# Diagnosis and Treatment of Thrombotic Thrombocytopenic Purpura

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**Review Article**

**ABSTRACT**

Thrombotic thrombocytopenic purpura (TTP) is a rare clinical emergency that is characterized by features of microangiopathic hemolytic anemia and thrombocytopenia. The availability of effective therapy with therapeutic plasma exchange has decreased the mortality rate from 90 % to approximately 20%. The historical pentad of clinical features once thought to be needed to make the diagnosis include fever, anemia, renal failure, neurological findings and thrombocytopenia. Currently, clinical diagnosis is made by existence of thrombocytopenia and microangiopathic hemolytic anemia unexplained by other causes. The variety of clinical presentations and the lack of specific laboratory diagnostic criteria make the diagnosis of TTP highly dependent on a high index of clinical suspicion and can be easily missed. Early recognition and appropriate treatment with plasma exchange in clinical settings is very important and is frequently life saving**.** Current knowledge in the etiopathogenesis, epidemiology, trends in the diagnosis and treatment are reviewed herein.

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# Le diagnostic et le traitement des cas de purpura thrombocytopénique thrombotique

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**Révision Article**

**Résumé**

Purpura Thrombopénique Thrombotique (PTT ) est l'une des rares cliniques d'urgence qui se caractérise par des fonctionnalités d' anémie hémolytique microangiopathique et la thrombocytopénie. La disponibilité de thérapies efficaces avec plasma thérapeutique exchange a diminué le taux de mortalité de 90 % à environ 20 %. La pentode historique des fonctions cliniques une fois jugé nécessaire pour faire le diagnostic de la fièvre, anémie, insuffisance rénale, troubles neurologiques et de thrombocytopénie. Actuellement, diagnostic clinique est faite par existence d'une thrombopénie et une anémie hémolytique microangiopathique inexpliquées par d'autres causes. La variété des présentations cliniques et de l'absence de laboratoire spécifique critères de diagnostic faire un diagnostic des TTP hautement tributaires d'un indice élevé de suspicion clinique et peut être facilement manquer. Reconnaissance précoce et un traitement approprié avec le plasma exchange dans les réglages cliniques est très important et est souvent sauver la vie**.** connaissances actuelles dans la etiopathogenesis, l'épidémiologie, les tendances dans le diagnostic et le traitement sont examinées ici.

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## INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life threatening disease which was first described in 1925 by Moschcowitz as a disease characterized by the pathological findings of hyaline microthrombi in many organs (1). It was first described in a teenager who had a sudden death. She had an abrupt onset and rapid progression of petechiae, pallor, paralysis and coma. At that time Moschcowitz thought there was a powerful poison that had both agglutinative and hemolytic properties. Multiple reports of the same disease followed and by 1966, Amorosi and Ultmann described TTP as a classic pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), change in mental status, renal failure and fever (2, 9).

In 1982, a defect in the processing of unusually large VWF was thought to be responsible for this disease (3,4). TTP is characterized by systemic platelet aggregation, organ ischemia, profound thrombocytopenia and fragmentation of red blood cells (2). The annual incidence of TTP syndrome in the United States is 4-11 cases per million individuals. It is more common in women between ages of 10 and 40. Incidence in blacks is nine times higher than in non-blacks (3). TTP has been shown to occur with demonstrably higher incidence in blacks and patients with preexisting autoimmune diseases like systemic lupus erythematosus (5, 6).

Epidemiological studies on TTP in Nigeria are scarce presently. A recent review of literature on TTP in Nigeria yielded three case reports highlighting TTP associated with Systemic Lupus Erythematosus (SLE) (7) and TTP associated with staphylococcus aureus endocarditis (8). Various clinicians and researchers worked on different treatment methods and discovery of effective and current gold standard therapy actually preceded the full discovery of the etiopathogenesis of the disease (9).

With effective treatment with therapeutic plasma exchange (TPE), the mortality has decreased from 90% to 20% (10,11). In clinical situations where there is a high index of clinical suspicion of the disease, renal insufficiency and neurologic symptoms are now late manifestations (12).

## CLASSIFICATION

TTP can be classified as congenital or acquired (13). It could also be classified as sporadic, intermittent and recurrent forms depending on the recurrence of the events (14,15).

A single acute episode describes the sporadic form while relapsing episodes with symptom free periods of months or years marks the intermittent forms. Frequent relapsing episodes recurring after regular symptom free intervals is seen in the recurrent forms which is usually familial (14, 15, 16).

The acute forms could be further classified as acute sporadic, idiopathic TTP or TTP associated with other conditions.
Congenital TTP also known as Upshaw Shulman Syndrome (USS) or Familial Relapsing TTP is caused by a genetic defect in the adisintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) gene, which results in a severe deficiency of ADAMTS13 enzyme causing persistence of unusually large Von Willebrand factor (UL-VWF). This is a rare condition (17). Acquired Idiopathic TTP has been attributed to a severe ADAMTS13 deficiency due to an Immunoglobulin G (Ig G) autoantibody. This is more common than the congenital type (18).

TTP can occur in association with autoimmune diseases, drugs like clopidogrel, cyclosporine, hematopoietic stem cell transplant, malignancy, infections, hormone replacement therapy and pregnancy (11).

## PATHOPHYSIOLOGY OF TTP

TTP is defined by an underlying defect in *adisintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) genes,* which results in ADAMTS13 enzyme deficiency (6) ADAMTS13 is a metalloprotease that cleaves the tyr1605-Met1606 bond in the central A2 subunit of Von Willebrand Factor

(VWF) (7). VWF is synthesized primarily by the endothelial cells. ULVWF multimers are formed and are stored in the Weibel –Palade bodies or secreted into the plasma. They mediate platelet aggregation and collagen binding. These ULVWF multimers depolymerize under normal conditions and the enzyme responsible for this is ADAMTS13.A severe deficiency of this enzyme activity to <5-10% is an abnormality specific for TTP (15, 18).

ADAMTS13 cleaves Ultra-large multimers of VWF (ULVWF) within platelet aggregates under flowing conditions; this usually limits platelet thrombus formation. In TTP, since ADAMTS13 is either absent congenitally or absent due to autoantibodies, platelets adhere to these ULVWF causing systemic platelet aggregation with microvascular thrombosis and occlusion. (19) Microangiopathic hemolytic anemia (MAHA) occurs as blood flows through the microcirculation, which is partially occluded by platelet aggregates. Evidence of MAHA is indicated by the presence of schistocytes on a blood film examination and elevated LDH (20).

The basis of Plasma exchange for treatment is the replacement of the missing ADAMTS13 enzyme and the removal of the inhibitory autoantibodies (20, 21).

**CLINICAL FEATURES**

Symptoms are nonspecific and can range from weakness, abdominal pain, bleeding, vomiting, and strokes, renal insufficiency. Occlusive ischemia of the brain or the GI tract or any organ can occur due to microvascular thrombi. Before the era of treatment, the pentad of fever, renal failure, thrombocytopenia and neurologic impairments were seen but are no longer needed for diagnosis. Typically otherwise unexplained MAHA evidenced by schistocytes and elevated LDH and thrombocytopenia strongly suggest the diagnosis (22).

**DIFFERENTIAL DIAGNOSIS**

These are often challenging since there are a number of disease conditions with thrombotic microangiopathy. Thrombotic microangiopathy can be seen in Post hematopoietic stem cell transplantation, HIV infection, HELLP syndrome, preeclampsia, medications like calcineurin inhibitors, ticlopidine, malignant hypertension, disseminated malignancy, vasculitis, catastrophic antiphospholipid syndrome. There are also TTP like syndromes including Hemolytic uremic syndrome (HUS) and atypical hemolytic uremic syndrome (aHUS).

**HEMOLYTIC UREMIC SYNDROME (HUS)**

This is defined as thrombotic microangiopathy associated with renal failure which typically occurs in children.
three forms have been identified (23).

**Typical HUS;** It is also known as diarrhea associated HUS (D+ HUS) and is rarely associated with ADAMTS13 deficiency. It occurs in about 80-90% of patients with HUS. Infections with Bacteria that produce Shiga toxins such as Escherichia coli O157:H7 have been implicated. Shiga like toxin mediated HUS has not been shown to respond to Plasma exchange therapy

**Atypical HUS**: (D- HUS) or a HUS is not associated with diarrhea and is seen in 10-15% of cases .This is associated with dysregulation of complement pathway in 60% of the patients .It has been shown to have limited response to TPE. It affects components of alternative complement pathway convertase C3bBb .A new drug, Eculizumab an anti-C5 complement monoclonal antibody has been approved for treatment of a HUS (24).

**DEAP–HUS** (deficiency of CFHR1 and CFHR3 proteins and autoantibody positive) HUS has been described. It is characterized by the presence of autoantibodies to central complement inhibitor factor H. The presence of DEAP-HUS was confirmed in the New Castle cohort where the frequency of deletion of CFHR1 and CFHR3 genes was around 10% (23).

**DIAGNOSIS**

The diagnostic criterion which includes thrombocytopenia and MAHA is present in many other syndromes making the diagnosis of TTP challenging (25). The value of ADAMTS13 measurements for establishing diagnosis and initiating treatment is uncertain (8). Patients can have ADAMTS13 deficiency and yet have nonspecific symptoms, while some patients will have the clinical symptoms and all the features of TTP without ADAMTS13 deficiency. In nine cohort studies, the frequency of ADAMTS13 deficiency among patients with idiopathic TTP was 33-100% (26). In another study reported, 80-100% of patients with Idiopathic TTP had undetectable ADAMTS13 level.

In the Oklahoma registry, 9 of the 22 patients with severe ADAMTS13 deficiency had no neurologic symptoms. They had nonspecific symptoms such as weakness; vomiting diarrhea (8). This makes the diagnosis challenging since many other diseases could have these symptoms as their presenting features. Other factors making the diagnosis even more challenging include discrepancies among the various assays and heterogeneous nature of the manifestations of TTP (8). Some syndromes other than TTP may have severe ADAMTS13 deficiency while some patients presenting with features of TTP may have normal levels of ADAMTS13 activity. There have been some studies suggesting that ADAMTS 13 assays may have a prognostic value. Patients with severe ADAMTS13 deficiency had a favorable prognosis when compared to those with detectable levels (11).

Zheng et al (11) noted that severe ADAMTS13 deficiency is associated with idiopathic TTP and low mortality, while TTP with detectable ADAMTS13 level is associated with high mortality. Those who have relapsing course of TTP are thought to be associated with ADAMTS13 deficiency caused by inhibitors (11). Therefore the key diagnostic clues are the presence of microangiopathic hemolytic anemia (presence of schistocytes on peripheral blood smear, increased LDH and decrease in serum haptoglobin) and thrombocytopenia in the absence of other causes like sepsis, disseminated cancer, malignant hypertension, disseminated intravascular coagulation. The heterogeneous nature of clinical manifestations of TTP makes it reasonable and important to follow up the patient even after the diagnosis is made. This is because continuous evaluation is necessary to rule out other causes of TTP. Ten percent of patients in the Oklahoma TTP-HUS registry were found to have other diagnosis other than TTP specifically sepsis or systemic cancer (12).

**TREATMENT MODALITIES**

**Plasma exchange therapy**

Plasma exchange also known as therapeutic plasma exchange (TPE) is the only treatment with evidence on its effectiveness. TTP is a category I indication for TPE in the American Society for Apheresis Guidelines for initiation of plasma exchange (27). This is attributed to the removal of ADAMTS13 autoantibodies and replacement of ADAMT13 enzyme (2, 8).

The Canadian Apheresis Group (CAG) in 1991 demonstrated that survival of TTP was improved with TPE compared with plasma infusion. They randomized patients to receive plasma exchange daily (1-1.5 times the predicted plasma volume)with fresh frozen plasma or plasma infusion (30ml/kg of body weight for one day then 15ml per kilogram per day), it demonstrated that survival at 6months among patients receiving plasma exchange as compared to plasma infusion was 78% and 63% respectively. It also showed initial higher response in the plasma exchange group within seven days and a lower rate of relapse than patients receiving plasma transfusion (10).

Even though plasma exchange is the standard treatment, plasma infusions could be used in patients in whom plasma exchange cannot be promptly started. It is also used for patients with severe or refractory disease between plasma exchange therapies and in Congenital TTP (17). In another study, there was no superiority in the use of cryo-

supernatant plasma, which is deficient in VWF when compared to fresh frozen plasma as replacement fluid (28,29).

Zheng et al (11) reported that plasma exchange was effective in patients with no ADAMTS13 inhibitors when compared to those with demonstrable inhibitor at presentation. Those with severe ADAMTS13 deficiency and a high titer inhibitor had more prolonged courses with more complications and required additional immunosuppressive treatment.

The recommended treatment is plasma exchange daily (1-1.5 times the predicted plasma volume) until platelet count is above 150,000 per cubic millimeter, and LDH near normal for 2-3 consecutive days. The role of tapering treatment over longer duration has not been studied prospectively but is used frequently. The British guidelines recommend glucocorticoid for all the patients with a diagnosis of TTP and they also recommend that plasma therapy be continued for a minimum of 2 days after the platelet count returns to normal (9).

Plasma exchange is not without risks. The prognosis of TTP without treatment is poor .The benefits associated with therapy outweigh the risks. In a cohort study of patients treated for TTP, it was noted that there were some catheter related and plasma related complications. Two percent of these patients died from catheter related complications 26 percent of the patients had plasma exchange related complications. These complications include catheter related infection, hypotension requiring dopamine and venous thrombosis (9).

**Immunosuppressive therapy**

It is thought that patients who have a high titer inhibitor may benefit from immunosuppressive regimen. The rationale is that plasma exchange only has a temporary effect since the disease has a presumed autoimmune basis (9, 27). These patients with high titer inhibitors may require not only glucocorticoids but also other immunosuppressive regimen like rituximab. It has also been noted that the duration of TPE required to achieve a durable response has decreased over the past 15yrs leading to a decrease in TPE related complications. This observation has supported the effectiveness of corticosteroids and rituximab. However there are no clinical trials to guide use of immunosuppressive agents.

In patients with relapses or exacerbations, Prednisone 1 – 2mg/kg daily until remission is achieved or 1gram methyl prednisone for 3days has been used (30). Small case series have suggested a benefit with more intensive therapy with rituximab, cyclophosphamide, vincristine or cyclosporine. Relapses are rare except in those with severe ADAMTS13 deficiency (11, 22, 30).

**Splenectomy**

The removal of the spleen is thought to reduce the B cell mass capable of forming autoantibodies. A reduced relapse rate has been noted in patients with relapsing TTP who had splenectomy during the hematologic remission. This was shown in small case series by Crowther MA *et al* (31, 32). The recommended approaches for those in remission are close monitoring and prompt medical attention especially with symptoms that might suggest relapse. There is uncertainty in the efficacy of any treatment to prevent relapse.

**Antiplatelet agents**

Some people include the use of antiplatelet therapy in the management of TTP. There is some evidence in favor of this but it remains controversial. However it seems to be used currently in patients with neurological complications such as strokes or TIA (33).

**Platelet transfusions**

There has been reluctance to transfuse platelets in TTP. However when thrombocytopenia with overt hemorrhage is present or prevention of bleeding with a surgical procedure that involves a high risk bleeding is present, platelet transfusion may be reasonable (24).

**Relapse**

A TTP relapse defined as recurrent disease occurring 30 days after reaching therapeutic response has been found to be more likely in patients with ADAMTS13 activity<10% than among patients with ADAMTS13 of 10% or more. Kremer et al noted that the relapse occurred within one year in patients with ADAMTS13 activity <10% as opposed to within 2 years in patients with ADAMTS13 >10%. There was no factor associated with relapse apart from male sex. He also noted that those treated with rituximab following relapse had no other relapses following treatment. Rituximab is being investigated and is not yet the standard treatment for relapse (21).

**Emerging research areas**

Since the discovery of ADAMTS13 as the enzyme implicated in TTP, there is a potential promising therapy in form of recombinant ADAMTS13. This has demonstrated the ability to overcome inhibitory ADAMTS13 autoantibodies in mouse models Inhibition of platelet- Von willebrand factor interaction to prevent micro vascular thrombosis represents an area that is being explored as potential therapeutic target. Other potential therapies that deserve evaluation include Inhibitors of polymerization of VWF multimers.

**CONCLUSION**

Thrombotic Thrombocytopenia is a disease that responds well to treatment but could be fatal if not treated. A high index of suspicion is needed and prompt initiation of therapeutic plasma exchange is needed. ADAMTS13 deficiency is not needed to make diagnosis or make decisions regarding initiation of therapy.

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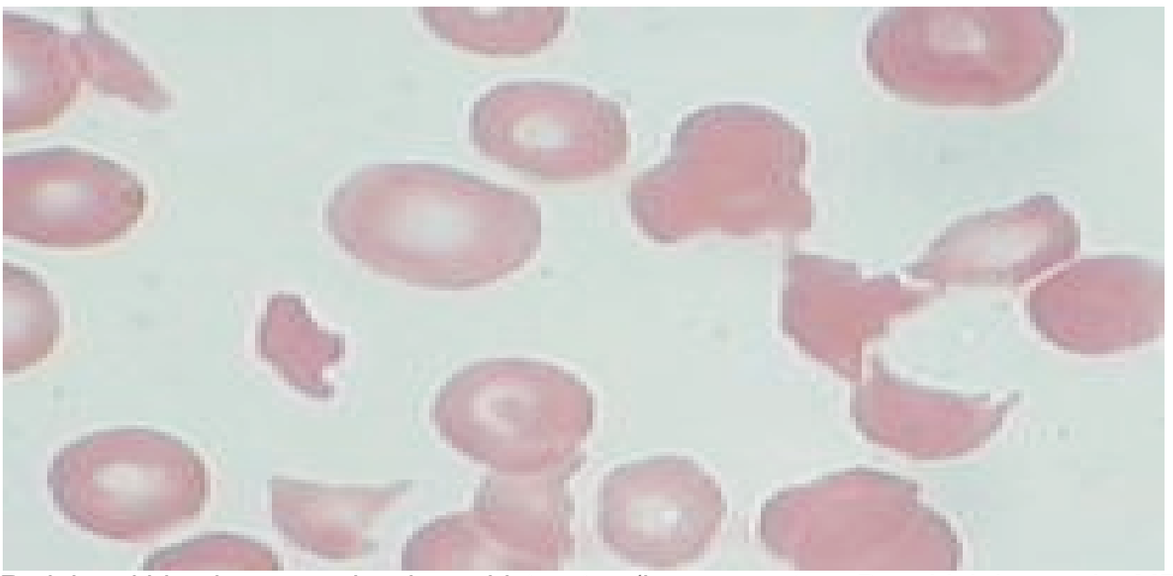
TTP syndromes

| Category | Associated factors | Etiology | Clinical findings** | Clinical course | Treatment |
|---|---|---|---|---|---|
| **Idiopathic TTP** | Female, black race and obesity | Severe ADAMTS13 deficiency is present in many patients | Fever, renal failure is rare. | Severe ADAMTS 13 deficiency is associated with high relapse rate | Plasma exchange is required |
| **Autoimmune disorders** | Female sex, young and middle age adults. | SLE, anti-phospholipid antibody syndrome, scleroderma. | Features of the autoimmune disorderwith renal failure | Has a chronic course with high mortality | Plasma exchange plus immunosuppressive therapy |
| **Pregnancy** | Post-partum or near term | Pregnancy ,ADAMTS13 deficiency may be present. | Differentials include preeclampsia HEELP syndrome | Most subsequent pregnancies are unaffected. | Plasma exchange plus immunosuppressive therapy may be required. |
| **Bloody Diarrhea** | Seen mainly in children | Shiga toxin producing bacteria typically E.coli O157;H7 | Typical in children with renal failure | 12% of the children may die or progress to ESRD | Use supportive care in children, immunosuppression is not necessary |
| **Drug toxicity; Immune mediated** | Older age, female sex is common with quinine. | Most common is quinine, others include clopidogrel and ticlopidine | Sudden onset of systemic symptoms with acute renal failure. | Progressive course with renal failure | Plasma exchange may be appropriate |
| **Drug toxicity; Cumulative &dose dependent** | Duration and dose of drug | Cancer chemotherapy | Insidious and progressive course | High mortality with chronic renal failure | Stop the causative agent |
| **Hematopoietic stem cell transplant** | Unrelated donor,HLA mismatch and active disease, | The precursor may be allogeneic transplant | Thrombotic microangiopathy limited to the kidney | High mortality | Plasmæxchange is unlikely to be of benefit |

** Thrombocytopenia and microangiopathic hemolytic anemia are part of the clinical findings.

Adapted from Thrombotic thrombocytopenic purpura by James N George.



Peripheral bloods smear showing schistocytes (image courtesy Donald J. Innes, Jr., MD)

**Treatment definitions in TTP**

| **Treatment response** | **Improved neurologic deficits with Platelet count >150x10 $^{9}$ for 2 consecutive days accompanied by normalizingLDH** |
|---|---|
| **Durable treatment response** | This is treatment response that has lasted at least 30days after discontinuation of plasma exchange |
| **Exacerbation** | This describes disease recurrence within 30 days after treatment response has been achieved. |
| **Relapse** | This is disease recurrence 30 days or longer after attaining therapeutic response |
| **Refractory disease** | If there is no treatment response by day 30 post treatment and/or no durable treatment response by Day 60. |

Adapted from Sarode *et al*