SZWECH, Jan, MATCZAK, Mateusz, JASIŃSKI, Karol, BRODA, Aleksandra, HOKSA, Kacper, JODŁOWSKI, Krzysztof, DUBNIEWICZ, Ewa, MAJEWSKA, Paula, STASZEK, Alicja and ŁOSKOT, Wiktoria. Clinical presentation and treatment of thrombotic thrombocytopenic purpura - analysis of recent diagnostic and therapeutic methods. Journal of Education, Health and Sport. 2025;79:57872. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.79.57872
https://apcz.umk.pl/JEHS/article/view/57872

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 16.01.2025. Revised: 02.03.2025. Accepted: 02.03.2025. Published: 03.03.2025.

Clinical presentation and treatment of thrombotic thrombocytopenic purpura - analysis of recent diagnostic and therapeutic methods

AUTHORS

Jan Szwech

Masovian Specialist Hospital, ul. Jana Aleksandrowicza 5, 26-617 Radom

ORCID: https://orcid.org/0009-0002-9312-8152

E-mail: szwechjan@gmail.com

Mateusz Matczak

Hospital of the Ministry of Interior and Administration in Lodz, ul. Północna 42, 91–425 Lodz

ORCID: https://orcid.org/0009-0000-9701-406X

E-mail: matczak.mateusz@icloud.com

Karol Jasiński

Provincial Hospital of St. Luke in Tarnow, 33-100 Tarnów, ul. Lwowska 178a

ORCID: https://orcid.org/0009-0004-6845-5199

E-mail: karol.jasinski99@gmail.com

Aleksandra Broda
Hospital of the Ministry of Interior and Administration in Lodz, ul. Północna 42, 91–425 Lodz
ORCID: https://orcid.org/0009-0004-5179-9411
E-mail: aleksandra.d.broda@gmail.com

Kacper Hoksa
Hospital of the Ministry of Interior and Administration in Lodz, ul. Północna 42, 91–425 Lodz
ORCID: https://orcid.org/0009-0007-9832-7093
E-mail: kacper.hoksa98@gmail.com

Krzysztof Jodłowski
Hospital of the Ministry of Interior and Administration in Lodz, ul. Północna 42, 91–425 Lodz
ORCID: https://orcid.org/0009-0003-9041-2091
E-mail: lek.krzysztofjodlowski@gmail.com

Ewa Dubniewicz
Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Lodz
ORCID: https://orcid.org/0009-0007-4191-6794
E-mail: edubniewicz@gmail.com

Paula Majewska
Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Lodz
ORCID: https://orcid.org/0009-0003-7934-397X
E-mail: majewskapaula14@gmail.com

Alicja Staszek
Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Lodz
ORCID: https://orcid.org/0009-0007-0323-8697
E-mail: staszekalicja0@gmail.com

Wiktoria Łoskot
University Clinical Hospital No. 2 of the Medical University of Lodz: Łódź, ul. Stefana Żeromskiego 113, 90-549 Łódź, PL
ORCID: https://orcid.org/0009-0001-5392-4835
E-mail: wiktoria.loskot98@gmail.com

Corresponding author:
Jan Szwech
E-mail: szwechjan@gmail.com

Abstract

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare hematologic disease caused by reduced ADAMTS13 (A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) activity. This disease can lead to a variety of symptoms and be difficult to diagnose. Correct diagnosis is very important to reduce mortality and initiate appropriate treatment. New treatment methods may offer better chances of survival from this potentially fatal disease.

Aim of the study

The aim of the article was to evaluation of different diagnostic pathways and the effectiveness of treatment of thrombotic thrombocytopenic purpura. Drawing the attention of the medical community to the discussed issue. Highlighting the importance of the issue due to the high mortality rate in the absence of treatment.

Materials and methods

The article was prepared by analyzing multiple databases, including PubMed, Google Scholar, and Elsevier covering the period from 2018 to 2024.

Conclusion

Thrombotic thrombocytopenic purpura (TTP) is a rare but serious disease, especially if appropriate treatment is not initiated. There is need a special attention to TTP, as treatment

needs to begin even before a definitive diagnosis is established, due to the lengthy wait for laboratory results. Although modern biological drugs are available, further research is needed to streamline treatment methods and provide new therapeutic opportunities.

Key words: thrombotic thrombocytopenic purpura, thrombocytopenia, ADAMTS13

1. TTP etiopathology and epidemiology

TTP can arise from different pathophysiological mechanisms, being either congenital or acquired. In the congenital form of TTP (congenital TTP; cTTP), mutations in the *ADAMTS13* gene are responsible for the disease. This type is inherited in an autosomal recessive manner. In the acquired form, the disease involves the production mainly immunoglobulin G type autoantibodies that inhibit ADAMTS13 activity, reffered to as immune-mediated thrombotic thrombocytopenic purpura (iTTP). Deficiency of ADAMTS13 leads to uprisings unusually large Von Willebrand Factor (VWF) multimers. VWF platelet-binding affinity depends on its molecular weight, with large VWF multimers more likely to form platelet clots than normal ones. In TTP, low ADAMTS13 activity causes Unusually Large Von Willebrand Factor (UL-VWF) multimers to remain uncleaved in the bloodstream. This promotes platelet adhesion and thrombosis in microvessels, leading to damage in organs like the kidneys, brain and others. [1,2,17]

ADAMTS13 plays a main role in the regulation of VWF during hemostasis, but requires further scientific research into the mechanisms of its function, regulation in the body, and potential therapeutic applications. [13] The first description of a case of TTP was described over 100 years ago by Dr. Eli Moschcowitz, although the term thrombotic thrombocytopenic purpura was used for the first time in 1947. [22]

Thrombotic thrombocytopenic purpura (TTP) is predominantly classified as immune TTP (iTTP), accounting for over 95% of cases, while congenital TTP (cTTP) is much rarer, representing less than 5%. Overall, this condition is extremely uncommon, affecting only 2 to 6 people per million. [3] Due to the rarity of the disease and its wide range of symptoms, epidemiological data are often inconsistent and limited. [6] There are significant disparities in the reported prevalence of the disease. For example, studies estimate it to be 13 cases per million in France, compared to 1 to 2.7 cases per million in the USA. Slightly more women

than men are affected by both types of disease. The proportion of male patients varies widely between studies, ranging from 7% to 55.6%, female sex and African ancestry is a risk factor of the iTTP. [4,29]

It is a dangerous disease - acute attacks of the disease are associated with a 90% mortality rate if appropriate treatment is not initiated. Mortality ranges from 10 to 20% in the case of treatment. Mortality is highest within the first six months following diagnosis. Older patients are at greater risk due to longer episodes of iTTP attacks and the presence of additional comorbidities like myocardial infarction, chronic kidney disease, cancer. In younger patients, disease episodes are associated with lower mortality, typically due to the absence of comorbidities and the lack of need for treatments unrelated to TTP. [6]

We can distinguish between primary iTTP, where are no any factor that may trigger disease, and secondary iTTP. There are many factors that can be responsible for the development of secondary iTTP, such as: pregnancy or infection (main causes), but also autoimmune diseases, drugs (e.g. Ticlopidine, oral contraception), vaccines. [4] Primary iTTP was more likely to result in a more severe disease course, such as lower platelet counts <20 x10^9/L, gastrointestinal symptoms, or neurological impairment. [8]

2. Diagnosis and symptoms

Diagnosing TTP is challenging due to limited access to ADAMTS13 testing and overlapping clinical symptoms with other thrombotic microangiopathies (TMA). It should be differentiated from disseminated intravascular coagulation (DIC), where APTT and PT are prolonged, and fibrinogen levels are decreased, unlike in TTP, where these remain normal. TTP must also be distinguished from typical and atypical haemolytic uraemic syndrome (aHUS), as well as drug-induced TMA. In cases of TMA, all other potential causes must be excluded. [8,29]

TTP is still an underdiagnosed disease and therefore requires special attention because delay in treatment may result in increased mortality. [18]

The main symptoms of TTP are: thrombocytopenia (<100 x10^9/L – usually 10-30x10^9/L), hemolytic anemia (80-100 g/L), renal failure - usually creatinine below 2mg/dL, fever, fluctuating neurological status (e.g) confusion, delirium). These symptoms occur in other TMA so the gold standard for diagnosis is the assessment of ADAMTS13 activity. [9] The pentad of these symptoms occurred only in 40% patients diagnosed with TTP. [15] Hemolytic anemia is characterized by the presence of schistocytes. These cells can occur among healthy

people, most likely they arise during damage caused by blood collection, while in the case of thrombotic microangiopathies (including TTP), their number is increased and they arise due to mechanical damage caused by microthrombi. An increase in schistocytes can occur after the onset of symptoms. Other symptoms of hemolytic anemia include: decreased haptoglobin, hyperbilirubinemia, increased lactate dehydrogenase (LDH). [8]

The occurrence of only thrombocytopenia and hemolytic anemia should prompt the performance of ADAMTS13 activity test. ADAMTS13 activity titer below 10% will allow for the diagnosis of TTP. When ADAMTS13 activity levels oscillates between 10% and 20%, the diagnosis can be uncertain. In such challenging cases, assessing the conformation of ADAMTS13 helps in identifying iTTP. [8, 15]

The plasma protease ADAMTS13 can exist in various conformations. Under physiological conditions, it predominantly adopts a "closed" conformation, which can be activated by different factors. Mouse antibodies have been developed that, by binding to the C-terminus of ADAMTS13, enable activation of the protease rather than inhibition. This led to the hypothesis that these antibodies may induce a shift to the "open" conformation.[17]

There are tools available to help clinicians make rapid decisions about diagnostics and ordering treatment before receiving ADAMTS13 activity result. These include two scales that assess the likelihood of iTTP: the French score and the PLASMIC score. They incorporate clinical and laboratory results such as creatinine and platelet count. *[3, 9]*

There are known two types of antibodies responsible for binding to ADAMTS13: neutralizing (inhibitor) and non-neutralizing (binding). Neutralizing antibodies inhibits protease in vitro, whereas non-neutralizing only binds to the protease without changing its activity. In clinical practice, only the neutralizing antibodies are measured while the binding antibodies are studied exclusively for scientific purposes. Most patients have high titers of inhibitor which can be measured. However, if these antibodies are not detected and the patient exhibits symptoms of the disease, iTTP should not be ruled out, as non-neutralizing antibodies, undetectable by standard tests (ELISA test), may be present. For this reason, in 10-15% of patients with iTTP, the antibody test result will be false negative.[2,9]

In pediatric patients with symptoms of TTP, the presence of the congenital form of TTP should be particularly considered, and *ADAMTS13* gene sequencing should be performed. Mutation of this gene may cause reduced ADAMTS13 activity, without the presence of antibodies. In case of poor response to standard treatment of iTTP, the possibility of

congenital TTP should be suspected. [9] In newborns with jaundice that does not respond to treatment, a serological conflict should first be ruled out, followed by considering the possibility of TTP. [7]

Recurrent strokes despite anticoagulant treatment may indicate the development of cTTP, even in adulthood. [12] Factors such as aPTT, troponins, LDH, albumin levels, as well as markers related to inflammation, such as the assessment of complement components like sC5b-9, can aid in identifying patients who require more intensive treatment. [19] Antibodies can be a marker of relapses in the remission phase. For this reason, it is worth testing for autoantibodies even in the latency phase and assessing the need for drugs or the risk of remission. [16]

3. Treatment

Treatment depends on the type of TTP. In the immune form, plasmapheresis is recommended to remove antibodies from the body, which one inhibit the ADAMTS13. In contrast, cTTP requires plasma infusions. These treatments have significantly reduced mortality rates from 90% to as low as 10%. [4,9,29]

Patients with a high probability of disease, as indicated by e.g. the PLASMIC score, should receive treatment with plasma therapy as soon as possible. [23]

Patients recovering from an acute episode of iTTP are at risk of relapse. To minimize this risk, treatment includes immunosuppressive drugs (e.g., glucocorticosteroids, cyclosporine, cyclophosphamide) and biological agents such as rituximab and caplacizumab. These medications act indirectly, helping to further control the symptoms of the disease.

Plasma exchange is often initiated as a first-line treatment for TTP, which is typically diagnosed based on clinical symptoms. Much less commonly, cryoprecipitate-poor plasma (CPP) has also been used in treatment and has shown even better outcomes in some cases. However, its limited availability has made it a less common option. [27] The purpose of plasma infusion is to supply the patient with the deficient ADAMTS13 protein, which has a half-life of approximately 5 days, necessitating repeated plasma infusions. In the case of cTTP, it produces similar effects to rhADAMTS13. [28]

Corticosteroids as immunosuppressive drugs (to suppress production of autoantibodies) are used in the treatment of iTTP the dose reduction regimen is determined based on the platelet

count and the results of the ADAMTS13 test, most often oral prednisolone is used at a dose of 1 mg/kg/day. [2]

Caplacizumab, a single-domain antibody, acts on the A1 domain of von Willebrand factor (VWF) to inhibit platelet adhesion and microthrombus formation. It received approval for routine clinical use in 2018. Patients receiving caplacizumab achieve platelet count normalization more quickly, require shorter hospital stays, and need fewer plasma exchange procedures. The use of this medicine may be associated with side effects, the most common of which are mucocutaneous bleeding, that resolved without intervention. [4,9,21.23,26] This medicine can also be safely used in children. [25]

Rituximab is an anti-human CD20 chimeric monoclonal antibody that suppresses ADAMTS13 inhibitor production by depleting B lymphocytes. Since Rituximab has a different mechanism of action compared to glucocorticoids or plasma exchange, it may be effective in patients resistant to these, treatments particularly in those with other autoimmune diseases, by reducing the number of inhibitory antibodies through the depletion of B lymphocytes. [19]

This drug has become a supportive therapy for first-line treatment. It is a safe medication with few side effects. The most common reactions are infusion-related, such as pyrexia, decreased blood pressure, urticaria, and hypoxemia, which respond well to premedication with an antihistamine. [2, 22] Rituximab is typically dosed similarly to its use in lymphoma patients; however, lower doses have also demonstrated comparable effectiveness.[23] The use of rituximab in relapse prevention has shown very good results, leading to the widespread adoption of rituximab for this purpose. It is important to note that approximately 15% of patients may be resistant to this drug or exhibit only a transient response. [5,22]

Drugs used as immunosuppression also included cyclosporine A (used when the patient was resistant to rituximab), bortezonib, or daratumumab. Surgical treatment in the form of splenectomy was also undertaken, which brought similar effects to the use of rituximab, but is a procedure with higher risk. [5,18]

There is a lack of a unified treatment strategy in the upcoming era of anti-vWF therapy, therefore further research is needed to standardize the treatment. [27]

Recombinant humanized ADAMTS13 (rhADAMTS13)

This is a new opportunity for treatment outcomes, especially for cTTP patients. This drug can also be used in patients with iTTP, but requires higher doses due to complete antibody saturation.[18] RADAMTS13 also shows promise for improving outcomes in long-term treatment and reducing the number of, for example, recurrent strokes. Treatment with recombinant ADAMTS13 is associated with a lower incidence of adverse effects compared to standard treatment, and these effects are typically mild or moderate. Additionally, recombinant ADAMTS13 treatment results in significantly higher ADAMTS13 activity in the serum (around 100%) compared to standard therapy. This drug has also been used in diseases such as arterial thrombosis (stroke, heart attack) and has shown good results. This brings hope for a new anticoagulant drug, but more research is needed.[12, 13, 14]

In the future, the use of rADAMTS13 may make it possible to implement regimens without the use of plasma therapy, which depends on donor availability and may not always be available in optimal quantities. [22]

Research is emerging that utilizes mRNA technology to deliver ribonucleic acid encoding ADAMTS13 to hepatocytes, which then translate this code into the required protein. The mRNA encoding the M5 variant of ADAMTS13, which may be resistant to inhibitory antibodies and exhibit a longer duration of action, has so far been studied in mice. [24]

4. Complications of disease

Complications of the disease can affect various systems, most commonly the cardiovascular system (manifesting as TIA, stroke, or myocardial infarction), the nervous system (e.g., depression, cognitive impairments), autoimmune diseases, and the excretory system. Late complications are the primary cause of mortality, as most appropriately treated patients survive the acute phase of iTTP. [4,5,6]

The risk of stroke in individuals who have survived an iTTP episode is five times higher than in the general population. Low ADAMTS13 activity following an acute episode is a significant risk factor for the aforementioned conditions, highlighting the importance of monitoring ADAMTS13 activity in these patients. [4,5,6]

Relapses of iTTP occur in 30-50% of patients, and these recurrences are often more resistant to treatment. The most significant risk factor for relapse is low ADAMTS13 activity. Other

potential factors include male gender, blood group O, black race, previous relapses, and younger age. [4,5,6]

5. TTP in pregnancy

Pregnancy may be a factor that will lead to the manifestation of iTTP as well as cTTP. In women of reproductive age who are at high risk of the disease, ADAMTS13 should be monitored, because studies report that low levels of enzyme activity before pregnancy will result in a high probability of disease recurrence during pregnancy. There is a possibility of recurrence of the disease in subsequent pregnancies, in women the treatment is preferred to plasma exchange and a small dose of corticosteroids although rituximab can be used during pregnancy; however, it may lead to a reduction in fetal B lymphocyte count. Therefore, rituximab should generally be avoided. TTP can be triggered by pregnancy, with symptoms, such as acute kidney injury (AKI), most often appearing during the second or third trimester. [5, 11, 30, 31]

1.6 Conclusion

Thrombotic thrombocytopenic purpura is a life-threatening but treatable condition. Advances in understanding its pathophysiology and the development of novel therapeutic options, such as caplacizumab and recombinant ADAMTS13, have improved outcomes. However, challenges remain in early diagnosis, relapse prevention, and treatment standardization. Continued research is needed to optimize management strategies and reduce long-term complications, particularly in high-risk populations, including pregnant women and patients with recurrent disease. Effective monitoring of ADAMTS13 activity and personalized treatment approaches remain critical in reducing morbidity and mortality.

Disclosure

Authors do not report any disclosures

Authors' contribution:

Conceptualization: Paula Majewska, Kacper Hoksa, Karol Jasiński

Methodology: Ewa Dubniewicz, Mateusz Matczak, Alicja Staszek, Kacper Hoksa

Investigation: Krzysztof Jodłowski, Aleksandra Broda, Wiktoria Łoskot, Jan Szwech, Alicja Staszek

Software: Ewa Dubniewicz, Wiktoria Łoskot, Jan Szwech,

Formal analysis: Kacper Hoksa, Mateusz Matczak, Aleksandra Broda
Writing: Jan Szwech
Resources: Paula Majewska, Alicja Staszek, Mateusz Matczak
Supervision: Wiktoria Łoskot, Krzysztof Jodłowski

All authors have read and agreed with the published version of the manuscript.

Funding statement:
The study did not receive special funding.

Institutional Review Board Statement:
Not applicable.

Informed Consent Statement:
Not applicable.

Data Availability Statement:
Not applicable.

Conflict of Interest Statement:
The authors declare no conflict of interest.

References

1. Du, P., Cristarella, T., Goyer, C., & Moride, Y. (2024). A Systematic Review of the Epidemiology and Disease Burden of Congenital and Immune-Mediated Thrombotic Thrombocytopenic Purpura. In *Journal of Blood Medicine* (Vol. 15, pp. 363–386). Dove Medical Press Ltd. https://doi.org/10.2147/JBM.S464365
2. Matsumoto, M., Miyakawa, Y., Kokame, K., Ueda, Y., Wada, H., Higasa, S., Yagi, H., Ogawa, Y., Sakai, K., Miyata, T., Morishita, E., & Fujimura, Y. (2023). Diagnostic and treatment guidelines for thrombotic thrombocytopenic purpura (TTP) in Japan 2023. *International Journal of Hematology*, *118*(5), 529–546. https://doi.org/10.1007/s12185-023-03657-0

3. Zheng, X. L., Vesely, S. K., Cataland, S. R., Coppo, P., Geldziler, B., Iorio, A., Matsumoto, M., Mustafa, R. A., Pai, M., Rock, G., Russell, L., Tarawneh, R., Valdes, J., & Peyvandi, F. (2020). ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*, *18*(10), 2486–2495. https://doi.org/10.1111/jth.15006
4. Du, P., Cristarella, T., Goyer, C., & Moride, Y. (2024). A Systematic Review of the Epidemiology and Disease Burden of Congenital and Immune-Mediated Thrombotic Thrombocytopenic Purpura. In *Journal of Blood Medicine* (Vol. 15, pp. 363–386). Dove Medical Press Ltd. https://doi.org/10.2147/JBM.S464365
5. Selvakumar, S., Liu, A., & Chaturvedi, S. (2023). Immune thrombotic thrombocytopenic purpura: Spotlight on long-term outcomes and survivorship. In *Frontiers in Medicine* (Vol. 10). Frontiers Media S.A. https://doi.org/10.3389/fmed.2023.1137019
6. Adeyemi, A., Razakariasa, F., Chiorean, A., & de Passos Sousa, R. (2022). Epidemiology, treatment patterns, clinical outcomes, and disease burden among patients with immune-mediated thrombotic thrombocytopenic purpura in the United States. *Research and Practice in Thrombosis and Haemostasis*, *6*(6). https://doi.org/10.1002/rth2.12802
7. George, J. N. (2022). Hereditary thrombotic thrombocytopenic purpura: The risk for death at birth. In *Research and Practice in Thrombosis and Haemostasis* (Vol. 6, Issue 8). John Wiley and Sons Inc. https://doi.org/10.1002/rth2.12840
8. Chiasakul, T., & Cuker, A. (n.d.). *Clinical and laboratory diagnosis of TTP: an integrated approach*. https://doi.org/10.1182/asheducation-2018.1.530
9. Karsenty, C. L., Kirk, S. E., Helber, H. L., Esquilin, J. M., Despotovic, J. M., & Grimes, A. B. (2022). Molecular Diagnosis Is Vital to the Accurate Classification and Management of Thrombotic Thrombocytopenic Purpura in Children. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.836960
10. Lämmle, B. (2023). A third form of thrombotic thrombocytopenic purpura? In *Haematologica* (Vol. 108, Issue 2, pp. 299–300). Ferrata Storti Foundation. https://doi.org/10.3324/haematol.2022.281095
11. Shah, S., & Verma, P. (2023). Pregnancy-Related Acute Kidney Injury: Do We Know What to Do? In *Nephron* (Vol. 147, Issue 1, pp. 35–38). S. Karger AG. https://doi.org/10.1159/000525492

12. Beltrami-Moreira, M., & DeSancho, M. T. (2022). Delayed diagnosis of congenital thrombotic thrombocytopenic purpura in a patient with recurrent strokes. *Journal of Thrombosis and Thrombolysis*, *53*(3), 734–738. https://doi.org/10.1007/s11239-021-02629-7
13. DeYoung, V., Singh, K., & Kretz, C. A. (2022). Mechanisms of ADAMTS13 regulation. In *Journal of Thrombosis and Haemostasis* (Vol. 20, Issue 12, pp. 2722–2732). John Wiley and Sons Inc. https://doi.org/10.1111/jth.15873
14. Scully, M., Antun, A., Cataland, S. R., Coppo, P., Dossier, C., Biebuyck, N., Hassenpflug, W.-A., Kentouche, K., Knöbl, P., Kremer Hovinga, J. A., López-Fernández, M. F., Matsumoto, M., Ortel, T. L., Windyga, J., Bhattacharya, I., Cronin, M., Li, H., Mellgĺrd, B., Patel, M., … Wang, L. T. (2024). Recombinant ADAMTS13 in Congenital Thrombotic Thrombocytopenic Purpura. *New England Journal of Medicine*, *390*(17), 1584–1596. https://doi.org/10.1056/nejmoa2314793
15. Bonnez, Q., Sakai, K., & Vanhoorelbeke, K. (2023). ADAMTS13 and Non-ADAMTS13 Biomarkers in Immune-Mediated Thrombotic Thrombocytopenic Purpura. In *Journal of Clinical Medicine* (Vol. 12, Issue 19). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/jcm12196169
16. Dainese, C., Valeri, F., Bruno, B., & Borchiellini, A. (2023). Anti-ADAMTS13 Autoantibodies: From Pathophysiology to Prognostic Impact—A Review for Clinicians. In *Journal of Clinical Medicine* (Vol. 12, Issue 17). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/jcm12175630
17. Halkidis, K., & Zheng, X. L. (2022). ADAMTS13 conformations and mechanism of inhibition in immune thrombotic thrombocytopenic purpura. In *Journal of Thrombosis and Haemostasis* (Vol. 20, Issue 10, pp. 2197–2203). John Wiley and Sons Inc. https://doi.org/10.1111/jth.15822
18. Coppo, P., Cuker, A., & George, J. N. (2019). Thrombotic thrombocytopenic purpura: Toward targeted therapy and precision medicine. In *Research and Practice in Thrombosis and Haemostasis* (Vol. 3, Issue 1, pp. 26–37). Blackwell Publishing Ltd. https://doi.org/10.1002/rth2.12160
19. Staley, E. M., Cao, W., Pham, H. P., Kim, C. H., Kocher, N. K., Zheng, L., Gangaraju, R., Lorenz, R. G., Williams, L. A., Marques, M. B., & Zheng, X. L. (2019). Clinical factors and biomarkers predict outcome in patients with immune-mediated thrombotic thrombocytopenic purpura. *Haematologica*, *104*(1), 166–175. https://doi.org/10.3324/haematol.2018.198275

20. Watanabe, A., Shiseki, M., Oishi, M., Kobayashi, M., Oshima, S., Osanai, S., Ryuzaki, M., Izuka, Y., Tanaka, N., Ishiyama, M., Shinohara, A., Kazama, H., Hagiwara, S., Yoshinaga, K., & Tanaka, J. (2021). Successful Rituximab treatment in thrombotic thrombocytopenic purpura patients complicated by other autoimmune disorders: Two case reports. *Internal Medicine*, *60*(17), 2859–2862. https://doi.org/10.2169/internalmedicine.6387-20
21. Scully, M., Cataland, S. R., Peyvandi, F., Coppo, P., Knöbl, P., Kremer Hovinga, J. A., Metjian, A., de la Rubia, J., Pavenski, K., Callewaert, F., Biswas, D., de Winter, H., & Zeldin, R. K. (2019). Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. *New England Journal of Medicine*, *380*(4), 335–346. https://doi.org/10.1056/nejmoa1806311
22. Graça, N. A. G., Joly, B. S., Voorberg, J., Vanhoorelbeke, K., Béranger, N., Veyradier, A., & Coppo, P. (2022). TTP: From empiricism for an enigmatic disease to targeted molecular therapies. In *British Journal of Haematology* (Vol. 197, Issue 2, pp. 156–170). John Wiley and Sons Inc. https://doi.org/10.1111/bjh.18040
23. Mazepa, M. A., Masias, C., & Chaturvedi, S. (2019). *How targeted therapy disrupts the treatment paradigm for acquired TTP: the risks, benefits, and unknowns*.
24. Liu-Chen, S., Connolly, B., Cheng, L., Subramanian, R. R., & Han, Z. (2018). MRNA treatment produces sustained expression of enzymatically active human ADAMTS13 in mice. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-26298-4
25. Taylor, A., Keogh, L., Dickens, E., Dutt, T., Grainger, J., Gregory, R., Mapplebeck, C., Richards, M., Stokley, S., Salta, S., Taylor, T., & Scully, M. (2024). Caplacizumab in pediatric immune thrombotic thrombocytopenic purpura: the UK TTP Registry experience. *Blood Advances*, *8*(17), 4563–4567. https://doi.org/10.1182/bloodadvances.2024013488
26. Lee, H. T., Park, U. B., Jeong, T. J., Gu, N., Lee, S. H., Kim, Y., & Heo, Y. S. (2021). High-resolution structure of the vWF A1 domain in complex with caplacizumab, the first nanobody-based medicine for treating acquired TTP. *Biochemical and Biophysical Research Communications*, *567*, 49–55. https://doi.org/10.1016/j.bbrc.2021.06.030
27. Mazepa, M. A., Raval, J. S., Brecher, M. E., & Park, Y. A. (2018). Treatment of acquired Thrombotic Thrombocytopenic Purpura in the U.S. remains heterogeneous: Current and future points of clinical equipoise. *Journal of Clinical Apheresis*, *33*(3), 291–296. https://doi.org/10.1002/jca.21600

28. Taylor, A., Vendramin, C., Oosterholt, S., della Pasqua, O., & Scully, M. (2019). Pharmacokinetics of plasma infusion in congenital thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*, *17*(1), 88–98. https://doi.org/10.1111/jth.14345
29. Sukumar, S., Lämmle, B., & Cataland, S. R. (2021). Thrombotic thrombocytopenic purpura: Pathophysiology, diagnosis, and management. In *Journal of Clinical Medicine* (Vol. 10, Issue 3, pp. 1–24). MDPI. https://doi.org/10.3390/jcm10030536
30. Coppo, P., & Veyradier, A. (2020). TTP in the setting of pregnancy: The story still has to be written. In *Journal of Thrombosis and Haemostasis* (Vol. 18, Issue 10, pp. 2775–2777). Blackwell Publishing Ltd. https://doi.org/10.1111/jth.15030
31. Fakhouri, F., Scully, M., Provôt, F., Blasco, M., Coppo, P., Noris, M., Paizis, K., & Kavanagh, D. (n.d.).*Management of thrombotic microangiopathy in pregnancy and postpartum: report from an international working group* DOI: 10.1182/blood.2020005221