



Closing the Gap

A roadmap to achieving optimal care for **Thrombotic Thrombocytopenic Purpura**



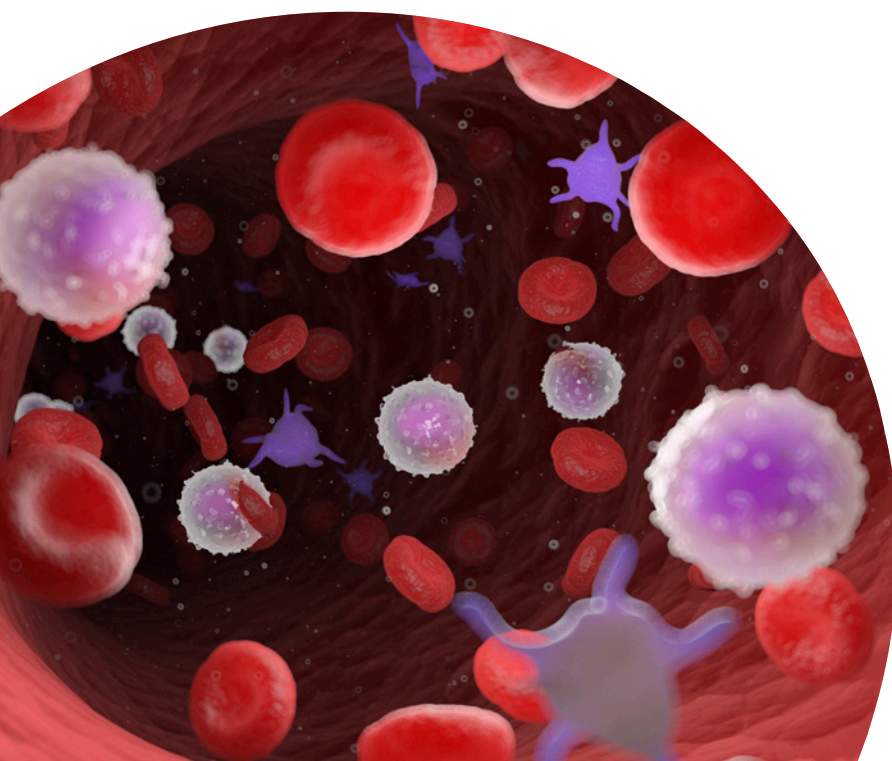
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Date of preparation: December 2023

This Expert Policy Paper has been initiated, organised and funded by Takeda and agreed upon by a working group of key experts with an interest in TTP

C-ANPROM/EUC/TTP/0004

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Foreword

As a patient who was diagnosed with Thrombotic Thrombocytopenic Purpura (TTP) aged 24, I had often felt uninformed and isolated with this extra-rare blood disorder that had impacted my life suddenly and very seriously. The impact of TTP affected my personality, my relationships, and my life trajectory*.

As a result of the diagnosis and the feelings of isolation I established a patient support group on a not-for-profit basis. The aim was to create a network of patients so that we could benefit from one another's understanding of this unusual situation. Twenty Five years later and as a registered charity in England, TTPNetwork now provides over 800 patients and their families with information, advocacy and peer support. Our charity helps those people to feel more in control of this lifelong condition and their own lives.

When I was approached to work with others who deliver similar services across Europe, Canada and Israel, I was curious as to what could be done to improve patient knowledge and access to care, given the low incidence of TTP, and the seemingly slow appetite for improvement among health care settings outside of the UK. In England we are incredibly fortunate to have a team of TTP specialists who have been committed to improving care for TTP patients and who, with the support of NHS England and TTPNetwork have designated eleven TTP Specialist Centres across the country. Centrally commissioned and led by University College Hospital London, these centres deliver services based on a specification that has been nationally agreed. The centres meet regularly to review activity and are required to report back centrally to the commissioner on their work.

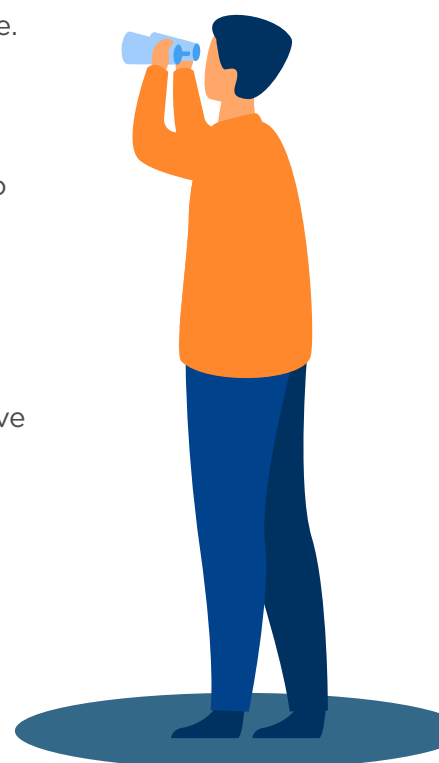
Early assessment of the centres (that have only been operational at the most, a year), show us that patients are pleased with the person-centred care and the wrap around support that includes a Clinical Specialist Nurse and access to psychological services. My wish is that all patients, across the globe, regardless of ethnicity, wealth or class, have access to this same level of high-quality care. The following roadmap, as you will read, puts us on the path to making this a reality. The recommendations over the following pages gives us an exciting opportunity to raise the profile of TTP and to work on raising the status of patients in healthcare settings, and enabling them to feel informed. It can also help in raising awareness among healthcare professionals.

Make no mistake, this is just the beginning. There is much work to be done and it will take time, but if we work as an international community, as the representatives who worked on this document have done, and we work with purpose, we can achieve great things. With these recommendations we can strive for improved health and social outcomes for those diagnosed with TTP and we can strive to minimise deaths from TTP.



Jo McIntyre
Founder, TTPNetwork

*Individual experiences may vary



Executive summary

Thrombotic thrombocytopenic purpura (TTP) is an ultra-rare but life-threatening thrombotic disorder that can lead to significant morbidity and mortality if not diagnosed and treated promptly. The condition causes small blood clots in blood vessels throughout the body, disrupting normal blood flow and supply, and leading to bleeding underneath the skin (bruising), impaired coagulation, damage to the red blood cells (which carry oxygen through the body), and organ dysfunction and failure (from lack of blood supply). There are 2 types of TTP: congenital (cTTP) and immune-mediated (acquired) (iTTP).ⁱ

The estimated annual incidence of TTP ranges from 3 to 11 cases per million people, and the disease is more common in older adults. TTP is associated with a high burden of disease, including significant comorbidities such as neurological deficits, renal impairment, and cardiovascular events, as well as a high mortality rate, even when appropriately treated.ⁱⁱ

Several barriers to optimal care can hinder the management of TTP. Delays in diagnosis are common, as the symptoms of TTP can be nonspecific and similar to those of other disorders. In addition, healthcare providers may lack awareness and knowledge about TTP, leading to misdiagnosis or delayed treatment. Access to specialised care centres with expertise in managing TTP can also be limited, particularly in rural or underserved areas. Finally, the optimal duration of treatment and the role of newer therapies are still being debated, and there is a lack of consensus on the most effective management of TTP.

In this roadmap, the experts involved in the Expert Policy Forum on TTP explore these barriers in-depth and discuss potential solutions to improve the management of TTP and ultimately enhance patient outcomes. These solutions include increasing awareness and education about TTP among healthcare providers, improving access to specialised care centres, and conducting further research to clarify the optimal management of the disease. A multidisciplinary approach to care, involving haematologists, neurologists, and other specialists as needed, is also emphasised. By addressing these barriers, it is hoped that the diagnosis and management of TTP can be improved, the burden of disease can be reduced, and patient outcomes can be improved.



Joe Brice

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Recommendations*



FOR NATIONAL HEALTH SYSTEMS

National health systems should **implement multidisciplinary and holistic teams** for rare diseases, including TTP. This multidisciplinary team should include at least haematology, neurology, nephrology, psychology, and intensive care services. Paediatric and obstetrics and gynaecology services should be part of this team in case the patient is a child or a woman.

National health systems should **recognise the key role medical societies and patient associations** play during the TTP patient journey and provide them the necessary tools and resources to work together to advance research, education, and advocacy efforts related to TTP.

National health systems should **create opportunities for HCPs to further develop their knowledge** of rare diseases, including TTP, as well as create or expand network of specialists, i.e., the European Reference Networks, to support referrals, education of both specialists and non-specialist HCPs, and knowledge transfer amongst the healthcare community.

National health systems should **create, implement, and support access to referral and expert centres** to ensure TTP patient optimal care, by engaging and supporting EU-wide initiatives, such as the European Reference Networks. Referral centres would not only ensure patient care, but would also support investigation and access to clinical trials, advancing research for TTP.

*The recommendations cited here are based on the output of discussions amongst the TTP Expert Policy Forum members and are not intended to be exhaustive



FOR PATIENT ORGANISATIONS

Patient organisations should **empower patients** with TTP by providing them with appropriate information and by improving their understanding of the disease and its management. The patient community should be supported with key volunteers (patients, healthcare professionals) that would act as a disease spokesperson, having the right knowledge and information about TTP, to whom patients can turn for information, advice, and support.

Patient organisations should leverage and actively support the **international TTP Awareness Day** in September to raise awareness of TTP among the general population.

Recommendations *(cont'd)*



FOR MEDICAL SOCIETIES

Medical societies should **raise awareness amongst HCPs** about triggering conditions and medication for TTP, including the management of these in the dedicated guidelines and recommendations for treatment and care of TTP.

Medical societies should **develop, review, and regularly update clinical guidelines** for disease management and care of iTTP (immune-mediated TTP) and cTTP (congenital TTP) to ensure key developments are taken into account, as well as ensure experts are aligned on definitions and support the approach to TTP as a chronic disease.

Medical societies must ensure that **regular monitoring of ADAMTS13** is included in their guidelines for disease management and care of TTP. Moreover, national health system planners and decision-makers must guarantee appropriate funding to support widespread access to diagnostic and monitoring equipment.



FOR POLICYMAKERS

Policymakers and medical societies should **promote and leverage the current initiatives at international level**, such as the European Reference Networks, to improve participation in data registries to support research and improve patient care.

Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is an ultra-rare disorder which if not promptly diagnosed and managed has significant morbidity and mortality rate.ⁱⁱⁱ Awareness of the disease is limited outside of the patient community, even among healthcare professionals (HCPs), leading to delays in access to diagnosis, treatment, and care.^{iv}

The Expert Policy Forum on TTP brings together healthcare professionals and patient representatives from several countries within Europe, Canada, and Israel to discuss challenges, identify solutions, and develop this roadmap to highlight the most pressing priorities for change to a wider set of policymakers and decision-takers. The Expert Policy Forum is keen to understand how it can advocate and contribute to improving standards of care, as well as kick-start the conversation about where policy and practice could be changed to benefit patients.¹



1. The terminology used by this Expert Policy Forum reflects the reality of the countries represented by its members.

About the Expert Policy Forum - Group and experts' biographies

The Expert Policy Forum on TTP was set up in September 2022, bringing together five specialist haematologists and seven patient organisation representatives from **Austria, Belgium, Bulgaria, Canada, Germany, Romania, Spain, Sweden, Israel**, and the **United Kingdom**. The experts involved in the forum at the point of publication are:



Bruce Morton

Answering TTP, Canada



Bruce Morton is an engineer and an MBA professional who lives in Ottawa, Canada. He works in the public key cryptography industry with a team which issues digital certificates to provide user trust for browsers and operating systems. Bruce is a family man and dedicates his time to his spouse and sons. He has been an iTTP patient since January 2012. In 2022, he has had a total of six TTP occurrences, but has survived them all and still has a positive look on life.



Dr Fredrik Celsing

Karolinska Hospital, Sweden



Dr Fredrik Celsing is a Specialist in Haematology and Internal Medicine, having worked over 32 years in the Haematology Department at Karolinska Hospital in Stockholm, Sweden. His career and work have special focus in acute leukaemia, TTP, and CNS lymphomas.



Gergana Sandeva

Answering TTP, Canada



Gergana Sandeva was diagnosed with TTP in January 2007, months prior to her first day of medical school at the University of Toronto. This diagnosis changed her life, as she was unable to start medical school and chose a career in clinical research. She completed her post graduate certifications as Clinical Research Associate and Clinical Research Professional and works as a Research Coordinator at Pharma Medica Research Inc.



Ioana Todorova-Yanakieva

Bulgarian Association Moschcowitz Syndrome, Bulgaria



Ioana Todorova-Yanakieva is a passionate TTP patients' supporter. After diagnosis, Ms Todorova-Yanakieva experienced three TTP episodes and faced significant TTP treatment-related challenges, which motivated the establishment of the Bulgarian non-profit patient association. She works as a Clinical Research Professional, with two master's degrees and extensive experience in healthcare. Her mission is to help patients get proper, affordable, and quality care (prevention, diagnosis, and treatment).



Dr Javier de la Rubia

University Hospital La Fe, Spain



Dr Javier de la Rubia is the Head of the Department of Haematology at the University Hospital La Fe and Professor of Haematology at the Universidad Católica in Valencia, Spain. He is a member of the advisory forum of the Spanish Group of Apheresis, and member of the European Haematology Association, and the International Working Group on TTP. His main research interests involve management of patients with multiple myeloma, and the study and management of patients with thrombotic microangiopathy. He has published over 200 peer-reviewed journal articles, several book chapters and more than 600 abstracts at national and international meetings.



Jo McIntyre

TTPNetwork, United Kingdom



Jo McIntyre is a TTP patient who established the not-for-profit patient organisation TTPNetwork, in 1998. Since her diagnosis, Ms McIntyre has experienced four episodes of TTP, and one threatened relapse. In addition to being the Founding Trustee of TTPNetwork, Ms McIntyre works in the domestic abuse sector.

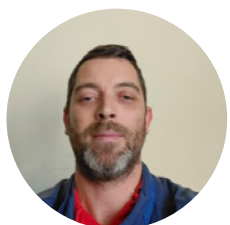


Professor Marie Scully MBE

University College London Hospitals, United Kingdom



Prof. Marie Scully is a Consultant Haematologist at University College London Hospitals (UCLH), currently acting as the clinical lead for haemostasis and thrombosis, having spent ten years as the clinical lead for blood transfusion. She runs specialist ITP and TTP clinics and works on obstetric haematology, as part of a team that specialises in treating varied and complex thrombosis, acquired and inherited bleeding disorders.



Kevin Claes

TTP Community, Belgium



Kevin Claes was diagnosed with TTP in 2011 and has had four TTP occurrences, from which he has recovered. Mr Claes works at Hansen Industrial Transmissions, is a trade union representative, and a member of the TTP Community in Belgium. The patient association is working to provide TTP patients and their families with the support and accurate information they need, strengthen the contact between patients, their relatives, medical professionals, research teams, promote awareness of the disease, and support research.



Dr Oleg Pikovsky

Soroka University Medical Center, Israel



Dr Pikovsky is a trained Clinical Haematologist and a Director of the Blood Bank and Pheresis unit at Soroka University Medical Centre in Israel. He is responsible for the hospital's transfusion and plasmapheresis services and specialises in various malignant and non-malignant haematological disorders, participating in different research projects. His primary interests are in transfusion medicine and coagulation.



Dr Paul Knöbl

Medical University of Vienna, Austria



Dr Paul Knöbl works as a Senior Physician in the Department of Medicine 1, Division of Haematology and Blood Coagulation, at the Medical University of Vienna as a specialist in internal medicine, haemato-oncology and critical care medicine. His scientific work focuses on blood coagulation, platelet disorders, diabetes, haematology, and sepsis. He has published more than 200 scientific articles, book chapters and reviews, and has edited books on acquired haemophilia and blood coagulation in critical illness.



Rainer Stähler

DHG e.V., Germany



Rainer Stähler is Process and Transformation Manager for a German software company, living in Ingelheim, Germany. He was diagnosed with severe haemophilia A and had to use a wheelchair after being prescribed the wrong treatment. After treatment with Factor VIII at seven years of age, Mr Stähler learned to walk again and became a competitive swimmer. He is chairman of the forum of the German Haemophilia Organization (DHG e.V.) and is married with three kids and a grandkid.



Rozalina Lapadatu

APAA, Romania



Rozalina Lapadatu is an activist, a professional advocating for social change and civic responsibility, and the founder of APAA (Association of Patients with Autoimmune Diseases). With more than 20 years' experience in pharma, governmental and private health, CSR, and NGO work she has unique expertise and a different point of view. She is a Stanford University trainer for "Self-management in arthritis and fibromyalgia course" in Romania and European Patient's Academy on Therapeutic Innovations Alumni.

The role of the Expert Policy Forum

The Expert Policy Forum on TTP aims to identify gaps and unmet medical needs in the care and management of TTP, as well as provide recommendations to address them. Moreover, the forum is working to increase awareness of TTP among healthcare professionals and the general public, to ensure that TTP is recognised and treated promptly and consequently improving patient outcomes. By advising Takeda on policies and guidelines related to the diagnosis and management, including treatment, of TTP, the forum's recommendations can help to ensure that the needs of the TTP community are addressed and that new treatments are made available.



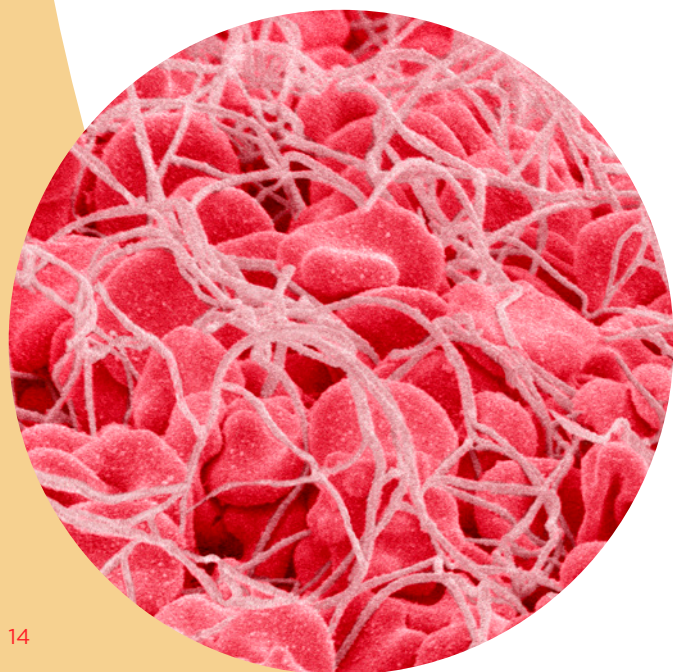
What is Thrombotic Thrombocytopenic Purpura?

What is TTP?

Thrombotic Thrombocytopenic Purpura (TTP) is a rare, acute, and life-threatening blood disorder that causes small clots in blood vessels throughout the body.^v TTP diagnosis is established through the assessment of serum ADAMTS13 activity level of less than 10% (the normal range should be 40-130%) or undetectable in acute phase.^{vi} Normally, platelets (a type of blood cells) float in the blood and form clots only to stop a bleeding.^{vii} In patients with TTP, platelets form clots when they're not supposed to, making it hard for blood to move through the blood vessel and get to the rest of the body.^{viii} There are 2 types of TTP: congenital (cTTP) and immune-mediated (acquired) (iTTP).^{ix}

TTP is a thrombotic microangiopathy (TMA) – a diverse group of disorders caused by blood clots in small blood vessels leading to multi-organ failure (due to lack of blood supply) and high mortality rate, even when appropriately treated.^x It was first clinically described in 1924, by Eli Moschcowitz, in a 16-year-old girl as a fatal TMA, with symptoms raging from weakness and fever to severe thrombocytopenia (low platelet level) and anaemia.^{xi} Until the 1990s, the cause of TTP remained unknown, and its outcome was fatal in ~90% of cases.^{xii} The disorder was then found to be caused by insufficient blood levels of a protein (enzyme) called ADAMTS13 that allows the blood to flow normally and clots to be formed only when necessary.^{xiii}

The ADAMTS13 enzyme is involved in regulating blood clotting by processing (cutting) a large protein called von Willebrand factor (vWF).^{xiv} vWF is a blood protein present in plasma and involved in haemostasis – the process to prevent and stop bleeding.^{xv} The deficiency in ADAMTS13 leads to the accumulation of ultra-large vWF in the plasma, thus forming platelet thrombi (clots) within the microcirculation.^{xvi} When untreated, the clots can partially or completely block blood flow to the organs, causing severe organ damage or eventually becoming fatal.^{xvii}





Congenital TTP - cTTP

Congenital TTP (cTTP) is caused by a problem in a gene that results in low levels of ADAMTS13 in the blood.^{xxviii}

cTTP has a prevalence of 0.5-2 cases per million people,^{xxix} often presents in childhood prior to 10 years of age,^{xx} and may be triggered by vaccinations, infections, or surgical procedures.^{xxi} Adult-onset cTTP are usually silent during childhood and classically revealed during the first pregnancy in women.^{xxii} Family consanguinity is also reported in cTTP.^{xxiii}



Immune-mediated (acquired) TTP - iTTP

Immune-mediated or acquired TTP (iTTP) is caused by a problem in the immune system that results in low levels of ADAMTS13 in the blood.^{xxiv} iTTP is the most common form of TTP and often develops during adulthood (90% of all TTP cases) or, more rarely, during childhood (10% of all TTP cases).^{xxv} The female predominance of the disease (sex ratio: ~2.5F/1M) and high rate of positive anti-ADAMTS13 autoantibodies underlies the strong autoimmune background of the disease.^{xxvi}

The disease has been linked to predisposing factors, such as gender (female), black ethnicity (African Americans or African-Caribbean), and obesity.^{xxvii}



Prevalence

TTP is a rare condition, with an annual incidence (new cases) of 3 to 11 cases per million people and a prevalence (total cases – both new and pre-existing) of 10 cases per million people.^{xxviii} The first acute episode occurs in adulthood in approximately 90% of cases and less frequently during childhood.^{xxix} Moreover, the deficiency in ADAMTS13 enzyme is related to a mutation occurring in both alleles of the ADAMTS13 gene in cTTP (5% of all TTP cases) or to the presence of autoantibodies against ADAMTS13 in immune-mediated TTP (95% of all TTP cases).^{xxx}

TTP patients can experience multiple relapses, even after many years of follow-up: after 10 years, 36% of patients can experience ≥ 1 episode.^{xxxi} Even when treated, the mortality rounds from 10% to 20%.^{xxxii}



Symptoms

Acute TTP events are life-threatening emergencies caused by blood clots, a low platelet count, and damaged red blood cells, and causes a myriad of symptoms, including: petechiae (red, brown, or purple spots of bleeding under the skin), purpura (purple bruises that are caused by bleeding under your skin), paleness, extreme tiredness, fever, fast heart rate or shortness of breath, headache, speech changes, confusion, coma, stroke, or seizure, a low amount of urine, or protein or blood in urine, nausea, vomiting, and diarrhoea.^{xxxiii}

Moreover, TTP may be either idiopathic (no known cause) or secondary to several clinical contexts (autoimmune disease, infection, haematopoietic stem cell or solid organ transplantation, neoplasia, drugs, pregnancy, etc.) and patients are likely to relapse due to persistent or recurrent ADAMTS13 deficiency. As the clinical presentation overlaps with other TMA syndromes, malignancies, and autoimmune disorders, the differential diagnosis is challenging and can take a long time.^{xxxiv} In the specific case of pregnancy, TTP occurs in 1 in 25,000 pregnancies, with the majority of cases occurring in the late third trimester or after giving birth. It has been associated with a high maternal and foetal mortality which approached 80% before the advent of plasma infusion and therapeutic plasma exchange.^{xxxv}



2. Coombs test - an immunology laboratory procedure used to detect the presence of antibodies against circulating red blood cells in the body



Diagnosis

Initial assessment is usually started based on clinical presentation and the analysis of medical and family history, physical exams, and tests, including urinalysis and renal function tests, complete blood count (CBC), peripheral blood smear, reticulocyte count, serum LDH, haptoglobin, ADAMTS13 activity and autoantibody assays, serum bilirubin, and direct antiglobulin test.^{xxxvi, xxxvii}

The initial diagnosis can be confirmed by evident thrombocytopenia (usually counts under $30,000 \times 10^9/L$), microangiopathic haemolysis with high reticulocyte count and schistocytes (more than 1% in blood smear), ischemic organ injury, undetectable serum haptoglobin concentration and elevated LDH levels. The direct Coombs test² should be negative, and the coagulation test should not be prolonged.^{xxxviii, xxxix}

A severe ADAMTS13 deficiency (activity <10 IU/dL) confirms TTP diagnosis.^{xi} Further investigations are necessary to determine the mechanism of ADAMTS13 deficiency: the diagnosis of iTTP is supported by positive anti-ADAMTS13 IgGs.^{xii}



2. Coombs test - an immunology laboratory procedure used to detect the presence of antibodies against circulating red blood cells in the body.



Disease management and treatment

A timely diagnosis and treatment of TTP are crucial for the patient to avoid acute disseminated microthrombosis and irreversible organ damage and death.^{xii} Currently, therapies for the treatment and management of TTP target the ADAMTS13 enzyme, the immune cells involved in anti-ADAMTS13 autoantibodies production, and the interaction between vWF and platelets.^{xiii}

A complete response to treatment is defined by a normal platelet count ($>150 \times 10^9/L$) for two consecutive days, normalisation of LDH, and clinical improvement. After 30 days post-discontinuation of treatment, the patient is considered to have a durable response. However, if the condition worsens within the 30-day period, the patient is considered to have an exacerbation of the disease. A relapse is characterised by recurrent disease 30 days or longer after reaching treatment response. On the other hand, refractory TTP is characterised by the absence of response to the treatment by day 30 and/or no durable response by day 60.^{xiv}



Disease management and treatment *(cont'd)*

Therapeutic plasma exchange (TPE) or plasma infusions remain the first line of treatment, targeting the deficiency in ADAMTS13. From the early 1990s, TPE improved TTP prognosis with 85% survival rate. Currently it is recommended that TPE is started upon suspicion of TTP in an acute episode or prophylactically in some cTTP patients to avoid episodes and infections, and manage surgical procedures, vaccinations, and pregnancy.^{xlv}

Up to 50% of patients are refractory or unresponsive to the first-line therapy.^{xlvi} In the case of iTTP, immunomodulation with steroids to limit the production of anti-ADAMTS13 autoantibodies can be used as adjunctive treatment to TPE. In case of suboptimal response to TPE, relapse, or exacerbation, anti-CD20 monoclonal antibodies are also used to achieve immunosuppression.^{xlvii} Other drugs can be helpful in refractory cases by suppressing the production of autoantibodies.^{xlviii}

More recently, anti-vWF immunoglobins were also found to inhibit the interaction between von Willebrand factor multimers and platelets.^{xlix} Lastly, splenectomy is considered to treat relapsing or refractory patients, as evidence suggests that splenic B cells that produce ADAMTS13 autoantibodies might escape to anti-CD20 therapy.^l

TTP relapses may expose the patient to the risk of death and preventing them is challenging.^{li} With a clinical relapse rate ranging between 25% and 40% rate of clinical relapse in immune-mediated TTP, monitoring of ADAMTS13 activity is recommended.^{lii, liii, liv} During clinical remission, a persistent ADAMTS13 activity <10 IU/dL is associated with a higher relapse rate and pre-emptive therapy may be considered to avoid clinical relapse of TTP with an advantageous risk-benefit balance.^{lv}



Burden of disease

TTP has both short and long-term consequences. When untreated, acute mortality rates can reach 90%^{lvi} with the majority of deaths occurring within 2 weeks of diagnosis.^{lvii} Cardiovascular complications, including stroke, heart failure, and acute coronary syndrome are common and in-hospital mortality is significantly higher in these patients.^{lviii}

The management of acute thromboembolism, encompassing conditions like stroke, acute myocardial infarction, or transient ischemic attack, demands a considerable allocation of healthcare resources. This entails hospitalisation for diagnostic procedures, the administration of thrombolytic agents and other pharmaceutical treatments, potential admission to intensive care or critical care units, and the provision of specialised nursing care. These interventions carry a substantial financial strain on the healthcare system.^{lix, lx, lxi} Moreover, rates of depression and cognitive deficits are considerably higher in TTP patients.^{lxii}

Recovery following an acute episode of iTTP is not a resolution of symptoms but the beginning of a long-term morbidity burden: hypertension, Systemic Lupus Erythematosus, and depression were significantly greater for TTP survivors.^{lxiii}

As patients who survive an acute episode of TTP are at risk of relapse and long-term morbidity, experts call for TTP to be seen and considered as a chronic disease with acute episodes.^{lxiv}

“ TTP has a different face for each patient, but the common element is the impact on patients’ everyday life. This can be tiredness, confusion, concentration loss, headaches or poor mental health. In addition, patients can also live with secondary effects from the medication they take for these associated symptoms. In my case, I’ve a knee protheses following cortisone intake. ”

Kevin Claes 
TTP Community

“ Being diagnosed with TTP is lifechanging, as it impacts patient’s lifestyle, quality of life and even your professional life. Most TTP patients cannot simply go back to their previous job and need to adapt to their new reality. This also has an impact of patients’ mental health as they feel they don’t contribute to society the same way. ”

 **Gergana Sandeva**
AnsweringTTP

TTP care today in Europe, Canada and Israel



Despite the recent progress in diagnosing and treating TTP, it remains a significant obstacle for healthcare professionals and patients alike. The evidence regarding how to accurately diagnose the condition early on, distinguish it from other types of thrombotic microangiopathy, and manage it during both acute episodes and remission is limited and disparate. As TTP is a rare disease, most healthcare professionals have limited experience in managing it and even among experts who frequently treat TTP patients, there are significant discrepancies in the approach to disease management.^{ixv}

The International Society on Thrombosis and Haemostasis (ISTH) recognised the necessity for up-to-date, evidence-based guidelines for TTP in 2018.^{ixvi} To fulfil this need, a panel of experts with various backgrounds, including haematologists, an intensive care physician, nephrologist, clinical pathologist, biostatistician, and patient representatives, was established to create guidelines that would aid patients, clinicians, and other healthcare professionals in making informed decisions regarding the initial diagnosis and management of acute TTP.^{ixvii}

At national level, TTP-specific guidelines are only available in a limited number of countries. In the context of this Expert Policy Forum, only three of the countries represented by the experts have national guidelines: the UK, Spain, and Sweden. The British guidelines, were sponsored by the British Committee for Standards in Haematology in 2012 and are currently being updated.^{lxviii} In 2022, the Spanish Apheresis Group published a set of recommendations for health professionals to homogenise disease management and serve as a reference framework for practice thus updating the guidelines already published in Spain in 2011.^{lxx} In Sweden, a group of clinicians, with representation from all healthcare regions, worked on national recommendations for immune-mediated TTP in adults and published them in 2019.^{lxix}

Patient registries are also a great tool in the management of the disease, as they can give a clearer picture of symptoms, treatment efficacy and evolution of the patient. However, TTP patient registries exist only in a minority of countries.

- In the United Kingdom, the University College London (UCL) Haemostasis Research Unit (HRU) collects and collates epidemiological data and supports sites participating in the United Kingdom Thrombotic Thrombocytopenic Purpura (TTP) Registry.^{lxxi} The UK TTP registry started in January 2009, involving UK collaboration from all sites treating TTP patients and aiming to determine the incidence, distribution of cases and epidemiology of TTP, including mortality and treatment regimes in the UK.^{lxxii}
- In Spain, Spanish Registry of Thrombotic Thrombocytopenic Purpura, created in 2004, aims to improve knowledge of the epidemiology, pathophysiology, and prognosis of TTP, as well as standardise the diagnostic and therapeutic criteria generating healthcare protocols.^{lxxiii}
- The German TTP Registry (RGTTP) was established in 2016 by the Centre for Thrombosis and Haemostasis (CTH) at the University Medical Centre Mainz and currently includes 115 patients. The registry collects retrospective data and, from the time of inclusion, the prospective data of a TTP patient over the long term. The registry also includes data on mortality related to acute episodes and on occurrence of relapses in the long term as primary endpoints.^{lxxiv}
- In 2006, the International Hereditary Thrombotic Thrombocytopenic Purpura Registry was established as an inclusive international cohort study for individuals who have confirmed or suspected cTTP and their relatives. The primary objective of the registry is to document the personal clinical progression and treatment needs of participants and determine potential triggers of acute TTP episodes and disease modifiers linked to the ADAMTS13 mutations responsible for the disease.^{lxxv}

While Rare Diseases plans or strategies are present in the majority of European countries, there is no explicit reference to TTP in any of those plans. Nonetheless, there are many EU policies and initiatives which aim to improve recognition and visibility of rare diseases in Europe, facilitating early dialogue between the industry (biotech and pharmaceutical companies), HTA bodies and payers, supporting evidence generation and improving care for rare disease patients. In fact, the European Commission is reviewing its Regulation on Orphan Medicinal Products^{lxxvi} and stakeholders are calling for an EU Action Plan for Rare Diseases. This revision represents a unique opportunity to update the regulatory framework, to make it more robust while driving innovation and improve access to treatments.^{lxxvii} Moreover, the European Commission has also recently adopted a revision of the legislation on Substances of Human Origin (SoHO) which includes provisions to ensure plasma supply and sustainability in Europe, and the manufacturing of plasma-derived therapies.^{lxxviii}

Similarly, the Canadian government has announced an investment of up to \$1.5 billion over three years to support the National Strategy for Drugs for Rare Diseases.^{lxxix} Of this amount, \$1.4 billion will be available to provinces and territories through bilateral agreements to improve access to new and emerging drugs for Canadians with rare diseases, support enhanced access to existing drugs, and improve early diagnosis and screening for rare diseases. Of the remaining amount, \$33 million will be allocated to Indigenous Services Canada's Non-Insured Health Benefits Program to support eligible First Nations and Inuit patients with rare diseases. Additionally, \$68 million will be invested in collaborative governance, data infrastructure, and research for drugs for rare diseases to improve consistency of access to drugs across the country.^{lxxx}

These investments align with the four pillars of Health Canada's national consultations on rare diseases, which include seeking national consistency in coverage for drugs, supporting patient outcomes and system sustainability, collecting and using evidence, and investing in innovation.^{lxxxi}



A roadmap to achieving optimal care for Thrombotic Thrombocytopenic Purpura patients

Prompt diagnosis and treatment of TTP are crucial to prevent significant morbidity and mortality.^{lxxxii} However, several barriers to optimal care, including delays in diagnosis, lack of awareness and knowledge about TTP among healthcare providers, and limited access to specialised care centres with expertise in managing TTP, can hinder the management of the disease. In this roadmap, the experts involved in the Expert Policy Forum on TTP explore these barriers in-depth and discuss potential solutions to improve the management of TTP and ultimately enhance patient outcomes.



Patient empowerment and engagement

Patient empowerment and engagement are fundamental components of modern healthcare, aimed at fostering collaboration between healthcare providers and patients to improve health outcomes. Empowering patients involves providing them with the knowledge, resources, and support to take an active role in managing their health and making informed decisions about their treatment options. Engaging patients means actively involving them in the decision-making process and valuing their input and preferences in determining the course of their care.

The Policy Advisory experts identified the need to improve HCP-patient communication and patient empowerment and education on disease monitoring – including symptoms' management, identification of relapses, and special conditions – and the need to empower patient organisations in their role as key elements to improve TTP patient care. In addition, patient representatives involved in the forum identified the lack of awareness among primary physicians of the mental health burden of TTP as a key barrier to optimal care in TTP.

1. Improving TTP patient wellbeing by providing access to multidisciplinary and holistic care, including psychological support

TTP is a complex disease involving a wide range of clinical features, including thrombocytopenia, anaemia, neurological symptoms, renal dysfunction, and fever. After recovery, patients are at higher risk of cognitive impairment (memory, concentration, and endurance), hypertension, depression, and relapsing.^{lxxxiii, lxxxiv} The complexity of the disease requires a multidisciplinary approach to care involving a range of HCPs, including haematologists, nephrologists, neurologists, and critical care specialists, as well as other professionals like social workers. However, access to such care is often limited, placing a significant burden on patients and their families.

Moreover, although roughly 40% of TTP survivors suffer from moderate or major depression and it frequently goes untreated, despite its higher incidence compared to the general population.^{lxxxv} Therefore, providing psychological support is essential for improving the quality of life of patients with rare diseases and their families. This support can be provided by psychologists, social workers, and other mental health professionals who have expertise in rare diseases. In addition, patient support groups and online communities can also provide a valuable source of emotional support for patients and their families.

“ Multidisciplinary teams should become the norm when treating TTP patients. The team in my centre includes haematologists, laboratory specialists, cardiologists, and members of the intensive care unit. The team also collaborates closely with gynaecologists when the patient is a woman. Communication and close coordination between the team are key, which is why we have also put in place an internal procedure to be followed as soon as TTP is diagnosed, to ensure the patient is taken care holistically. ”

Dr Javier de la Rubia 

University Hospital La Fe

Recommendation: National health systems should implement multidisciplinary and holistic teams for rare diseases, including TTP. This multidisciplinary team should include at least haematology, neurology, nephrology psychology, and intensive care services. Paediatric and obstetrics and gynaecology services should be part of this team in case the patient is a child or a woman.

2. Enhancing patient education and strengthening HCP-patient communication

Patients who have experienced an acute TTP episode are at risk of relapse and require careful, long-term follow-up. Adherence to this follow-up requires a good understanding of the disease. A recent study found that TTP literacy was low in 24% of patients, intermediate in 43%, and high in 33%.^{lxxxvi} The study also identified several knowledge gaps among the participants, including the necessity of daily plasma exchange during the acute phase (39%), a lack of awareness of the risk of relapse (47%), and insufficient knowledge among women regarding pregnancy and the associated risk of relapse (30%).^{lxxxvii}

Patient understanding of the disease is key. Empowering patients by improving their understanding of the disease and its management can increase patient involvement in dealing with the condition, resulting in better adherence to recommendations and earlier symptom detection, thereby maximising physician resources and improving the quality of care. In addition, patient education can be, in some cases, extremely important not just for the patient, but also for its family. For example, in the case of cTTP understanding of the disease and symptoms is important in the case the cTTP patient has siblings due to its genetic origin.

Moreover, empowering patients can facilitate communication and improve HCP-patient relationships. Ineffective communication between HCPs and patients, along with their families, is often cited as a reason for poor care experiences.^{lxxxviii} This can lead to complaints from patients and their families, leaving patients feeling dissatisfied, frustrated, anxious, and uncertain, which can negatively impact their ability to adhere to recommended treatments. On the contrary, good communication between clinicians and their patients not only positively impacts clinical outcomes, but also the patients' experience of care, influencing emotional health, symptom resolution, function, and physiological measures such as blood pressure, as well as reducing reported pain and drug usage.^{lxxxix} Therefore, it is crucial to empower patients to actively participate in their management plans development and decision-making, as well as to ensure that effective communication skills are prioritised as part of delivering high quality care.

“ Information is key for patients. In Germany we have regional representatives who have the right knowledge and information about blood disorders. This is crucial for patients as they can turn to their regional representatives to ask questions about their disease or to simply keep in contact, which helped quite a lot during the COVID-19 pandemic. ”

Rainer Stähler 
DHG e.V.

Recommendation: Patient organisations should empower patients with TTP by providing them with accurate information and by improving their understanding of the disease and its management. The patient community should be supported with key volunteers (patients, healthcare professionals) that would act as a disease spokesperson, having the right knowledge and information about TTP, to whom patients can turn for information, advice, and support.

3. Empowering patient organisations as key stakeholders in the patient journey

Medical societies and patient associations play a crucial role in advancing research, education, and advocacy efforts related to TTP and other rare blood disorders. By bringing together HCPs, researchers, and patients, these organisations can help to raise awareness of TTP, promote best practices for diagnosis and disease management, and advocate for policies that support the TTP community.

Within the context of haemophilia and other rare blood disorders, medical societies and patient associations are especially important in recognising and addressing the unique challenges faced by individuals with TTP. Because TTP is a rare condition, many HCPs may not have experience diagnosing or treating it. Medical societies can help bridge this gap by providing central education and training programmes for healthcare providers, as well as by setting guidelines and standards of care for TTP.

Patient associations can also play a critical role in supporting individuals with TTP and their families. These organisations provide resources and information on managing the condition and connect patients with other individuals who have experienced similar challenges by sharing information online, organising roundtables, support groups or developing their presence on social media. Patient associations can also advocate for policies and funding that support research and access to care for individuals with TTP. By working with medical societies and other stakeholders, patient associations can help ensure that the needs of the TTP community are heard and addressed.







“ The role of patient organisations is essential when a patient receives a TTP diagnosis. Information about peer led support groups should be provided to patients at the earliest opportunity. This will enable the patient and their loved ones to make contact and receive support from the patient group and their community at the time they need it most. In other words, it should be part of the basic standard of care to refer patients to advocacy and support groups. ”

Jo McIntyre
TTPNetwork



Recommendation: National health systems should recognise the key role medical societies and patient associations play during the TTP patient journey and provide them the necessary tools and resources to work together to advance research, education, and advocacy efforts related to TTP.

Challenges and recommendations to achieve TTP optimal care - patient empowerment and engagement

 AREA	 CHALLENGE	 RECOMMENDATION	 GOAL	 STAKEHOLDER
 <p>PATIENT EMPOWERMENT AND ENGAGEMENT</p>	<p>Improving TTP patient wellbeing by providing access to multidisciplinary and holistic care, including psychological support</p>	<p>Improve TTP patient wellbeing by putting in place multidisciplinary and holistic teams by national public health systems. This multidisciplinary team should include at least haematology, neurology, nephrology psychology, and intensive care services. Paediatric and obstetrics and gynaecology services should be part of this team in case the patient is a child or a woman</p>	<p>Multidisciplinary and holistic teams are in place for rare diseases, including TTP, are integrated in national health systems</p>	<p>National healthcare services, healthcare professionals, medical societies and policymakers, patient organisations</p>
	<p>Enhancing patient education and strengthening HCP-patient communication</p>	<p>Empower patients with TTP by providing them with accurate information and improving their understanding of the disease and its management. The patient community should be supported with key volunteers (patients, healthcare professionals) that would act as a disease spokesperson, having the right knowledge and information about TTP, to whom patients can turn for information, advice, and support</p>	<p>TTP patients are empowered thanks to the creation of communication channels and activities that provide accurate information and improve their understanding of the disease and management</p>	<p>Patient organisations, national healthcare services, healthcare professionals, medical societies and the pharmaceutical industry</p>
	<p>Empowering patient organisations as key stakeholders in the patient journey</p>	<p>Recognise the key role medical societies and patient associations play during the TTP patient journey, providing them the necessary tools and resources to work together to advance research, education, and advocacy efforts related to TTP</p>	<p>Medical societies and patient associations leading role in the TTP patient journey is recognised by providing them the necessary tools and resources to work together to advance research, education, and advocacy efforts related to TTP</p>	<p>Policymakers, national healthcare services, healthcare professionals, medical societies and the pharmaceutical industry</p>



Disease awareness and education



Despite advances in medical knowledge and technology, many HCPs still lack awareness and understanding of rare diseases, including TTP.^{xc} Due to the rarity of the condition, HCPs may have limited exposure and experience during their training and practice, as well as not be able to easily access resources and research. The lack of awareness and understanding of rare diseases among HCPs is a significant challenge that can result in serious consequences for patients, including disability, reduced quality of life, and premature death. Therefore, improving education and awareness among HCPs is essential to ensure that patients receive timely and appropriate care.

The Expert Policy Forum on TTP has identified disease awareness and education as key barriers to optimal care in TTP. These include limited pathways for HCPs' education and knowledge transfer, inadequate monitoring of special conditions (such as vaccination and pregnancy), and lack of recognition of TTP in rare and blood disease medical societies.



1. Creating pathways for HCPs' education and knowledge transfer

Limited understanding of TTP among HCPs, especially among non-specialists, can result in delays in diagnosis, inappropriate management, and limited access to appropriate care.^{xci} The delays in access to diagnosis and care are often due to a lack of awareness and understanding of rare diseases among HCPs,^{xcii} highlighting the need for increased education and training for HCPs in this field.

Improving knowledge transfer and creating opportunities for HCPs' education on TTP is essential to address this issue. Education and training programmes can improve HCPs' understanding of the disease, including symptoms, diagnosis, and management. Such programmes can also help to increase awareness of the prevalence and symptoms of the disease, their impact on patients' lives, and the challenges faced by patients and their families. Furthermore, education can help HCPs to stay up to date with the latest research and treatment options, which is critical for improving patient outcomes. Education programmes and appropriate pathways for knowledge transfer between specialist and non-specialist HCPs can significantly improve their knowledge and skills in managing the disease, resulting in earlier diagnosis, improved management, and better patient outcomes.

“ Developing education programmes to raise awareness of TTP among healthcare professionals is an absolute priority, focusing on general practitioners, neurologists and emergency units, as these are the first practitioners patients will see. Education of healthcare professionals is key to ensure optimal care and early diagnosis of TTP. ”

Dr Paul Knöbl 
Medical University of Vienna

“ In my centre, our primary care physicians have been trained in TTP early recognition and awareness, which has helped in early diagnosis of the disease, which is crucial for patients. ”

Dr Oleg Pikovsky 
Soroka University
Medical Centre

Recommendation: National health systems should create opportunities for HCPs to further develop their knowledge of rare diseases, including TTP, as well as create or expand network of specialists, i.e., the European Reference Networks, to support referrals, education of both specialists and non-specialist HCPs, and knowledge transfer amongst the healthcare community.

2. Ensuring monitoring of triggering special conditions and management

TTP can be triggered by certain conditions or medications.^{xciii} Patients may display a linked clinical condition, including bacterial infection, HIV infection, pregnancy, the use of certain drugs, cancer, systemic lupus erythematosus, antiphospholipid syndrome, and organ transplantation.^{xciv}

In the specific case of pregnancy, TTP may be acquired due to immune regulation changes or a symptomatic episode of congenital TTP.^{xcv} Its acute occurrence can lead to significant maternal/foetal morbidity and mortality and require urgent management.^{xcvi} Moreover, management of pregnant women with TTP depends on the stage of pregnancy and foetal compromise, and delivery may not necessarily resolve the TTP episode. In patients with previously acquired TTP who become pregnant, HCPs must ensure frequent monitoring and interventions if a consistent drop in ADAMTS13 activity is observed. In the case of congenital TTP, monitoring and plasma infusions are necessary throughout pregnancy.^{xcvii}

“ I personally had my first TTP episode triggered by a pregnancy. It was manifested by a heavy bleeding, which is kind of common during pregnancy and often considered a Disseminated Intravascular Coagulation (DIC syndrome). I had to undergo an abortion because of that. The proper diagnosis has been neglected as no one ever suspected the bleeding was of a hematologic origin and was considered pregnancy related with the focus being more on the pregnancy rather than the cause of the low thrombocyte count. Three years after the first episode, I was following hormone replacement therapy (HRT) to prevent the growth of an ovarian cyst. This HRT has provoked a very severe life-threatening relapse. In other words, both episodes have been linked to gynaecological triggers. Gynaecologists need to understand the disease and be aware HRT might cause serious hematologic conditions and that pregnancy itself might provoke a TTP episode in a certain subset of women. Despite the fact TTP is a rare disease, awareness is crucial as it might impact not only womens' lives but also the proper development of the fetus and the birth of a healthy child. ”

Ioana Todorova-Yanakieva



Bulgarian Association Moschcowitz Syndrome

Recommendation: Medical societies should raise awareness amongst HCPs about triggering conditions and medication for TTP, including the management of these in the dedicated guidelines and recommendations for treatment and care of TTP.

3. Promoting awareness-raising campaigns, both for the healthcare community and the general public, and supporting the organisation of an International TTP day

The forum believes that by raising awareness among HCPs and the general public, patients with TTP will be more likely to receive timely and appropriate care. Moreover, awareness-raising campaigns can help to reduce the stigma and isolation experienced by those living with TTP, supporting patient empowerment and leading to improved quality of life and mental health outcomes.

Awareness-raising campaigns can also play an important role in driving research and funding for rare diseases and TTP. Greater awareness can lead to increased advocacy efforts, which in turn can result in more funding and resources for research. Therefore, it is important to establish an International TTP day to specifically focus attention on this rare and often life-threatening condition. This day could serve as an opportunity to educate the public and HCPs about TTP, raise awareness about the challenges faced by those living with the condition, and advocate for increased research and funding. By establishing an International TTP day, stakeholders can work together towards improving outcomes and quality of life for those affected by this rare disease.


Case study

The International TTP Day is already organised by AnsweringTTP Foundation in Canada, bringing the TTP community together to raise funds to support research, education, and support. The TTP Awareness Day takes place every year, on the third Saturday of September. A similar celebration could be extended to European countries to expand geographical scope and build momentum.



Recommendation: Patient organisations should leverage and actively support the International TTP Day in September to raise awareness of TTP among the general population.

Challenges and recommendations to achieve TTP optimal care - disease awareness and education

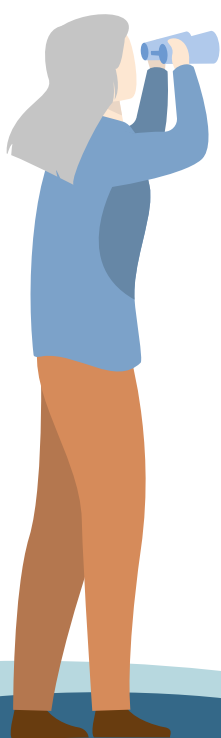
AREA	CHALLENGE	RECOMMENDATION	GOAL	STAKEHOLDER
 DISEASE AWARENESS AND EDUCATION	Limited understanding of TTP among HCPs, especially among non-specialists, that can result in delays in diagnosis, inappropriate management, and limited access to appropriate care	Create opportunities for HCPs to further develop their knowledge of rare diseases, including TTP, as well as create or expand network of specialists, i.e., the European Reference Networks, to support referrals, education of both specialists and non-specialist HCPs, and knowledge transfer amongst the healthcare community.	Healthcare professionals have further developed their knowledge of rare diseases, including TTP, as well as expanded network of specialists	National health services, healthcare professionals and medical societies, patient organisations
	TTP can be triggered by certain conditions or medications, adding to the diseases' complexity	Raise awareness amongst HCPs about triggering conditions and medication for TTP, including the management of these in the dedicated guidelines and recommendations for management and care of TTP.	Specialists and non specialist healthcare professionals have a better understanding of triggering conditions and medication for TTP	Medical societies, national healthcare systems, patient organisations
	Awareness of TTP among patients, HCPs, and the general public is low	Leverage and actively support the international TTP Awareness Day in September to raise awareness of TTP among the general population.	The international TTP Awareness Day in September is established as a key date to raise awareness	Patient organisations, healthcare professionals, pharmaceutical industry, policymakers



Patient-centric health systems

Rare diseases need a specialised management, as HCPs may have limited exposure, knowledge, and experience of these conditions. Developing clear guidelines that would help first line professionals and specialists would ensure better patient care. In addition, establishing and improving referral centres, would help centralise the knowledge about the disease, resources, and support needed for TTP patients.

The experts of the Expert Policy Forum agreed on the need to focus on early detection of the disease, which the first step being the measurement of ADAMTS13 levels in patients. Better access to ADAMTS13 testing, including faster provision and availability of results, would significantly improve patient diagnosis. In addition, enhanced patient registries would support a better understanding of the disease and lead to improved diagnosis, management, and care.

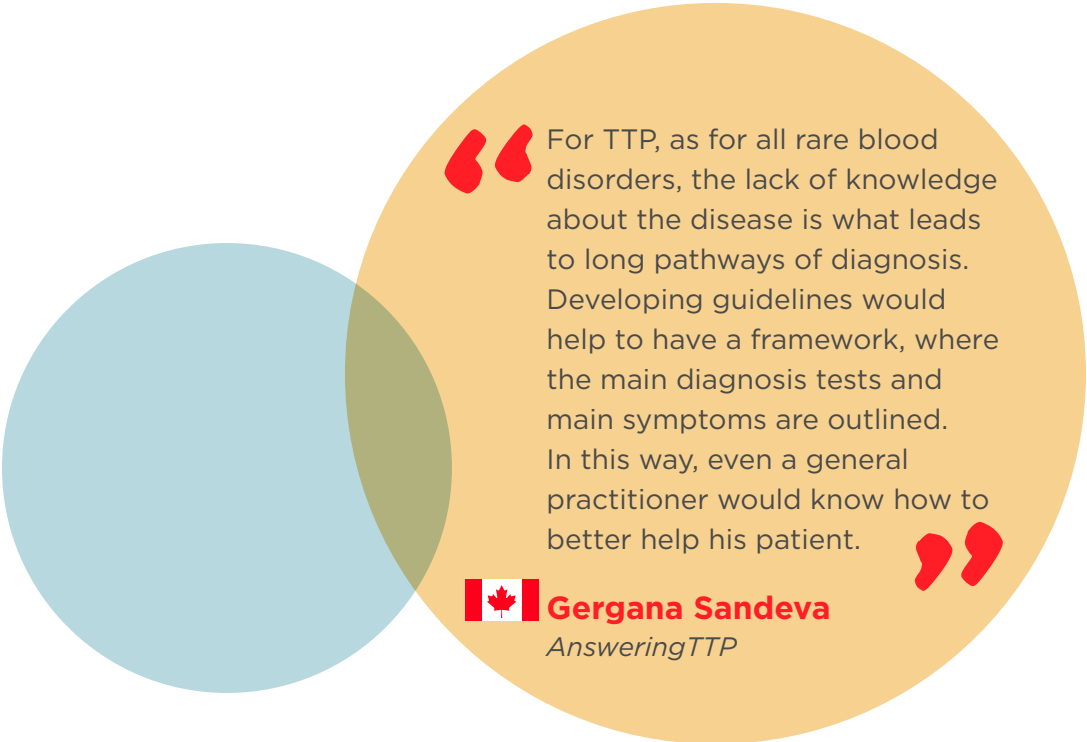


1. Developing and implementing guidelines and aligning on definitions and disease management pathways

Creating guidelines and aligning on definitions and disease management pathways in TTP is crucial for ensuring that patients receive consistent and effective care. Guidelines can help to establish best practices for diagnosis, treatment, and management of TTP, as well as provide a framework for healthcare providers to follow. Due to the different nature of cTTP and iTTP, specific guidelines are needed for both. In addition, aligning on definitions and disease management pathways can also help to improve communication and collaboration between healthcare providers and patient advocates, which can lead to better outcomes for patients.

Although the International Society on Thrombosis and Haemostasis has created guidelines on the management of TTP,^{xcviii} the management landscape is rapidly evolving, and guidelines need to be more regularly reviewed and updated to support the uptake of innovative treatments and the context at national level. Moreover, different terminologies are still being used by different experts, creating additional barriers to disease awareness and knowledge transfer, and the recognition of increased morbidity and mortality among patients following recovery is prompting calls for TTP to be addressed as a chronic disorder rather than a disorder of acute episodes and complete recovery.

Thus, seeking alignment and international consensus on the lifelong management and care of TTP as a chronic disease, creating guidelines addressing treatment pathways for iTTP and cTTP, and seeking alignment on terminology and definitions is essential to ensuring that patients receive the care and support they need over the long term.



“ For TTP, as for all rare blood disorders, the lack of knowledge about the disease is what leads to long pathways of diagnosis. Developing guidelines would help to have a framework, where the main diagnosis tests and main symptoms are outlined. In this way, even a general practitioner would know how to better help his patient. ”



Gergana Sandeva

AnsweringTTP

Recommendation: Medical societies should develop, review, and regularly update clinical guidelines for management and care of iTTP (immune-mediated TTP) and cTTP (congenital TTP) to ensure key developments are taken into account, as well as ensure experts are aligned on definitions and support the approach to TTP as a chronic disease.

2. Improving access to referral and expert centres

Access to referral and expert centres is crucial for TTP patients, as these centres provide specialised care and expertise in the management of this complex condition. Expert and referral centres have clinicians with extensive experience in diagnosing and treating TTP and can provide additional resources and support, such as access to clinical trials or specialised laboratory testing that may not be available elsewhere.



“ In England, the existence of guidelines developed by the NHS and the set-up of 10 specialised Referral centres have substantially improved TTP patients’ journey. This provides the centres with the best tools and mechanisms to take care of patients in a holistic way.

Professor Marie Scully MBE

*University College
London Hospitals*



Recommendation: National health systems should create, implement, and support access to referral and expert centres to ensure TTP patient optimal care, by engaging and supporting EU-wide initiatives, such as the European Reference Networks. Referral centres would not only ensure patient care, but would also support investigation and access to clinical trials, advancing research for TTP.

3. Ensuring early detection and access to ADAMTS13 testing

The level and activity of ADAMTS13 may be assessed in a vast array of clinical conditions, including the detection and monitoring of TTP. There are different ways to measure ADAMTS13, but specifically measuring ADAMTS13 activity is considered to be the most clinically meaningful. There are several commercial and in-house assays available, but they often take several hours to complete and are best performed in batches. This can delay urgent testing needed for patient management decisions. Recently, rapid ADAMTS13 activity assays have become available, providing faster than standard commercial or in-house testing and access to urgent/emergency testing.^{xcix}

The rapid identification or exclusion of TTP is crucial for timely and accurate diagnosis, allowing for prompt initiation of treatment, thus improving patient outcomes and reducing the risk of complications. Moreover, ADAMTS13 testing is essential for monitoring disease activity and responses to treatment, as well as ensuring optimal management of TTP. Thus, experts recommend increasing uptake of diagnostic tools and increasing access to ADAMTS13 testing to allow for early detection and improved disease management.

“ I have had a recurrence of TTP five times. Before the first three recurrences we only tested for platelets. This test only indicated that I did or didn't have TTP, but gave no warning. Before the fourth time, we also tested for ADAMTS13, but it took many weeks to get the result back. Before my sixth time, not only did we test, but we also had a plan in the event that ADAMTS13 activity levels dropped. We almost avoided TTP, but I think we reacted too late. All patients are different, so we keep on learning. ”

Bruce Morton 

AnsweringTTP

“ We need more patient and healthcare professionals' knowledge of what TTP is and related symptoms. Patients should be empowered and have more awareness of their disease and possible symptoms, in order to monitor them and to react as quickly as possible when an episode starts. Early diagnosis is key to provide patients with the adequate treatment as soon as possible. For that, ADAMTS13 levels and other related markers should not only be tested when patients are presenting symptoms, but on a regular basis to ensure patients monitoring and early diagnosis in case there's a new episode. ”

Gergana Sandeva 

AnsweringTTP

Recommendation: Medical societies must ensure that regular monitoring of ADAMTS13 is included in their guidelines for management and care of TTP. Moreover, national health system planners and decision-makers must guarantee appropriate funding to support widespread access to diagnostic and monitoring equipment.

4. Improving data collection and patient registries

Data collection and registries are essential tools in healthcare and research. They help HCPs and researchers to better understand diseases and their impact on patients, leading to improved diagnosis, management, and care. In rare diseases such as TTP, data collection and registries are particularly important to provide valuable insights into the disease, enabling HCPs to develop better treatment options and improve patient outcomes.

The European Reference Networks (ERNs) provide a unique opportunity to collaborate on rare diseases like TTP. By connecting HCPs and researchers across Europe, ERNs can facilitate data collection and sharing, leading to a better understanding of rare diseases and improved patient outcomes. Implementing registries specific to TTP can help HCPs better diagnose and treat patients, as well as track patient outcomes over time.

Therefore, implementing registries and sharing data through ERNs and similar networks can improve care for TTP patients, by allowing HCPs to expand their understanding of this rare disease and develop more effective treatments.

“ Patient registries are a very important tool for us physicians and national registries should be implemented in all countries. However, to be relevant, registries need to be updated regularly, which can translate into an additional burden for healthcare professionals. ”







Dr Javier de la Rubia

University Hospital La Fe




Recommendation: Policymakers and medical societies should promote and leverage the current initiatives at international level, such as the European Reference Networks, to improve participation in data registries to support research and improve patient care.


Challenges and recommendations to achieve TTP optimal care - patient-centric health systems

 AREA	 CHALLENGE	 RECOMMENDATION	 GOAL	 STAKEHOLDER
 <p>PATIENT-CENTRIC HEALTH SYSTEMS</p>	<p>The management landscape is rapidly evolving and there is lack of alignment on terminology and management as a chronic disease</p>	<p>Develop, review, and regularly update clinical guidelines for management and care of iTTP (immune-mediated TTP) and cTTP (congenital TTP) to ensure key developments are taken into account, as well as ensure experts are aligned on definitions and support the approach to TTP as a chronic disease.</p>	<p>Clinical guidelines for management and care of iTTP and cTTP exist and ensure experts are aligned on definitions and support the approach to TTP as a chronic disease</p>	<p>Medical societies, national healthcare systems, patient organisations</p>
	<p>Optimal management of TTP requires access to specialised care and expertise</p>	<p>Create, implement, and support access to referral and expert centres to ensure TTP patient optimal care, by engaging and supporting EU-wide initiatives, such as the European Reference Networks. Referral centres would not only ensure patient care, but would also support investigation and access to clinical trials, advancing research for TTP.</p>	<p>Referral and expert centres to ensure TTP patient optimal care have become the norm across Europe, Canada and Israel</p>	<p>National health systems, medical societies, healthcare professionals, patient associations</p>
	<p>Monitoring of ADAMTS13 is a lengthy and not easily accessible process</p>	<p>Ensure that regular monitoring of ADAMTS13 is included in their guidelines for management and care of TTP. Moreover, national health system planners and decision-makers must guarantee appropriate funding to support widespread access to diagnostic and monitoring equipment.</p>	<p>Regular monitoring of ADAMTS13 is included in the TTP patient journey</p>	<p>National health systems, medical societies, payers, industry</p>
	<p>Patients are not included in registries and data on TTP is limited</p>	<p>Promote and leverage the current initiatives at international level, such as the European Reference Networks, to improve participation in data registries to support research and improve patient care.</p>	<p>Data registries participation improves through the promotion and leveraging of initiatives at international level</p>	<p>Policymakers, medical societies and healthcare professionals, patient associations</p>


Roadmap summary

Challenges and recommendations to achieve TTP optimal care - summary

AREA	CHALLENGE	RECOMMENDATION	GOAL	STAKEHOLDER
 <p>PATIENT EMPOWERMENT AND ENGAGEMENT</p>	<p>Improving TTP patient wellbeing by providing access to multidisciplinary and holistic care, including psychological support</p>	<p>Improve TTP patient wellbeing by putting in place multidisciplinary and holistic teams by national public health systems. This multidisciplinary team should include at least haematology, neurology, nephrology psychology, and intensive care services. Paediatric and obstetrics and gynaecology services should be part of this team in case the patient is a child or a woman</p>	<p>Multidisciplinary and holistic teams are in place for rare diseases, including TTP, are integrated in national health systems</p>	<p>National healthcare services, healthcare professionals, medical societies and policymakers, patient associations</p>
	<p>Enhancing patient education and strengthening HCP-patient communication</p>	<p>Empower patients with TTP by providing them with accurate information and improving their understanding of the disease and its management. The patient community should be supported with key volunteers (patients, healthcare professionals) that would act as a disease spokesperson, having the right knowledge and information about TTP, to whom patients can turn for information, advice, and support</p>	<p>TTP patients are empowered thanks to the creation of communication channels and activities that provide accurate information and improve their understanding of the disease and management</p>	<p>Patient organisations, national healthcare services, healthcare professionals, medical societies and the pharmaceutical industry</p>
	<p>Empowering patient organisations as key stakeholders in the patient journey</p>	<p>Recognise the key role medical societies and patient associations play during the TTP patient journey, providing them the necessary tools and resources to work together to advance research, education, and advocacy efforts related to TTP</p>	<p>Medical societies and patient associations leading role in the TTP patient journey is recognised by providing them the necessary tools and resources to work together to advance research, education, and advocacy efforts related to TTP</p>	<p>Policymakers, national healthcare services, healthcare professionals, medical societies and the pharmaceutical industry</p>

AREA	CHALLENGE	RECOMMENDATION	GOAL	STAKEHOLDER
 <p>DISEASE AWARENESS AND EDUCATION</p>	<p>Limited understanding of TTP among HCPs, especially among non-specialists, that can result in delays in diagnosis, inappropriate management, and limited access to appropriate care</p>	<p>Create opportunities for HCPs to further develop their knowledge of rare diseases, including TTP, as well as create or expand network of specialists, i.e., the European Reference Networks, to support referrals, education of both specialists and non-specialist HCPs, and knowledge transfer amongst the healthcare community.</p>	<p>Healthcare professionals have further developed their knowledge of rare diseases, including TTP, as well as expanded network of specialists</p>	<p>National health services, healthcare professionals and medical societies, patient associations</p>
	<p>TTP can be triggered by certain conditions or medications, adding to the diseases' complexity</p>	<p>Raise awareness amongst HCPs about triggering conditions and medication for TTP, including the management of these in the dedicated guidelines and recommendations for management and care of TTP.</p>	<p>Specialists and non specialist healthcare professionals have a better understanding of triggering conditions and medication for TTP</p>	<p>Medical societies, national healthcare systems, patient organisations</p>
	<p>Awareness of TTP among patients, HCPs, and the general public is low</p>	<p>Leverage and actively support the international TTP Awareness Day in September to raise awareness of TTP among the general population.</p>	<p>The international TTP Awareness Day in September is established as a key date to raise awareness</p>	<p>Patient organisations, healthcare professionals, pharmaceutical industry, policymakers</p>



AREA	CHALLENGE	RECOMMENDATION	GOAL	STAKEHOLDER
 <p>PATIENT-CENTRIC HEALTH SYSTEMS</p>	<p>The management landscape is rapidly evolving and there is lack of alignment on terminology and management as a chronic disease</p>	<p>Develop, review, and regularly update clinical guidelines for management and care of iTTP (immune-mediated TTP) and cTTP (congenital TTP) to ensure key developments are taken into account, as well as ensure experts are aligned on definitions and support the approach to TTP as a chronic disease.</p>	<p>Clinical guidelines for management and care of iTTP and cTTP exist and ensure experts are aligned on definitions and support the approach to TTP as a chronic disease</p>	<p>Medical societies, national healthcare systems, patient organisations</p>
	<p>Optimal management of TTP requires access to specialised care and expertise</p>	<p>Create, implement, and support access to referral and expert centres to ensure TTP patient optimal care, by engaging and supporting EU-wide initiatives, such as the European Reference Networks. Referral centres would not only ensure patient care, but would also support investigation and access to clinical trials, advancing research for TTP.</p>	<p>Referral and expert centres to ensure TTP patient optimal care have become the norm across Europe, Canada and Israel</p>	<p>National health systems, medical societies, healthcare professionals, patient associations</p>
	<p>Monitoring of ADAMTS13 is a lengthy and not easily accessible process</p>	<p>Ensure that regular monitoring of ADAMTS13 is included in their guidelines for management and care of TTP. Moreover, national health system planners and decision-makers must guarantee appropriate funding to support widespread access to diagnostic and monitoring equipment.</p>	<p>Regular monitoring of ADAMTS13 is included in the TTP patient journey</p>	<p>National health systems, medical societies, payers, industry</p>
	<p>Patients are not included in registries and data on TTP is limited</p>	<p>Promote and leverage the current initiatives at international level, such as the European Reference Networks, to improve participation in data registries to support research and improve patient care.</p>	<p>Data registries participation improves through the promotion and leveraging of initiatives at international level</p>	<p>Policymakers, medical societies and healthcare professionals, patient associations</p>

Conclusion

Living with a rare disease can be an incredibly challenging experience for both patients and their families, as they often involve complex symptoms and unpredictable courses, challenging pathways to accurate diagnosis and timely care, and highly impact patients' daily lives, posing physical, emotional, and financial burdens.

Despite recent advancements in treatments for some rare diseases, there remains significant unmet medical needs for many others. In the case of TTP, despite increased availability of more treatment options, patients are still facing significant barriers to optimal care, including delays in diagnosis, lack of awareness and knowledge about TTP among healthcare providers, and limited access to specialised care centres with expertise in managing TTP.

To address these challenges, the Expert Policy Forum on TTP has reached a consensus on three main topics that require urgent attention: patient empowerment and engagement, disease awareness and education, and patient-centric health systems. The forum believes that a patient-centred approach is key to optimising care for TTP, and that patients must be empowered to take an active role in their own care, supported by comprehensive disease education and awareness initiatives. Moreover, the forum recommends that health systems adopt patient-centric models of care that prioritise individualised management plans, focus on outcomes that matter most to patients, and support the implementation of a holistic and multidisciplinary approach to care. Lastly, the forum recommends international collaboration in TTP, as well as the establishment of appropriate networks and registries to support knowledge transfer between HCPs and advance research in this field.

In conclusion, the Expert Policy Forum emphasises the importance of addressing unmet needs in rare diseases, such as TTP, to ensure that patients receive optimal care and achieve better outcomes. By working together, we can ensure that patients living with TTP receive the care and support they need to live full and meaningful lives.



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