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Review

Epidemiology, Clinical Presentation, and Treatment of Thrombotic Thrombocytopenic Purpura

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Abstract

Thrombotic Thrombocytopenic Purpura (TTP) is a critical medical condition characterized by thrombocytopenia, hemolytic anemia, and organ damage due to microvascular clotting. This review delves into TTP's epidemiology, clinical presentation, and treatment methods. Advances in understanding the disease's pathophysiology have allowed significant improvements in management strategies. The shift from traditional therapies like therapeutic plasma exchange and corticosteroids to innovative, targeted treatments such as rituximab and caplacizumab marks a significant positive effect. These novel therapies offer less invasive, patient-centric approaches, heralding a new era in TTP treatment. The review also highlights the future directions of TTP research and therapy, emphasizing the need for continued innovation and tailored care strategies. This evolution in TTP management underscores a move towards personalized medicine, focusing on improving outcomes and the quality of life for patients. The dynamic nature of TTP treatment is shifting towards more effective, patient-focused therapeutic options, reflecting the ongoing advancements in the field.

Keywords: *Thrombotic Thrombocytopenic Purpura, Microvascular clotting, Therapeutic plasma exchange, Rituximab, Caplacizumab*

Introduction

Thrombotic thrombocytopenic purpura (TTP) represents a critical health condition, predominantly marked by a significant reduction in the enzyme A Distintegrin and Metalloprotease with ThromboSpondin type 1 repeats, member 13 (ADAMTS13) (1). This enzyme is crucial for breaking down the von Willebrand factor (vWF), a key protein in blood clotting. When ADAMTS13 is deficient, unusually large vWF multimers accumulate, both on the surfaces of endothelial cells and in the bloodstream. These large multimers attract platelets, leading to the formation of platelet-rich clots in the smaller blood vessels. These clots can cause blockages in various organs, leading to ischemia. The central nervous system, heart, and digestive tract are commonly affected, but the condition can impact almost any organ. The disease is indicated by two primary symptoms: consumptive thrombocytopenia and microangiopathic hemolytic anemia. Consumptive thrombocytopenia arises due to the formation of microclots, while microangiopathic hemolytic anemia is a consequence of red blood cells breaking apart as they pass through these clots, exacerbated by increased pressure in these small blood vessels. This process results in the appearance of fragmented red blood cells, known as schistocytes, in the blood smears of patients. Additionally, elevated levels of serum lactate dehydrogenase (LDH) indicate not just hemolysis but also widespread tissue ischemia (2).

Statistically, TTP is more frequent in adults, particularly women, with a 3:1 female to male ratio. Most cases occur between the ages of 30 and 50. It is a rare disease, with around 13 cases per million people and 1 to 2 new cases per million annually (3). Survivors of immune-mediated TTP (iTTP) often experience an array of long-term health issues, including autoimmune diseases, hypertension, and major depression, which may contribute to a reduced life expectancy. More than 90% of TTP cases occur in adults, with a smaller percentage, about 10%, in children (3-5).

TTP is a serious, life-threatening condition if not promptly treated. However, early diagnosis and appropriate treatment have led to remission rates as high as 90% (6). Management strategies initially focused on replenishing the deficient ADAMTS13 through plasma administration. In congenital TTP (cTTP), this involves donor plasma, while in iTTP, it combines removing the patient's plasma and replacing it with donor plasma, a process known as therapeutic plasma exchange (TPE). Corticosteroids were later added to the treatment protocol. Recent advancements in understanding TTP's underlying mechanisms have led to the development of new therapies. These treatments target the production of autoantibodies or the interaction between platelets and vWF multimers. Such advancements are poised to significantly alter the therapeutic approach to TTP in the coming years.

Methodology

This study is based on a comprehensive literature search conducted on December 14, 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the epidemiology, clinical presentation, and treatment of thrombotic thrombocytopenic purpura. There were no restrictions on date, language, participant age, or type of publication.

Discussion

The initial identification of TTP was made by Moschowitz in 1924, who described a condition characterized by a combination of five symptoms: low platelet count (thrombocytopenia), fever, anemia, hemiparesis, and blood in the urine (hematuria). Autopsies of patients showed extensive clotting in the small blood vessels of various organs. In 1982, Moake and colleagues observed unusually large vWF multimers in a patient with recurrent TTP. These large vWF multimers are believed to

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stick to platelets, leading to the blockage of small blood vessels (7).

Epidemiology and natural history of TTP

The incidence of TTP is estimated at 2 cases per million people annually (8). National and regional registries have been crucial in understanding the demographics and clinical characteristics of this rare condition, with key findings summarized in various studies (3, 8-13). It is known that iTTP is more common in adults, typically presenting around the fourth decade (14). Women are more frequently affected, with a female to male ratio ranging from 2 to 3:1. Blacks experience a seven times higher incidence compared to non-blacks (9). TTP in infants usually indicates a congenital form. In the French registry, genetic mutations in ADAMTS13 were found in about 3% of adult-onset TTP patients (18 years and older), often related to a first pregnancy (3). Therefore, it is recommended to assess women who have their first TTP episode during pregnancy for the hereditary form of the disease. iTTP can occur as a primary condition or secondary to other factors like autoimmune diseases such as systemic lupus erythematosus, cancer, infections, pregnancy, and certain medications. These contributing factors were identified in 27% to 69% of patients with thrombotic microangiopathy (TMA) and severe ADAMTS13 deficiency (3, 5, 6). A comprehensive evaluation, including history, physical exam, and lab tests, is essential for all TTP patients to rule out these conditions.

The introduction of plasma exchange significantly reduced TTP mortality, but it remains fatal in 5% to 16% of cases. Compared to other TMAs, TTP patients generally have a better outlook, including shorter hospital stays, quicker recovery of platelet counts, and higher overall survival rates (11).

Approximately 95% of TTP patients normalize their platelet count with acute treatment, and 87% achieve remission. Nonetheless, the decline in platelet count necessitating renewed plasma exchange within 30 days and recurrence of TTP after 30 days are common, occurring in 53% and 30% to 50% of patients, respectively (8). Relapses tend to be less severe, possibly due to earlier detection and intervention, and these patients typically need fewer plasma exchange treatments. However, response, exacerbation, and mortality rates do not significantly differ between initial and relapse episodes (8, 15, 16).

Clinical manifestations and diagnosis of TTP

When diagnosing TTP, it is crucial to consider TTP in all patients displaying microangiopathic hemolytic anemia (MAHA) and thrombocytopenia unless there is a clear alternate cause. While MAHA and thrombocytopenia are common in TTP, the extent of organ involvement can vary greatly **(Table 1)** (14).

Table 1. Summary of the frequency of different clinical features in acute TTP episodes (14).

Clinical presentation	Frequency (%)
MAHA with thrombocytopenia	100
Neurological abnormalities - Major	39-80
Neurological abnormalities - Minor	27-42
Fever	10-32
Gastrointestinal symptoms	35-39
Renal involvement	10-75
Classic pentad	7

MAHA, nearly always present in TTP cases, is characterized by the presence of schistocytes (fragmented red blood cells) in blood smears (17, 18). In healthy individuals, these schistocytes may appear due to blood drawing procedures, but in TTP and other thrombotic microangiopathies (TMAs), they result from mechanical damage to red cells. TTP often features more than 1% schistocytes, although a lower count does not rule out TTP (19). In contrast to other TMAs, TTP patients usually show higher schistocyte percentages. Thrombocytopenia in TTP is typically severe, and

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signs of abnormal bleeding occur in about 46% of patients (6).

TTP can also present atypically, with manifestations like acute pancreatitis or bloody diarrhea, which might be confused with Shiga toxin–associated HUS (20, 21).

Visceral organ involvement varies, with the nervous system being the most commonly affected. Symptoms range from mild, like headaches, to severe, including strokes and seizures (17, 18). Gastrointestinal symptoms are also frequent, and while severe renal dysfunction is rare in TTP, it is more common in older patients. This helps differentiate TTP from hemolytic uremic syndrome (HUS), where severe renal failure is more prevalent.

Clinical prediction scores aid in determining whether to start plasma exchange, a critical decision given the overlap in clinical presentation with other TMAs. The PLASMIC score, based on basic clinical and lab parameters, categorizes patients into low, intermediate, or high risk for severe ADAMTS13 deficiency. This score is useful in guiding initial management, especially where rapid ADAMTS13 testing is not available.

Laboratory diagnosis involves ADAMTS13 activity assays, which measure the enzyme's activity in plasma. These assays have limitations, including interference from high bilirubin levels or other factors. The ADAMTS13 functional inhibitor assay and anti-ADAMTS13 antibody assay further assist in differentiating iTTP from cTTP and confirming the diagnosis.

The diagnostic process for TTP is multifaceted, integrating clinical features, laboratory tests (**Table 2),** and ongoing patient monitoring. In cases of suspected TTP, the PLASMIC score and ADAMTS13 activity measurement are crucial, with immediate plasma exchange recommended for intermediate to high-risk patients. Persistent severe ADAMTS13 deficiency, especially in conjunction with negative antibody assays, may suggest cTTP, prompting further genetic testing. The integration of clinical judgment with these diagnostic tools is essential in confirming the diagnosis of TTP.

Table 2. Laboratory Findings (14).

Laboratory findings	Values
Median platelet count, X10^9/L	10-17
Median creatinine, µmol/L	0.96-1.42
Median LDH, U/L	1107-1750
Median hematocrit, %	20-27

Treatment

Without appropriate treatment, TTP has a mortality rate exceeding 90%. However, since the introduction of plasma-based therapy, the long-term survival rate has drastically improved, potentially exceeding 90%.

Plasma Therapy in TTP

Over 25 years ago, the effectiveness of plasma therapy in TTP was established. A pivotal trial comparing plasma exchange with plasma infusion alone showed significantly higher complete remission rates with plasma exchange. The study did not clarify whether the benefit was due to the removal of a harmful agent or the replacement of a missing factor. Current understanding suggests that plasma exchange is more effective in acquired TTP due to its dual action of removing IgG inhibitors of ADAMTS13 and replenishing the deficient protein. Plasma infusion suffices for patients with genetic ADAMTS13 deficiency. Daily plasma exchange is recommended until the resolution of neurological symptoms and normalization of serum LDH and platelet count, with an additional 2-3 days of treatment thereafter. Most patients respond within 3 weeks, typically within 10 days. However, 20% to 40% may experience disease exacerbation within 30 days of stopping plasma exchange, and about 30% relapse within the first year. Plasma exchange has complication rates as high as 30%, mainly due to issues related to central venous catheter insertion and allergic reactions (2).

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Rituximab

Rituximab, an anti-CD20 antibody, has shown efficacy in reducing autoantibodies and restoring normal ADAMTS13 activity in TTP. When combined with plasma exchange and corticosteroids, it has resulted in more than 90% remission in acute episodes and a reduced relapse rate. However, its long-term impact on relapse rates is uncertain. The use of rituximab during remission is controversial due to inconsistent results in maintaining ADAMTS13 activity (2).

Caplacizumab

Caplacizumab is a novel therapeutic agent targeting the interaction between platelets and vWF to prevent microthrombi formation in TTP. Originally investigated as ALX-0081 and ALX-0681 for intravenous and subcutaneous uses, this bivalent nanobody derived from camelid antibodies is distinctive for its small size, rapid pharmacokinetics, irreversible binding to the A1 domain of vWF multimers, and its ability to avoid cellular or complement activation. Initially researched for myocardial infarction, its effectiveness in TTP was more significant, which shifted the focus of its development. Caplacizumab has been shown to quickly inhibit vWF activity in preclinical iTTP models, leading to rapid platelet count recovery and reduced LDH levels, although it does not affect existing microthrombi (22, 23). Clinical trials have highlighted its efficacy in achieving steady-state concentration through daily administration, and significant reductions in time to platelet count normalization and iTTP-related complications have been observed.

Evidence from real-world applications in France and Germany corroborates its efficacy, with data pointing towards its inclusion in frontline therapy regimens to prevent adverse outcomes. Caplacizumab has been associated with a reduced need for therapeutic plasma exchange (TPE) sessions, decreased plasma volume requirements, and shorter hospital stays (24, 25). Most side effects, such as mild mucocutaneous bleeding, were manageable, and no treatment-related deaths were reported. Studies are ongoing to evaluate its long-term efficacy and safety (26).

Corticosteroids

Corticosteroids are commonly used alongside plasma exchange, particularly in autoimmune TTP. While they show little benefit alone, their anti-inflammatory and immunosuppressive properties make them a logical choice in combination therapy (2).

Splenectomy

Splenectomy, previously a primary treatment for TTP, is now reserved for patients unresponsive to plasma exchange and rituximab. It may decrease relapse frequency in chronic relapsing TTP (2).

Other Treatment Modalities

Several other modalities are considered in addition to primary therapies. Antiplatelet agents, such as aspirin and dipyridamole, have shown limited efficacy, with only about a 10% response rate, and are not recommended to enhance the response to plasma exchange.

Immunosuppressive agents like cyclosporine, cyclophosphamide, and vincristine are utilized in cases where critical illness does not respond to standard treatments. The role of intravenous immunoglobulin remains uncertain due to its unclear effectiveness. Supportive care, an integral part of TTP management, includes administering low-dose aspirin following the recovery of platelet counts, along with folate supplementation and hepatitis B vaccination. In terms of blood product transfusions, red blood cell transfusions are safe for treating symptomatic anemia related to TTP. However, platelet transfusions, once discouraged due to the risk of inducing thrombotic events, are now considered in life-threatening bleeding situations, despite recent studies indicating an increased risk of arterial thrombosis and acute myocardial infarction associated with these transfusions (2).

Future directions

Future directions include the development of treatments like caplacizumab and recombinant

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human ADAMTS13 (rhADAMTS13), potentially making TPE obsolete and enabling more convenient outpatient or home-based care. However, the implementation of these innovations requires a thorough clinical evaluation, especially regarding their cost-effectiveness. Moreover, optimizing post-remission follow-up protocols, including regular monitoring of ADAMTS13 activity and tailored rituximab administration, is essential to prevent relapses and manage patients with inadequate responses to existing therapies. Finally, there is a need to explore whether these advanced treatment regimens can mitigate the incidence of comorbidities associated with long-term TTP management and reduce premature mortality. As the field of TTP treatment continues to progress, ongoing research and the development of new therapeutic strategies will be crucial in writing the future chapters of TTP management.

Conclusion

The management TTP is evolving with a shift towards precision medicine, integrating therapeutic plasma exchange, immunosuppression, and new agents like caplacizumab for improved outcomes. Future strategies, such as caplacizumab and recombinant ADAMTS13, aim to reduce traditional treatment reliance, enhance outpatient care, and necessitate ongoing research for optimizing treatment and follow-up, underscoring the importance of personalized approaches and consistent monitoring.

Disclosure

Conflict of interest

There is no conflict of interest

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Ethical consideration

Non applicable

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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