimed to distinguish TTP from HUS because no deficiency was found in the latter; however, the clinical criteria used to distinguish TTP from HUS in this study were not provided.4

Endothelial cell injury is hypothesized to be another important etiologic factor in some forms of TTP and HUS. Deficiency of vWF-CP has not been shown in cases occurring after chemotherapy or BMT, consistent with the theory that endothelial injury resulting from cytotoxic regimens or immune mechanisms may be the primary pathogenic mechanism.18,19 Endothelial injury, regardless of its etiology, may result in widespread release of unusually large vWF forms, theoretically overwhelming physiologic degradation systems and resulting in a relative deficiency of vWF-CP, analogous to the aforementioned cases of autoimmune or familial deficiency.

CLINICAL MANIFESTATIONS

Most patients with TTP present with no identifiable precipitating factor. The classic description of TTP consists of a pentad of microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic manifestations, and renal insufficiency. These clinical manifestations are the result of platelet agglutination in the arterial microvasculature. Not all patients will exhibit the 5 components of this pentad, and by the time all criteria are fulfilled, severe end-organ ischemia (central nervous system, renal) has developed. Therefore, in the appropriate clinical context, the diagnosis should be considered with the detection of otherwise unexplained microangiopathic hemolytic anemia and thrombocytopenia to avoid a potentially harmful delay in treatment.13 Fatigue and dyspnea on exertion may be accompanied by pallor and scleral icterus, resulting from acute fulminant hemolytic anemia. Thrombocytopenic purpura and mucosal bleeding may be present, although the latter is less common even with profoundly reduced platelet counts. Symptoms and signs of microvascular ischemia may occur in the cerebral (confusion, focal neurologic deficits), retinal (visual disturbances), renal (oliguria, hypertension), coronary (chest pain, conduction defects), and mesenteric (abdominal pain) circulation and suggest widespread platelet microaggregate formation and an urgent need for therapy. Neurologic disturbances, which may include sensory motor deficits, aphasia, seizures, and coma, can fluctuate and are often reversible with expeditious treatment.20 High spiking fevers and rigors are not characteristic of TTP and suggest sepsis. This is important to exclude as associated disseminated intravascular coagulation (DIC) may mimic TTP.

LABORATORY ABNORMALITIES

Severe anemia and thrombocytopenia (platelet count <20 × 10^9/L) are characteristic of TTP.21 The sine qua non on the peripheral blood smear is the presence of fragmented red blood cells (schistocytes or helmet cells) of microangiopathic hemolysis. The diagnostic importance of this finding warrants careful review of the blood smear in all suspected cases. An elevated reticulocyte count and indirect bilirubin level and absent serum haptoglobin reflect ongoing intravascular hemolysis. The serum lactate dehydrogenase (LDH) level is often increased dramatically, reflecting not only red blood cell destruction but also ongoing tissue ischemia. Despite widespread platelet agglutination, TTP is not a primary disorder of coagulation or thrombin activation, and coagulation studies, such as the activated partial thromboplastin time (APTT), the pro-
Table 2. Characteristic Laboratory Abnormalities in Patients With TTP and HUS*

<table>
<thead>
<tr>
<th>Abnormality</th>
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<tr>
<td>Microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>Fragmented red blood cells (schistocytes) on peripheral blood smear</td>
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<tr>
<td>Reticulocytosis</td>
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<tr>
<td>Increased indirect bilirubin level</td>
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<tr>
<td>Decreased haptoglobins</td>
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<tr>
<td>Negative direct Coombs test</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Platelet count often lower than 20 × 10^9/L</td>
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<tr>
<td>Coagulation studies</td>
</tr>
<tr>
<td>Normal APTT and PT</td>
</tr>
<tr>
<td>Negative DIC screen</td>
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<tr>
<td>Markedly increased LDH level (tissue ischemia and hemolysis)</td>
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<tr>
<td>Variably increased creatinine level (HUS &gt; TTP)</td>
</tr>
</tbody>
</table>

*APTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; HUS = hemolytic uremic syndrome; LDH = lactate dehydrogenase; PT = prothrombin time; TTP = thrombotic thrombocytopenic purpura.

thrombin time (PT), and the fibrinogen concentration, are characteristically normal. Test results for DIC are usually negative. Varying degrees of renal insufficiency may occur (Table 2).

The first-generation assays that measure vWF-CP activity involve electrophoresis and immunoblotting, are time and labor intensive, and are generally available only through dedicated research laboratories. Newer, less cumbersome techniques for determining vWF-CP activity are being developed. The vWF-CP assay may soon be available to clinical laboratories and would provide results within a clinically relevant time frame. However, prospective testing and clinical correlation will be necessary to define the ultimate role of such assays in the diagnosis and management of TTP and HUS, which currently remain clinical diagnoses.

DIFFERENTIAL DIAGNOSIS

Important conditions that may mimic TTP or HUS include sepsis, disseminated malignancy, systemic vasculitis, and preeclampsia or eclampsia (Table 3). These may all be associated with microangiopathy, primarily due to associated DIC. Unlike TTP, coagulation abnormalities reflect DIC, and the degree of hemolysis and thrombocytopenia is less profound. Sepsis with DIC must be excluded in the acutely ill patient with fever, thrombocytopenia, and multiorgan dysfunction. Appropriate antimicrobial and supportive therapy should be initiated as soon as appropriate cultures have been obtained while a further diagnostic evaluation proceeds. Patients with preeclampsia or eclampsia may have microangiopathic hemolytic anemia, seizures, and thrombocytopenia, but hematologic manifestations are generally milder than in patients with TTP. A platelet count of less than 20 × 10^9/L in the absence of DIC favors the diagnosis of TTP. Determination of the plasma antithrombin III level has been reported to be helpful, being reduced and normal in preeclampsia and TTP, respectively. Evans syndrome (concomitant occurrence of autoimmune hemolytic anemia and immune thrombocytopenic purpura) may be distinguished based on a positive direct Coombs test result, lack of red blood cell fragmentation (schistocytes), and notable absence of other organ involvement. Heparin-induced thrombocytopenia with thrombosis is a cause of thrombocytopenia and ischemic manifestations but may also be distinguished by absence of hemolysis and red blood cell fragmentation.

PLASMA EXCHANGE THERAPY

Plasma exchange is the most important component of therapy and is indicated for all patients with suspected TTP and HUS. At present, no evidence exists that additional treatment modalities alter outcome. Before empirical use of plasma infusion or plasma exchange therapy, TTP was associated with an almost inevitably fatal outcome. Following the observation of improvement after administration of plasma infusions, trials of plasma exchange were soon reported, with evidence of superior outcomes and survival in 80% to 90% of patients. A randomized controlled trial comparing plasma infusion with plasma exchange therapy definitively confirmed the superior of the latter. The response rate to plasma exchange was 78% compared with 49% in the plasma infusion group, with mortality rates of 22% and 37%, respectively. Interestingly, patients ineligible for randomization because of renal failure (clinically defined HUS) and concerns about volume overload with plasma infusions received plasma exchange therapy with equally favorable results, challenging the common belief that plasma exchange is less effective for HUS than for TTP.

The recent demonstration of vWF-CP inhibition or deficiency provides 1 explanation for the efficacy of this previously empirical therapy. Plasma infusions provide replace-
ment for the missing or inhibited vWF-CP, and plasma exchange simultaneously removes pathogenic autoantibody and agglutinating large multimeric forms of vWF. If plasma exchange therapy is not available immediately, infusions of fresh frozen plasma (FFP) can be used until plasma exchange can be arranged. However, because plasma infusion is less effective and may result in pronounced volume overload, it is not an acceptable alternative to plasma exchange.

Schedule and Duration
Plasma exchange therapy, replacing 1 calculated plasma volume daily with either FFP or cryosupernatant plasma, should be initiated as soon as the diagnosis is suspected. Cryosupernatant plasma (plasma that remains after cryoprecipitate is prepared), which is depleted of vWF, has a theoretical advantage and is used in some centers either initially or in cases of refractory disease. A recent randomized prospective clinical trial showed comparable efficacy of these 2 therapies in the management of newly diagnosed acute idiopathic TTP. Responses to plasma exchange vary, in both time to response and duration of therapy required to maintain response. Initially, plasma exchange should be performed daily until remission is evident, as determined by normalization of the platelet count and LDH level with resolution of any ischemic manifestations. These variables must be determined daily to monitor response.

Typically, an initial response is observed within the first week, but achievement of remission may require considerably more time, and the duration of plasma exchange needed is highly variable. In 1 large retrospective multicenter study of patients with idiopathic TTP, 50% and 70% of patients attained clinical remission by the end of 1 and 2 weeks of daily plasma exchange, respectively. The remaining 30% of patients required an additional 1 to 2 weeks of daily plasma exchange to achieve remission. Once remission has been observed for several days, plasma exchange therapy may be tapered gradually and ultimately discontinued. Of note, disease activity may recur rapidly (evidenced by a precipitous decline in platelet count and an abrupt increase in LDH level) as the frequency of plasma exchange is reduced or withdrawn, necessitating emergent reinstitution of daily plasma exchange. Several attempts at tapering and discontinuing plasma exchange may be necessary. Presently, this is the only strategy to determine whether a durable remission has been attained.

Complications
Plasma exchange is not an innocuous procedure, and patients and physicians must be informed of potential risks. The major risk relates to complications from the central venous catheter. A prospective study of 71 consecutive patients treated for clinically suspected TTP reported a major complication rate, including fatalities, of 30%. Complications included hemorrhage after central line placement, catheter-induced thrombosis requiring line removal, pneumothorax requiring chest tube placement, and line-related systemic bacterial and fungal infections. Infusion of large volumes of plasma is associated with the potential risk of blood-borne pathogen transmission, although no transfusion-transmitted infections were observed in that study.

ANCILLARY THERAPY
Glucocorticoids
Glucocorticoids have been used variably based on historical data of the possible efficacy of corticosteroids in the era before plasma therapy and reports of resolution of less severe cases with high-dose prednisone alone. Because of the efficacy of plasma exchange therapy, assessing the additional benefit of ancillary therapies has been difficult. A recent summary of several series reporting outcomes with plasma exchange for patients with TTP found no difference in response rates with or without the addition of glucocorticoids. Given the recent demonstration of an autoimmune pathogenesis in a substantial proportion of patients with TTP, a stronger rationale for their use now exists. Although evidence from a randomized trial is lacking, dosages of prednisone of 1 to 2 mg/kg per day have been recommended. Once remission is achieved and plasma exchange therapy has been discontinued, the corticosteroid dose is gradually tapered to cessation.

Antiplatelet Agents
As with glucocorticoids, the efficacy of plasma exchange therapy has made it difficult to assess the additional benefit of antiplatelet agents. Some investigators have reported an increase in hemorrhagic complications, especially in patients with severe thrombocytopenia. Only 1 prospective randomized study has compared plasma exchange with and without concurrent antiplatelet therapy (aspirin and dipyridamole). No statistically significant difference in either overall response or bleeding was shown. Nevertheless, because of the potential for hemorrhagic complications without proven benefit, these agents cannot currently be recommended for patients with TTP who have profound thrombocytopenia. Aspirin may have a role once the platelet count increases with successful plasma exchange therapy.

Platelet Transfusions
Platelet transfusions are generally contraindicated in patients with TTP, unless major hemorrhage is evident or an invasive procedure is required. Thrombotic thrombocytopenic purpura is a disorder of microcirculatory thrombosis, and severe hemorrhage is rare. Several reports, largely
anecdotal, have described rapid clinical demise after administration of platelets. In patients who died, postmortem examinations revealed extensive platelet aggregate formation in the central nervous system. In a large clinical series, 11 patients experienced rapid clinical deterioration after platelet transfusion, with the mean serum creatinine level increasing from 1.1 mg/dL to 7.7 mg/dL in less than 24 hours.

Supportive Care
These often critically ill patients require appropriately intensive supportive care. Red blood cell transfusions are usually indicated based on the initial hemoglobin level and degree of hemolysis. Hypertension due to renal vascular ischemia may necessitate medical intervention. Hemodialysis may be indicated for severe renal insufficiency. Seizures may develop during the course of illness, and anticonvulsant therapy is indicated in such patients. Heparin therapy has no role in the management of these patients and should be avoided.

SPECIFIC SUBTYPES AND TRIGGERS OF TTP AND HUS
Multiple triggers and associations of TTP and HUS, including infection, drugs, malignancy, chemotherapy, BMT, and pregnancy, have long been recognized (Table 1).

Escherichia coli 0157:H7
A TTP or HUS-like syndrome may develop after bacterial gastrointestinal infections caused by certain strains of Shiga toxin--producing E coli (E coli 0157:H7). This syndrome may occur in up to 15% and 5% of affected children and adults, respectively. These syndromes are caused by Shiga-like toxins elaborated by the E coli that are absorbed into the systemic circulation. Preferential binding of these toxins to specific glycolipid receptors on vascular endothelial cells leads to endothelial injury and localized intravascular thrombosis. The renal vascular endothelium is particularly susceptible, accounting for the prominence of renal failure in these patients (clinical HUS). However, other vascular territories may be involved, causing other ischemic symptoms and neurologic manifestations. The onset of TTP or HUS is typically 2 to 14 days after the onset of diarrhea, which may have resolved completely by the time the syndrome manifests. Reported risk factors include extremes of age (<4 and >70 years), leukocytosis, and use of antimotility agents and antibiotics for the bacterial enterocolitis. In children these microangiopathic syndromes are often self-limited and resolve with supportive care, which may include temporary hemodialysis. Although the mortality rate in children is low (3%-5%), long-term follow-up studies have demonstrated chronic renal insufficiency in a significant percentage of affected children. The clinical picture in adults differs, with high mortality rates reported in the susceptible elderly population. The previously held notion of lack of benefit from plasma exchange has been challenged in a recent publication outlining significantly reduced mortality rates among elderly patients treated with plasma exchange compared with historical data of supportive care alone (31% vs 92%).

Human Immunodeficiency Virus
An increased incidence of TTP among patients with HIV type 1 infection has been well described. Thrombotic thrombocytopenic purpura can develop at any stage of HIV infection and may be the presenting manifestation, although most cases of TTP present later during the course of HIV. The presentation is identical to that of acute idiopathic TTP. Nevertheless, the differential diagnosis of fever, anemia, thrombocytopenia, and neurologic symptoms is much broader in the HIV patient population and may lead to diagnostic and therapeutic delay. The response rate to plasma exchange, if initiated in a timely manner, is comparable to that in non–HIV-positive patients with acute TTP. The reported reduced survival of patients with HIV and TTP relates primarily to the stage of the underlying infection and the degree of associated immunosuppression, rather than to the diagnosis of TTP per se. The pathogenesis remains to be defined but may be related to immune dysregulation, opportunistic infection, endothelial damage from direct endothelial cell infection by HIV, or aberrant cytokine expression.

Pregnancy and Postpartum
Pregnancy is the most common condition associated with TTP. The incidence of TTP during pregnancy and the postpartum period is higher than expected, with cases of pregnancy-related TTP estimated at 10% in reported series. Diagnostically, the distinction of TTP from severe preeclampsia, a more common cause of thrombotic microangiopathy during pregnancy, is difficult but critical. In the absence of plasma exchange, TTP is almost uniformly fatal, whereas expediting delivery, as for patients with severe preeclampsia, has little or no effect on the course of TTP. Although TTP can occur at any time during pregnancy or the postpartum period, it usually presents earlier during pregnancy (median gestational age at onset, 23.5 weeks) than does preeclampsia. Before the introduction of plasma exchange therapy, maternal survival was rare. Early recognition of TTP and prompt initiation of plasma exchange have resulted in a marked reduction in maternal mortality and some successful pregnancy outcomes.
high, largely because of placental infarction caused by thrombotic occlusion of the decidual arterioles. No reports have described transmission of TTP to the fetus. Subsequent pregnancies may precipitate a relapse, and patients should be cautioned about this possible outcome. 

Drugs

Drug-induced TTP is a well-described phenomenon, and multiple drugs have been causally implicated, including mitomycin, cyclosporine, tacrolimus, quinine, and, more recently, the related thienopyridine antiplatelet agents ticlopidine and clopidogrel. Ticlopidine and clopidogrel are clinically important because of widespread use and potential to precipitate a fulminant syndrome identical to acute idiopathic TTP, often within 1 month of initiation. The initial manifestation of this complication may be erroneously attributed to progression of the underlying ischemic atherosclerotic disease (cerebrovascular and coronary), for which these agents were prescribed. Without early recognition and initiation of plasma exchange, outcome can be fatal. Among reported cases, patients treated with plasma exchange had a significantly reduced mortality rate. Investigators have estimated that TTP occurs in 1 in 1600 to 1 in 5000 ticlopidine-treated patients.

In view of the more favorable safety profile of clopidogrel (no cases of TTP in large phase 3 studies of >20,000 closely monitored subjects), it has largely replaced ticlopidine for the prevention of stroke and thrombosis after coronary stenting. A recent report described 11 cases of acute TTP related to clopidogrel use. The onset occurred within 2 weeks of drug initiation in 10 of 11 patients. All were treated with plasma exchange, but 1 patient died despite undergoing plasma exchange therapy shortly after TTP diagnosis. Plasma samples in 2 patients were available for further testing. In both these patients, vWF-CP activity was undetectable, and IgG inhibitors to the protease were present during the acute episode, consistent with an autoimmune mechanism.

Cancer and Chemotherapy-Related TTP

The association between TTP and cancer is well established. Most commonly, TTP is associated with advanced gastric adenocarcinoma and breast cancer, but it has also been reported in association with lung cancer, thymoma, and lymphoma. In patients with cancer, DIC and TTP may coexist, leading to diagnostic confusion. Chemotherapy-related TTP or HUS has been reported most commonly after initiation of mitomycin, but other agents have also been implicated, including bleomycin, cisplatin, and gemcitabine. This syndrome has been attributed to chemotherapy-induced endothelial cell injury and circulating immune complexes to tumor-associated antigens. The relative importance of the underlying malignancy itself and the implicated chemotherapeutic agent is often difficult to determine. Plasma exchange therapy is less successful for chemotherapy-related TTP than for classic TTP. Immunoabsorption with plasma perfusion over a staphylococcal protein A column (a procedure that results in the removal of immune complexes) has been reported to be effective and should be considered in patients who do not respond to standard plasma exchange therapy.

Bone Marrow Transplantation

Thrombotic thrombocytopenic purpura is a well-recognized complication of BMT, and multiple contributing pathogenic factors have been implicated. These include endothelial cell injury due to toxic-conditioning regimens (high-dose chemotherapy and total body irradiation), infections, use of drugs such as cyclosporine and tacrolimus, and a possible graft-vs-host effect on the endothelium. The 2 last-mentioned factors could account for the more frequent occurrence of TTP in the allogeneic vs the autologous BMT setting. Responses to plasma exchange are suboptimal. Unfortunately, alternative treatment options are limited; the current standard practice is to proceed with plasma exchange therapy and replace cyclosporine (or tacrolimus) with alternative immunosuppressive therapy once the diagnosis is suspected. Plasma exchange with cryosupernatant, alternating with immunoabsorption and plasma perfusion over a staphylococcal protein A column, has been reported to be more effective than standard plasma exchange in such patients. In general, vWF-CP deficiency has not been detected in posttransplant recipients in whom endothelial cell injury is likely the primary pathogenic event.

Relapsed TTP

A retrospective review of a large series of patients with TTP who were treated with contemporary plasma-based therapy found that the relapse rate at 10 years was 36%. These relapses occurred at varying intervals from the time of remission, ranging from 8 months to 9 years. Some patients had multiple relapses, and no predictive factors were identified. Other investigators have reported similar relapse rates. Generally, relapses of TTP respond to reinitiation of the previously successful treatment. No maintenance therapy, such as plasma infusions or aspirin, has been shown to prevent relapse.

The role of splenectomy, performed while the patient is in remission to prevent relapse, is controversial. The proposed mechanisms of efficacy include removal of a prominent site of autoantibody production or microvascular occlusive lesions, which result in high shear stress with propagation of the microangiopathic syndrome.
vestigators have reported small series showing benefit of splenectomy in preventing relapse. Given that relapses occur infrequently and may occur only after prolonged follow-up and that relatively few patients have been uniformly treated, establishing efficacy of any particular intervention in preventing relapse has been difficult.

Refractory TTP

Despite the use of plasma exchange therapy, some patients with TTP fail to respond. The incidence of refractory disease varies with the underlying associations. A minority of patients with classic acute TTP fail to respond to therapy. However, chemotherapy or BMT-related TTP is more often refractory. Management of the patient with refractory TTP is difficult, poorly defined, and associated with a grim prognosis. Some investigators recommend intensification of plasma exchange by increasing the volume or the frequency. Many other interventions reported anecdotally and in some small series have been beneficial. These include vincristine, intravenous immunoglobulin, plasma exchange with cryosupernatant (if FFP was used initially), staphylococcal protein A immunoadsorption, azathioprine, cyclosporine, and splenectomy. The role of splenectomy in the setting of refractory disease is controversial, with reports of both beneficial and detrimental effects. A high mortality rate from splenectomy performed at the time of active disease has been reported. Vincristine has been used frequently with some reported success in the management of refractory disease. Nevertheless, similar to the evaluation of therapy proposed to prevent relapse, the reported benefits may represent a true response, a delayed effect of previously administered treatments, or a spontaneous remission. Often, several interventions are initiated simultaneously or in rapid succession because of urgency or desperation. This approach, in addition to the variable clinical course of TTP, makes anecdotal reports and small series largely impossible to interpret.

CONCLUSIONS

Early diagnosis and timely initiation of plasma exchange therapy are essential aspects in the successful management of TTP. The diagnosis is not dependent on the fulfillment of all components of the classic pentad and should be suspected when microangiopathic hemolytic anemia and thrombocytopenia are found in the absence of other causes. Key laboratory studies to confirm the diagnosis include peripheral blood smear showing fragmented red blood cells (schistocytes), increased levels of indirect bilirubin and LDH with absent serum haptoglobins (reflecting intravascular hemolysis), and normal results on coagulation studies (APTT, PT, and a negative DIC screen). If TTP or HUS is suspected, plasma exchange therapy should be initiated immediately. Plasma exchange is performed daily until several days after remission is achieved (defined by normalization of the platelet count and LDH level and resolution of ischemic symptoms) and can be tapered gradually. The recent demonstration of an immune mechanism in a substantial proportion of patients with TTP provides a rationale for concurrent treatment with glucocorticoids. Plasma exchange has led to the current improved outcomes in what had previously been almost universally fatal disorders. Nevertheless, morbidity and mortality rates remain unacceptably high. New insights into the pathogenesis of TTP and HUS promise to improve further the management and outlook of these potentially devastating syndromes.

REFERENCES


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Questions About TTP and HUS

1. Which one of the following laboratory variables would not be expected in a patient with TTP?
   a. Low platelet count
   b. Elevated indirect bilirubin level
   c. Normal APTT and PT values
   d. Spherocytes on a peripheral blood smear
   e. High serum LDH value

2. If plasma exchange therapy is not available immediately, which one of the following therapeutic options would be best until plasma exchange can be initiated?
   a. Platelet transfusion
   b. FFP infusions
   c. Red blood cell transfusions
   d. Hemodialysis
   e. Intravenous immunoglobulin

3. Which one of the following explains the etiology of most cases of TTP?
   a. Drugs
   b. Idiopathic
   c. Familial
   d. Iatrogenic
   e. Paraneoplastic

4. Which one of the following is not a reported risk factor for the development of TTP or HUS after E coli 0157: H7 enterocolitis?
   a. Extremes of age
   b. Leukocytosis
   c. Use of antimotility agents for the bacterial enterocolitis
   d. Use of antibiotics for the bacterial enterocolitis
   e. Hypotension

5. Which one of the following therapeutic or supportive measures is not indicated in the management of TTP?
   a. Heparin
   b. Red blood cell transfusions
   c. Glucocorticoids
   d. Plasma exchange
   e. Antihypertensive agents

Correct answers:
1. d, 2. b, 3. b, 4. e, 5. a