Ministry of Interior - State Secretariat for Healthcare

NATIONAL ADVISORY BOARD OF HEALTHCARE

Medical Guideline

On the treatment of thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS)

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The authors' independence was not infringed during the drafting of this medical guideline.

The National Advisory Board of Healthcare sections listed above endorse the contents of this medical guideline in a documented manner.

Other contributors to the guideline

Patient organisation(s) with consultative capacity:

Did not take part

Other organisation(s) with consultative capacity:

Did not take part

Professional society(ies) with consultative capacity:

Did not take part

Independent expert(s):

Did not take part

II. FOREWORD

Evidence-based medical guidelines provide guidance in decision-making for healthcare professionals and other users in a specific medical environment. Medical guidelines developed and applied based on a systematic methodology have been scientifically proven to improve quality of care. The set of recommendations presented in the medical guideline has been created based on the highest standard of scientific findings available and factoring in clinical experience, patient perspectives and the idiosyncrasies of the Hungarian healthcare system alike. This guideline defines sector-neutral recommendations. Although medical guideline recommendations represent the best practices based on the most recent evidence at the time of their publication, they are no substitute for the decisions of healthcare professionals in every situation, so they may be diverged from in warranted cases in a documented manner.

III. SCOPE

Healthcare considerations:	Medical care for patients with thrombotic microangiopathies (thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome)
Stage(s) of the medical care process:	Diagnostics, therapy, risk assessment, care
Affected patient group:	All patients with thrombotic thrombocytopaenic purpura and haemolytic uraemic syndrome
Affected patient group Specialty area:	0102 haematology 0105 nephrology
Form of care:	J1 Outpatient specialist treatment, specialist practice J7 Outpatient specialist treatment and care D1 Diagnostics F1 Inpatient specialist treatment, active inpatient treatment F2Inpatient specialist treatment, chronic inpatient treatment F6 Inpatient specialist treatment, emergency treatment A1 Primary care
Level of progressivity:	Levels I - II - III
Other specification:	None

IV. DEFINITIONS

1. Definitions

ADAMTS13 relapse: ADAMTS13 activity falling below 20% again after a partial or complete ADAMTS13 remission.
Amotosalen-UVA: a method for pathogen inactivation of blood products by using amotosalen as a photoactivating agent and irradiating the product with ultraviolet "A" rays.
amotosalen-UVA-FFP: FFP pathogenically inactivated using amotosalen-UVA technology.
APA syndrome: antiphospholipid syndrome.
CD36 receptor: scavenger receptor expressed on platelets, phagocytes, liver, fat and muscle cells.
HELLP syndrome: Haemolysis, elevated liver enzymes, low platelet count.
Clinical exacerbation: platelet count falling below 150 G/L (other cause excluded) after achieving a clinical response but before achieving clinical remission, with or without new or progressive ischaemic organ damage, within 30 days of completion of plasma exchange or anti-VWF therapy.
Clinical relapse: platelet count again falling below 150 G/L after clinical remission (other causes excluded) with or without new ischaemic organ damage. Clinical relapse should be supported by evidence of severe ADAMTS13 deficiency.
Clinical remission in TTP: clinical response without plasma exchange and anti-VWF treatment: at least for 30 days or if ADAMTS13 remission (partial or complete) is achieved, whichever occurs first.

Clinical response in TTP: platelet count maintained above 150 G/L, LDH not exceeding one and a half times the upper normal value, without clinical signs of new or progressive ischaemic organ damage.
Methylene blue: a compound used to inactivate viruses in plasma preparations.
Methylene blue-FFP: FFP inactivated by methylene blue virus.
Plasmapheresis/plasma exchange: A blood cleaning procedure (extracorporeal circulation) using a specifically developed cell or plasma separator where approximately 40–60 mL/kg of plasma is removed from the patient and replaced by a substitution solution with a composition dependent on the indication (crystalloid, synthetic colloid, albumin, fresh frozen plasma). The purpose of the procedure is to remove intravascular (non-dialysable) macromolecules and, in some cases, replace deficient plasma components (such as the ADAMTS13 enzyme, complement regulator proteins, etc.) in large volumes.
Plasma transfusion: administration of fresh frozen plasma using a transfusion set.
Refractory TTP: Persistent thrombocytopenia (<50 G/L) and LDH elevation despite 5 plasma exchanges and immunosuppressive therapy.
Partial ADAMTS13 remission: ADAMTS13 activity is 20% or higher but below the lower limit of the normal range.
Riboflavin-UV: a method for inactivating pathogens in blood products by using riboflavin (vitamin B2) as a photoactivating agent and irradiating the product with ultraviolet rays.
Riboflavin-UV-FFP: FFP pathogen inactivated using the riboflavin-UV method.
SD plasma: FFP virus inactivated by solvent-detergent method.
Solvent-detergent (SD): a virus inactivation method for killing viruses with lipid envelopes.
Complete ADAMTS13 remission: ADAMTS13 activity exceeds the lower limit of the normal range.

2. Acronyms

ANA – Anti-nuclear antibody
ANCA – Anti-neutrophil cytoplasmic antibody
AKI – acute kidney injury
ADAMTS13 – A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13;
aHUS– atypical HUS
anti-Gbm – Anti-glomerular basement membrane antibody
APA – antiphospholipid antibody
BCSH – British Society for Haematology
BF – Complement factor B
BSC – Best supportive care
C3 – Complement component C3
C4 – Complement component C4
C5 – Complement component C5
CD46 – Membrane cofactor protein, or cluster of differentiation antigen 46
CFB – Complement factor B
CFH – Complement factor H
CFHR1 – Complement factor H-related 1
CFI - Complement factor I
CMV – Cytomegalovirus
CRP – C-reactive protein
DGKE – diacylglycerol kinase epsilon
DIC – disseminated intravascular coagulation
DNA – deoxyribonucleic acid
dsDNA – double stranded DNA
EBV – Epstein-Barr virus
EHEC – Enterohaemorrhagic E. coli
ENA – extractable nuclear antigen
ESRD – End stage kidney disease
FcRN – neonatal Fc receptor
FFP – fresh frozen plasma
HBV – Hepatitis B virus
HCV – Hepatitis C virus
HELLP – haemolysis, elevated liver enzymes, low platelet count
FH – complement factor H
HIV – human immunodeficiency virus
HUS – haemolytic uraemic syndrome

IBD – inflammatory bowel disease
FI – complement factor I
ISU – immunosuppressant treatment
ITP – immune thrombocytopenia
iTTP – immune thrombotic thrombocytopenic purpura
IVIG – intravenous immunoglobulin
LDH – lactate dehydrogenase
LMWH - low-molecular weight heparin
LPS – lipopolysaccharide
MAHA – microangiopathic haemolytic anaemia
MCP – membrane cofactor protein (CD46)
Met 1606 – methionine 1606
MMACHC – methylmalonic aciduria and homocystinuria
NAC – N-acetylcysteine
NEAK – National Health Insurance Fund
OGYÉI – National Institute of Pharmacy and Nutrition
PCR – polymerase chain reaction
PEX – plasma exchange
PLG – plasminogen
PNH – paroxysmal nocturnal haemoglobinuria
RIPA – ristocetin-induced platelet aggregation
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
SLE – systemic lupus erythematosus
SP-HUS – *Streptococcus pneumoniae*-associated HUS
SSC – Systemic sclerosis
STEC-HUS – Shiga toxin-producing Escherichia coli-associated haemolytic uremic syndrome
THBD – thrombomodulin
TMA – thrombotic microangiopathy
TTP: thrombotic thrombocytopaenic purpura
Tyr 1605 – tyrosine 1605
ULVWF – ultra-large VWF
USS – Upshaw-Schulman syndrome
VTEC / STEC – Verotoxin- / Shiga toxin-producing Escherichia coli
VWF – von Willebrand factor

3. The level of evidence
The classification system used for the level of evidence is based on the GRADE nomenclature [193].

In the text, the development group rated scientific evidence and its credibility and scientific support in parentheses following the text description, for instance: (A). The development group used the following levels:

Evidence level A (A)	Based on several randomised, controlled trials or studies or the meta-analysis of studies. Further research is unlikely to alter the reliability of the evidence.
Evidence level B (B)	Evidence from at least one randomised, controlled trial or several non-randomised studies with the same conclusion. Further research is likely to alter the reliability of the evidence and the evidence may change in the future.
Evidence level C (C)	Only corroborated by professional consensus that is based on the coherent opinion of experts, case presentations or the results of small trials. Further research is very likely to alter the reliability of the evidence and the evidence may change in the future.
Evidence level D(D)	Used to classify expert opinions based on domestic professional consensus within a system.

4. The ranking of recommendations
The system used for ranking recommendations is based on the GRADE nomenclature [193].

In the text, the development group classified recommendations in parentheses following the text description, for instance: (1). The development group used the following levels:

1, Strong (grade 1)	The recommendation is classified as strong if clinicians are unanimously convinced that the patient benefit that can be achieved based on recommendation outweighs (or does not outweigh) the expected risk or burden. Strong recommendations can apply generally to all patients, and the following terms can be validly used: 'recommended' or 'must'.
2, Weak (grade 2):	A recommendation is classified as weak if clinicians deem that the benefits and risks/burden are balanced or if there is uncertainty in assessing the balance of benefits to risks/burdens. A recommendation is also classified as weak if the patient's opinion or preference may impact the clinical decision. Weak recommendations may only be applied with great caution in clinical decisions, and the following terms should be used for them: 'should be considered', 'suggested' or 'should be contemplated'.

When the adapted guidelines used a different classification system, the Hungarian development group adopted the classification used by the BCSH Guideline [1] and classified recommendations from other adapted guidelines using this system. If adapted guidelines assigned a different grade to a specific recommendation, the development group applied the lower recommendation classification grade.

V. INTRODUCTION

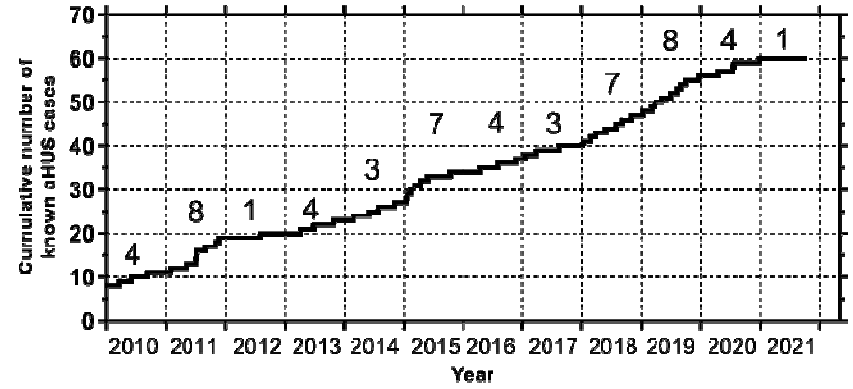
1. The topic's situation in Hungary, choice of topic

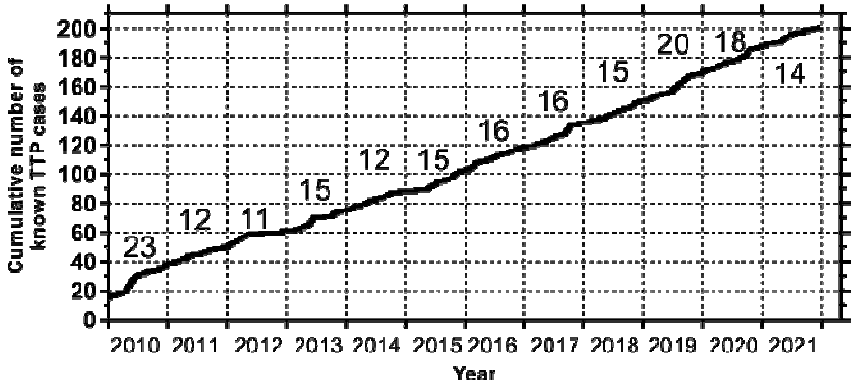
Research aimed at elucidating the pathomechanism of thrombotic microangiopathies has yielded significant results in recent decades. Searching for underlying molecular mechanisms has become routine practice. Knowing these results is currently essential for choosing the right treatment strategy. TTP and HUS are highly similar clinical syndromes that are both classified as thrombotic microangiopathies. They both involve microvascular platelet aggregation, however the localisation and extent of aggregation differs substantially, and therefore so does the clinical presentation.

Most modern, cost-effective methods are available in Hungarian medical care. However, a systematically structured medical guideline to help identify the patients in need of medical care and give them evidence-based care seems called for, taking into consideration that numerous major changes have emerged on the disease group since the 2017 publication of the last medical guideline on the condition, which warranted the drafting of an entirely new medical guideline.

Given the fact that thrombotic microangiopathies are not notifiable diseases and that there is currently no way to accurately code the different forms of the disease based on ICPM, no systematicsurvey has been conducted to determine the epidemiological situation in Hungary. Since 2010, the FüstGyörgy Complement Diagnostic Laboratory of the Department of Internal Medicine and Haematology of Semmelweis University has been providing complement and ADAMTS13 diagnostic measurements to all healthcare providers in Hungary. Figure 1 shows the evolution of the number of cases detected by the Laboratory since 2010. By the end of 2021, 60 patients with complement-mediated atypical HUS and 201 patients with ADAMTS13-deficient TTP had been diagnosed in this laboratory, corresponding to an incidence of 0.43 aHUS/year/million people and 1.43 TTP/year/million people, but the real incidence may be higher.

Figure 1: Annual trends in the number of patients diagnosed with aHUS and TTP at the FüstGyörgy Complement Diagnostic Laboratory of the Department of Internal Medicine and Haematology of the Semmelweis University. The curve shows the cumulative number of cases, and the numbers above the curve show the number of cases diagnosed in a given year.





2. User group

This medical guideline has been created to provide recommendations based on the most recent evidence for the daily practice of the physicians active in the professions specified in the scope of this guideline.
It also strives to provide clear guidance to healthcare decision-makers and providers of medical care by acting as a reference for designing services based on the most recent evidence.
This medical guideline can be recommended to all patients and their relatives, patient representative bodies and NGOs to provide concise professional information on the steps involved in treatment provided in Hungary.

3. Contacts for official Hungarian and foreign medical guidelines

Antecedents to this medical guideline:
This development addresses the issues of the following outdated medical guideline.

Author:	Ministry of Human Capacities, National Advisory Board of Healthcare, Transfusiology and Haematology Section
Title:	Medical Guideline — On the treatment of thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS)
Type:	Clinical Medical Guideline
ID no.:	002019
Effective:	24.01.2017 – 24.01.2020

This publication is a revision of the above medical guideline, factoring in the international guidelines published in recent years.

Links to foreign medical guidelines:
This guideline has been created using the recommendations of the following foreign guidelines.

On the treatment of thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS)

Author(s):	M Scully, S Cataland, P Coppo, J de la Rubia, K D Friedman, J Kremer Hovinga, B Lämmle, M Matsumoto, K Pavenski, E Sadler, R Sarode, H Wu, International Working Group for Thrombotic Thrombocytopenic Purpura.
Scientific organisation:	International Working Group for Thrombotic Thrombocytopenic Purpura
Title:	Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies [2].
Publication data:	-
Access:	Journal of Thrombosis and Haemostasis, 15: 312–322. doi: 10.1111/jth.13571.

Author(s):	X. Long Zheng, Sara K. Vesely, Spero R. Cataland, Paul Coppo, Brian Geldziler, Alfonso Iorio, Masanori Matsumoto, Reem A. Mustafa, Menaka Pai, Gail Rock, Lene Russell, Rawan Tarawneh, Julie Valdes, Flora Peyvandi:
Scientific organisation:	International Society on Thrombosis and Haemostasis
Title:	ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura [3].
Publication data:	https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.15006
Access:	J ThrombHaemost. 2020;18:2486–2495. (DOI: 10.1111/jth.15006)

Author(s):	X. Long Zheng, Sara K. Vesely, Spero R. Cataland, Paul Coppo, Brian Geldziler, Alfonso Iorio, Masanori Matsumoto, Reem A. Mustafa, Menaka Pai, Gail Rock, Lene Russell, Rawan Tarawneh, Julie Valdes, Flora Peyvandi
Scientific organisation:	International Society on Thrombosis and Haemostasis
Title:	ISTH guidelines for treatment of thrombotic thrombocytopenic purpura [4].
Publication data:	https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.15010
Access:	J ThrombHaemost. 2020;18:2496–2502. (DOI: 10.1111/jth.15010)

Author(s):	X. Long Zheng, Sara K. Vesely, Spero R. Cataland, Paul Coppo, Brian Geldziler, Alfonso Iorio, Masanori Matsumoto, Reem A. Mustafa, Menaka Pai, Gail Rock, Lene Russell, Rawan Tarawneh, Julie Valdes, Flora Peyvandi
Scientific organisation:	International Society on Thrombosis and Haemostasis
Title:	Good practice statements (GPS) for the clinical care of patients with thrombotic thrombocytopenic purpura [5].
Publication data:	https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.15009
Access:	J ThrombHaemost. 2020;18:2503–2512. (DOI: 10.1111/jth.15009)

Author(s):	Mary Hughes, Carl Prescott, Nicole Elliott, Amanda I Adler)
Scientific organisation:	The National Institute for Health and Care Excellence (NICE)
Title:	NICE guidance on caplacizumab for treating acute acquired thrombotic thrombocytopenia purpura [6].
Publication data:	-
Access:	Lancet Haematol. 2021 Jan;8(1):e14-e15. doi: 10.1016/S2352-3026(20)30406-3.

Author(s):	Lucy Fox, Solomon J. Cohney, Joshua Y. Kausman, Jake Shortt, Peter D. Hughes, Erica M. Wood, Nicole M. Isbel, Theo de Malmanche, Anne Durkan, Pravin Hissaria, Piers Blombery, Thomas D. Barbour
Scientific organisation:	-
Title:	Consensus opinion on diagnosis and management of thrombotic microangiopathy in Australia and New Zealand [7].
Publication data:	-
Access:	Nephrology (Carlton). 2018 Jun;23(6):507-517. doi: 10.1111/nep.13234.

Author(s):	Masanori Matsumoto, Yoshihiro Fujimura, Hideo Wada, Koichi Kokame, Yoshitaka Miyakawa, Yasunori Ueda, Satoshi Higasa, TakanoriMoriki, Hideo Yagi, Toshiyuki Miyata, Mitsuru Murata, For TTP group of Blood Coagulation Abnormalities Research Team, Research on Rare and Intractable Disease supported by Health, Labour, and Welfare Sciences Research Grant
Scientific organisation:	**-**
Title:	Diagnostic and treatment guidelines for thrombotic thrombocytopenic purpura (TTP) 2017 in Japan [8].
Publication data:	https://link.springer.com/article/10.1007/s12185-017-2264-7
Access:	Int J Hematol. 2017;106:3-15. (DOI 10.1007/s12185-017-2264-7)

Author(s):	Ronald S Go, Jeffrey L Winters, Nelson Leung, David L Murray, Maria A Willrich, Roshini S Abraham Hatem Amer, William J Hogan, Ariela L Marshall, Sanjeev Sethi, Cheryl L Tran, Dong Chen, Rajiv K Pruthi, Aneel A Ashrani, Fernando C Fervenza, Carl H Cramer, Vilmarie Rodriguez, Alexandra P Wolanskyj, Stephan D Thomé, C Christopher Hook
Scientific organisation:	Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group
Title:	Thrombotic Microangiopathy Care Pathway: A Consensus Statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group [9].
Publication data:	**-**
Access:	Mayo Clin Proc. 2016 Sep;91(9):1189-211. doi:10.1016/j.mayocp.2016.05.015. Epub 2016 Aug 3.

On the treatment of thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS)

Author(s):	Adam Cuker, Spero R Cataland, Paul Coppo, Javier de la Rubia, Kenneth D Friedman, James N George, Paul N Knoebl, Johanna A Kremer Hovinga, Bernhard Lämmle, Masanori Matsumoto, Katerina Pavenski, Flora Peyvandi, Kazuya Sakai, Ravi Sarode, Mari R Thomas, Yoshiaki Tomiyama, Agnès Veyradier, John-Paul Westwood, Marie Scully
Scientific organisation:	-
Title:	Redefining outcomes in immune TTP: an international working group consensus report [10].
Publication data:	-
Access:	Blood. 2021 Apr 8;137(14):1855-1861. doi: 10.1182/blood.2020009150.

Author(s):	Marie Scully, Beverley J. Hunt, Sylvia Benjamin, Ri Liesner, Peter Rose, Flora Peyvandi, Betty Cheung, Samuel J. Machin and on behalf of British Committee for Standards in Haematology
Scientific organisation:	British Committee for Standards in Haematology
Title:	Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies [1].
Publication data:	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2012.09167.x/pdf
Access:	British Journal of Haematology. 2012:158:(3):323–335

Author(s):	Sarode R, Bandarenko N, Brecher ME, Kiss JE, Marques MB,Szczepiorkowski ZM, Winters JL
Scientific organisation:	American Society for Apheresis (ASFA)
Title:	Thrombotic thrombocytopenic purpura: 2012 American Society for Apheresis (ASFA) consensus conference on classification, diagnosis, management, and future research [11].
Publication data:	http://onlinelibrary.wiley.com/doi/10.1002/jca.21302/pdf
Access:	Journal of Clinical Apheresis.2014:29:(3):148-67

Author(s):	Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, Coppo R, Emma F, Johnson S, Karpman D, Landau D, Langman CB, Lapeyraque AL, Licht C, Nester C, Pecoraro C, Riedl M, van de Kar NC, Van de Walle J, Vivarelli M, Frémeaux-Bacchi V; for HUS International.
Scientific organisation:	HUS International
Title:	An international consensus approach to the management of atypical hemolytic uremic syndrome in children [12].
Publication data:	http://www.ouhsc.edu/platelets/documents/C-tmaarticle.pdf
Access:	Pediatr Nephrol. 2016 Jan;31(1):15-39

Author(s):	M. Salvadori, E. Bertoni
Scientific organisation:	-
Title:	Update on hemolytic uremic syndrome: Diagnostic and therapeutic recommendations [13].
Publication data:	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3832913/pdf/WJN-2-56.pdf
Access:	World J Nephrol. 2013 Aug 6;2(3):56-76.

Medical Guideline **002168**

On the treatment of thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS)

Author(s):	Campistol JM, Arias M, Ariceta G, Blasco M, Espinosa L,Espinosa M, Grinyó JM, Macía M, Mendizábal S, PragaM,Román E, Torra R, Valdés F, Vilalta R, Rodríguez de Córdoba S
Scientific organisation:	-
Title:	An update for atypical haemolytic uraemic syndrome: Diagnosis and treatment. A consensus document [14].
Publication data:	http://digital.csic.es/bitstream/10261/80425/1/P1-E547-S3861-A11781-EN.pdf
Access:	Nefrologia. 2013;33(1):27-45

Author(s):	Zuber J, Fakhouri F, Roumenina LT, Loirat C, Frémeaux-Bacchi V; French Study Group for aHUS/C3G
Scientific organisation:	French Study Group for aHUS/C3G
Title:	Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies [15].
Publication data:	http://www.nature.com/nrneph/journal/v8/n11/pdf/nrneph.2012.214.pdf
Access:	Nat Rev Nephrol. 2012 Nov;8(11):643-57.

Author(s):	GemaAriceta, NesrinBesbas, Sally Johnson, Diana Karpman, Daniel Landau, Christoph Licht, Chantal Loirat, Carmine Pecoraro, C. Mark Taylor, Nicole Van de Kar, Johan VandeWalle, Lothar B. Zimmerhackl - The European Paediatric Study Group for HUS
Scientific organisation:	The European Paediatric Study Group for HUS
Title:	Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome [16].
Publication data:	http://link.springer.com/article/10.1007/s00467-008-0964-1
Access:	Pediatr Nephrol (2009) 24:687–696

Author(s):	Taylor CM, Machin S, Wigmore SJ, Goodship TH; working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society
Scientific organisation:	Working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society
Title:	Clinical Practice Guidelines for the management of atypical Haemolytic Uraemic Syndrome in the United Kingdom [17].
Publication data:	http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2009.07916.x/epdf
Access:	British Journal of Haematology. 2010:148:(1):37-47

Author(s):	Johnson S, Stojanovic J, Ariceta G, Bitzan M, Besbas N, Frieling M, Karpman D, Landau D, Langman C, Licht C, Pecoraro C, Riedl M, Siomou E, van de Kar N, Walle JV, Loirat C, Taylor CM
Scientific organisation:	-
Title:	An audit analysis of a guideline for the investigation and initial therapy of diarrhea negative (atypical) hemolytic uremic syndrome [18].
Publication data:	http://link.springer.com/article/10.1007%2Fs00467-014-2817-4
Access:	Pediatr Nephrol. 2014 Oct;29(10):1967-78.

Related to the following Hungarian medical guideline(s):
This guideline is not related to any other Hungarian medical guideline.

VI. MEDICAL DETAILS OF THE RECOMMENDATIONS

INTRODUCTION

Research aimed at elucidating the pathomechanism of thrombotic microangiopathies has yielded significant results in recent decades. Searching for underlying molecular mechanisms has become routine practice. Knowing these results is currently essential for choosing the right treatment strategy. TTP and HUS are highly similar clinical syndromes that are both classified as thrombotic microangiopathies. They both involve microvascular platelet aggregation, however the localisation and extent of aggregation differs substantially, and therefore so does the clinical presentation.
Figure 2 shows the classification of thrombotic microangiopathies. **Table 1** shows typical age-related occurrence.

Figure 2: Classification of thrombotic microangiopathies [12].

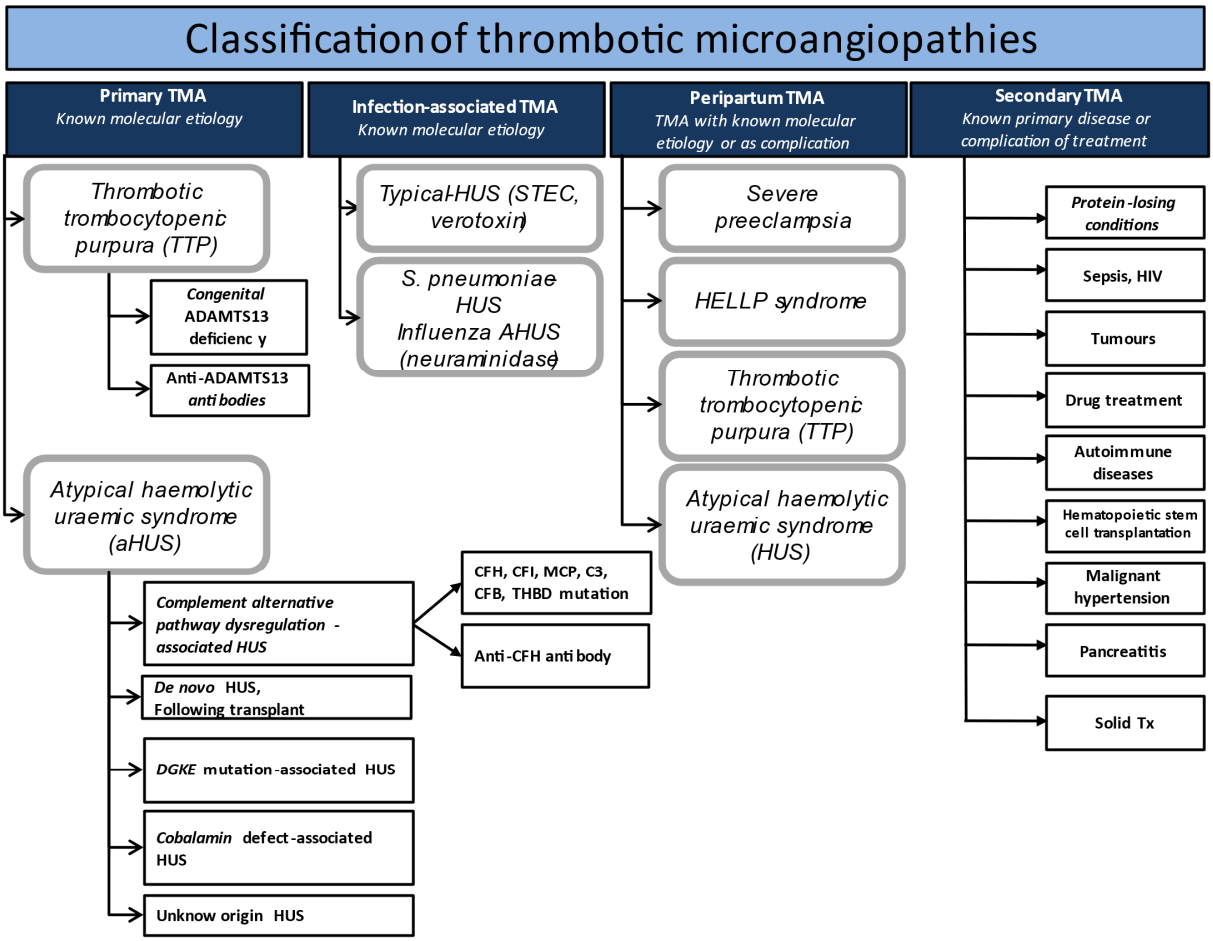


Table 1: TTP and HUS: age-related onset of clinical conditions with a known pathomechanism [19].

Typical age-related onset	Probable diagnosis	Clinical presentation	Tests confirming the diagnosis
From neonate to adult age	Congenital TTP (Upshaw-Schulman sy)	severe jaundice, 'burgundy' urine without any significant haematuria, similar symptoms in blood relatives or siblings, neonatal death	ADAMTS13 activity <10% Absence of ADAMTS13 inhibitor ADAMTS13 genetic mutation
Pregnancy	'Late-onset' USS	absence of foetal development or foetal death (42%), or clinical TTP in the third trimester	
Neonates – <6 months of age	Methylmalonic aciduria-HUS (Cobalamin-C defect)	feeding difficulties, stunted growth and development, hypotension	hyperhomocysteinaemia, hypomethionaemia, methylmalonic aciduria, MMACHC mutation
Neonate <1–2 years of age	Diacylglycerol kinase epsilon (DGKE) mutation	hypertension, haematuria, proteinuria, renal failure	DGKE genetic mutation
< 2 years	Pneumococcal-associated HUS (neuraminidase-associated HUS)	fever, invasive S. pneumoniae infection: pneumonia, meningitis, septicaemia (empyema, subdural abscess)	positive direct Coombs, T antigen activation, positive culture (blood, cerebrospinal fluid), PCR
>6 months – <5 years	STEC-HUS (formerly D+HUS)	Acute gastroenteritis, (bloody) diarrhoea in the past two weeks in a STEC or Shigelladysenteriae endemic region	stool culture: MacConkey agar: 0157:H7, PCR: Shiga toxin serum: anti-LPS antibodies
From adolescence to adult age	Autoimmune TTP	haematological symptoms neurological symptoms + renal involvement of varying degree fever	ADAMTS13 activity <10% ADAMTS13 inhibitor
From birth to adulthood	Complement-mediated aHUS	haematological symptoms symptoms of acute kidney injury symptoms suggestive of atypicality (Table 8)	complement C3, C4alternative total complementFH, FB, FI, MCP expressionanti-FH antibody complement genetic test

HUS: haemolytic uraemic syndrome; TTP: thrombotic thrombocytopaenic purpura; ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; MMACHC: methylmalonic aciduria and homocystinuria; PCR: polymerase chain reaction; STEC: Shiga toxin-producing Escherichia coli; LPS: lipopolysaccharide; FH: complement factor H; FI: complement factor I; FB: complement factor B; MCP: membrane cofactor protein (CD46)

THROMBOTIC THROMBOCYTOPAENIC PURPURA (TTP) OR MOSCHCOWITZ SYNDROME

Incidence

Previously estimated at 1/1 million [20], the most recent data suggest an annual prevalence of about 10/1 million and a new case rate of 1-2/1 million [21]. This is only partially due to greater familiarity with the condition and the easing of diagnostic criteria. Approx. 2/3 of patients are women, within the 30–40-year age group, but the condition may occur at any age.

Definition of the condition

Thrombotic thrombocytopaenic purpura is a clinical entity classified among thrombotic microangiopathies. The clinical condition was first described by Dr Eli Moschcowitz in 1924. The characteristic clinical pentad includes

thrombocytopenia caused by platelet consumption, microangiopathic haemolytic anaemia, fluctuating neurological symptoms, renal involvement and fever. However, the full pentad can be detected only in a very small percentage of cases [21], the first 3 symptoms (triad) being much more common. *Unexplained thrombocytopenia and microangiopathic haemolytic anaemia (diad) are sufficient for confirming the diagnosis.* The basis of pathological events is uncontrolled platelet aggregation and disseminated microthrombi formation (containing platelets and von Willebrand factor) in the small blood vessels. Mortality is currently approximately 5–20% compared to over 90% before the 1970s. Acquired idiopathic, congenital/familial and secondary forms of TTP are also known. Its clinical course may be episodic or relapsing. Due to the similarity of clinical and laboratory symptoms, particularly in the adult literature, TTP was not distinguished from HUS in the past, and was referred to as TTP/HUS or HUS/TTP. Today however, we must strive to establish an accurate diagnosis because the two conditions differ not only in terms of pathomechanism, but also the required therapy.

Pathomechanism

A significant decrease in the activity of the ADAMTS13 (a distintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) metalloprotease enzyme was observed in the majority of patients [22, 23].

The enzyme's physiological role is to decompose the von Willebrand factor (VWF); it cleaves the peptide bond between Tyr1605 and Met1606. In its absence, the cleavage of endothelial VWF does not take place, resulting in the appearance of so-called ultra-large VWF (ULVWF) multimers in the bloodstream. Their adhesiveness to normal multimers is far greater; the shear stress creates direct aggregation of platelets in the small blood vessels. The decrease in enzyme activity may be caused by both the IgG isotype autoantibody acting as an inhibitor (roughly 90%) or a genetically defined defect (roughly 10%) in enzyme function. Rarely, despite deficient activity, no inhibitor can be detected, but the normalisation of ADAMTS13 activity upon treatment suggests other mechanisms of action that are not yet clear [21]. Other cases may consist of a relative deficiency of the enzyme resulting from consumption. TTP is characterised by "deficient" (insufficient) enzyme activity of under 10%; a slight decrease can be demonstrated in many different clinical conditions.

The ADAMTS13 enzyme is predominantly produced by the liver; its gene is located on chromosome 9 at location q34. The enzyme's half-life is approx. 1 week *in vitro* and just 2–4 days *in vivo*. At the same time, in the event of genetic enzyme deficiency, replacement of the enzyme via FFP transfusion yields a far longer, 1–4-week asymptomatic state. The contradiction is assumed to stem from the binding of the enzyme to the endothelium, which would serve as a sort of reservoir. According to preliminary data, the CD36 receptor [24] may play a role in this. It is important to note that the absence of ADAMTS13 enzyme activity alone does not cause TTP and only increases the risk of developing the disease. Diffuse endothelial activation or a different trigger mechanism is necessary to launch the process. The most common clinical triggers are infections (respiratory, urinary tract or gastrointestinal), pregnancy and surgery.

In a small percentage of cases, ADAMTS13 activity is normal or barely decreased, and the precise pathomechanism is not yet fully understood. The clinical and laboratory symptoms may overlap significantly with atypical haemolytic uraemic syndrome and secondary thrombotic microangiopathies. It is important to clarify the pathomechanism as soon as possible, as the therapies applied are different today. This requires taking a detailed clinical history that includes the family, researching comorbidities and triggers and taking a blood sample before starting treatment (to clarify the molecular mechanism, see below).

Recent clinical data suggest that ADAMTS13 plays an important role in the overall protection against arterial thrombosis: in non-TTP patients, ADAMTS13 activity levels in the lowest quartile may increase the risk of acute ischaemic stroke [25, 26].

Clinical symptoms

The clinical presentation of TTP is very diverse and may copy many different clinical conditions depending on the localisation of the ischaemia caused by microthromboses. The disease generally has a sudden onset without a typical prodromal phase.

Haematological symptoms:

- Symptoms caused by thrombocytopaenia: severe bleeding is rare even in the case of severe thrombocytopaenia: purpura and petechiae are observed most frequently on the skin and mucous membranes; gastrointestinal, gynaecological, ocular fundus or other bleeding is rare. Sometimes no bleeding symptoms can be detected despite the low platelet count.
- Symptoms of intravascular haemolysis: no or mild jaundice, burgundy-brown urine. This may be accompanied by symptoms of anaemia to varying degrees. Rarely, the onset of the condition may be similar to ITP, in which case anaemia and possibly schistocytosis only present several days later.

Neurological symptoms:
It is detected in 70-80% of cases. Common and characteristic symptoms include violent headaches (sometimes occurring as a prodrome) and fluctuating levels of consciousness, frequently perceived aphasia, focal neurologic signs and seizures may also occur. The symptoms often 'shift' and often cannot be tied to a single focus, and typical stroke may also occur rarely.
Gastrointestinal symptoms:
Epigastric pain, nausea and vomiting are common symptoms, diarrhoea is a rare symptom. Pancreatitis can occur both as a trigger or a complication.
Renal symptoms:
Abnormal urine results (proteinuria, microhaematuria, haemoglobinuria) are very common, but in some cases, urinary abnormality may be absent or mimic tubular necrosis. According to the French study group's data, the vast majority of ADAMTS13-deficient patients had an initial creatinine level of <200 micromol/L [27]. For a precise assessment of acute kidney injury (AKI), see **Table 7** below; the increasing creatinine and the evolution of diuresis may provide guidance to the extent and dynamics of AKI. Stage 3 AKI (failure) is rare.
Cardiovascular symptoms:
Heart failure, arrhythmia, acute myocardial infarction and hypertension are uncommon, but may occur.
Fever:
Part of the pentad, and does not stem from infection. In the presence of fever, any potential infection must always be investigated and treated, as it may have a role in triggering and maintaining the condition.
Other symptoms:
TTP involves the entire body, so any organ may be affected, although the liver (the liver primarily produces the ADAMTS13 enzyme) and the lungs are mostly spared. Over 10% of patients require artificial respiration due to coma which occurs in some cases.
It is not always easy to diagnose TTP. The diversity of symptoms in some cases and conversely, the absence of symptoms and the clinical presentation reminiscent of ITP and Evans syndrome (ITP and autoimmune haemolytic anaemia) may be misleading. Ischaemic symptoms (stroke, myocardial infarction, 'acute abdomen' etc.) may not only precede the characteristic haematological abnormalities, but may also dominate the clinical presentation.

Diagnosis
Confirming *unexplained thrombocytopaenia and microangiopathic haemolytic anaemia (diad)* is still enough today to establish the clinical diagnosis of TTP and to begin therapy. **Table 2** specifies the laboratory tests necessary for diagnosis and the immediate start of treatment, **Table 3** specifies the tests required for a differential diagnosis and for choosing the optimal therapy, and **Table 4** contains the main conditions to be distinguished.

Recommendation 1
The clinical diagnosis necessary for starting treatment must be based on the clinical history, clinical symptoms, a physical exam and the results of the routine laboratory tests specified in Table 2 [1]**. (1A)**

Table 2: Tests necessary to determine and begin immediate treatment of thrombotic microangiopathies (TTP and HUS) to be performed urgently [1]. and see **Table 5** too.

The diagnosis requires	**Typical value**
direct Coombs test	negative
complete blood count	thrombocytopenia (TTP<30 G/l; HUS <150 G/l), anaemia, reticulocytosis
peripheral blood smear	schistocytosis+ nucleated red blood cells, spherocytes, polychromasia basophilic stippling
serum haptoglobin	low/unmeasurably low
serum indirect bilirubin	normal/slightly abnormal/rarely elevated

Lactate dehydrogenase (LDH)	high (most often 1000–5000 IU/L)
transaminases	normal/slightly abnormal
screening coagulogram (PT, APTI, fibrinogen)	normal/slightly abnormal
Increased creatinine	TTP: often moderate, creatinine remains below 200 micromol/L HUS: often significant, for an accurate assessment of the degree of acute kidney injury, see Table 7
troponin	normal/varying degrees of increase
C-reactive protein (CRP)	normal/slightly abnormal
procalcitonin	normal/slightly abnormal (renal failure: high)
complete urine	varying degrees of haemoglobinuria, proteinuria, (micro)haematuria

Recommendation 2
In order to determine the aetiology, the blood samples for the tests listed in Table 3 must be drawn before the first plasma exchange or plasma transfusion [194] and if necessary, stored under adequate conditions, sent to the laboratory or along with the patient if the patient is transferred [1]**. (1B)**

Table 3: Tests required for differential diagnosis and the selection of targeted therapy for thrombotic microangiopathies (TTP and HUS). [1, 12-14, 17, 28-30].

Tests required for differential diagnosis and the selection of therapy	**Comment**
pregnancy test	for women of childbearing age
eye exam, ocular fundus exam	If malignant hypertension is suspected
kidney biopsy if feasible, histological exam	To confirm the final diagnosis of TMA, to assess the reversibility of kidney damage
virology (HIV, hepatitis A/B/C/E, CMV, EBV, +/- other)	the blood sample must be drawn and sent to the laboratory prior to starting therapy
screening test for autoimmune disease (RF, ANA, dsDNA, ENA screening, C3, C4, lupus anticoagulant, antiphospholipid antibodies, In the event of acute kidney injury: ANCA, anti-GBM as well	the blood sample must be drawn and sent to the laboratory prior to starting therapy
ADAMTS13 activity, antigen, inhibitor, genetic test	prior to starting therapy, the blood sample must be drawn and stored according to the specialist laboratory's requirements or sent to the laboratory
complement screening test + complement genetic test + flow cytometry (CD46)	prior to starting therapy, the blood sample must be drawn and stored according to the specialist laboratory's requirements or sent to the laboratory
stool culture + verotoxin PCR	diarrhoea at the onset of the condition or in the 1–2 weeks directly preceding onset
Examination of cobalamin metabolism (plasma, homocysteine, plasma + urine methylmalonic acid, vitamin B12 level, genetic test)	it is recommended in all paediatric cases and in the event of hyperhomocysteinaemia in young adults

Recommendation 3
ADAMTS13 activity and inhibitor profile must be defined at least from a blood sample taken before the first plasma exchange/plasma transfusion in all cases clinically considered to be TTP [1]**. (1B)**

Table 4: Main clinical conditions to be excluded in the differential diagnosis of TTP and HUS [1, 12-14, 17, 28-30].
Immune thrombocytopenia
Autoimmune haemolytic anaemia
Evans syndrome (autoimmune haemolytic anaemia and thrombocytopaenia)
Disseminated intravascular coagulation
(Pre)eclampsia, HELLP syndrome
Cobalamin C deficiency (children, young adults), vitamin B_{12} deficiency (adults)
Secondary thrombotic microangiopathies (see **Table 11**)
Thrombocytopaenia and/or other causes of haemolysis

Clinical forms

Congenital/familial TTP (cTTP)-Upshaw-Schulman syndrome (USS) [31].
The underlying cause is the homozygous or double heterozygous genetic mutation of the ADAMTS13 enzyme (up to now, >150 mutations have been described); the inheritance pattern is autosomal recessive. <10% of all TTP cases fall into this group. More severe early onset and milder late onset clinical forms are known. Cumulative occurrence of the latter has been observed during pregnancy [32].

Recommendation 4
USS must be considered in the event of severe jaundice presenting in neonates. The clinical onset may sometimes occur during childhood or even adulthood [1].(1A)

Recommendation 5
USS must be considered in the event of thrombocytopaenia of unknown origin in childhood or adulthood [1]. (1B)
The most severe cases begin during the neonatal period; the most characteristic clinical manifestations include severe neonatal jaundice and continental thrombocytopaenia. Follows the course of a chronic cyclical cTTP with relapses. Exhibits characteristic periodicity, with relapses generally occurring every 3–4 weeks. Mono- and oligosymptomatic forms are both known. Childhood symptoms are mild, reminiscent of ITP or atypical (Coombs-negative) Evans syndrome, with the characteristic clinical presentation unfolding only in young adulthood, as a result of pregnancy, infection, alcohol abuse, surgery, vaccination, stress, etc. Rarely, the presentation of the first episode may be delayed until age 50 [1]. Common symptoms in these patients may include headache, migraine and abdominal pain, which may occur even with normal blood count parameters and may respond well to plasma therapy [33].

Recommendation 6
A diagnosis of USS can be established based on an ADAMTS13 enzyme activity of under 10% and the resulting deficiency in the inhibitor. The diagnosis can be confirmed by demonstrating the homozygous or compound heterozygous genetic mutation of the ADAMTS13 gene [1]**. (1A)**

Recommendation 7
USS should be considered in primary blood relatives even if the patient is asymptomatic — an ADAMTS13 screening test is recommended, particularly in pregnant patients [1, 32]**. (1D)**
In the case of certain mutations, onset in adulthood or particularly during pregnancy is characteristic [32]. These must be distinguished from the idiopathic form based on non-normalising deficient (<10%) ADAMTS13 activity, the resulting deficiency in the anti-enzyme antibody/inhibitor, and the ULVWF multimers detectable in the blood stream during asymptomatic periods. The genetic test may confirm the diagnosis. Screening tests for primary blood relatives are recommended even in the absence of clinical symptoms.

Acquired autoimmune TTP (iTTP)
Idiopathic TTP is far more common than the familial form and is most often based on an autoimmune mechanism; ADAMTS13 enzyme deficiency develops due to the presence of inhibiting autoantibodies. It is therefore now also called autoimmune TTP (the abbreviation refers to “immunological pathomechanism”, iTTP).

Acute (or episodic) and chronic relapsing (intermittent) forms of the condition are known. In the latter, relapses follow each other irregularly.

Recently, it has become more widely accepted that iTTP refers to only a group of TMAs due to ADAMTS13 deficiency caused by anti-ADAMTS13 inhibitory autoantibodies [2]. Clarifying the exact pathomechanism is important because targeted therapies should be selected according to the molecular mechanism.

In patient groups with TTP clinically previously considered idiopathic, there is contradicting data on the frequency of deficient ADAMTS13 activity. According to numerous studies, nearly 100% of patients with idiopathic TTP fall within this group, with the inhibitor detectable in the blood stream in approximately 90% of patients at the onset of the condition and in an even higher percentage later on [11]. By contrast, the ratio of non-ADAMTS13 deficient patients is significant in mainly older studies, and moreover, these patients responded to the plasma exchange [34, 35]. The latter patient group was characterised by a weaker response to plasma exchange, higher mortality but a low relapse rate [36]. For the time being, it has not been decided whether the latter patient group forms a subgroup of idiopathic TTP of unknown (non-ADAMTS13) mechanism or based on an as yet undiscovered mechanism is rather classified as aHUS or secondary TMA [28, 37].

The following 2 scoring systems are now used to clinically differentiate between iTTP with ADAMTS13 deficiency and HUS [3]: the French score [27] and the PLASMIC score [38]. The two scoring systems consider the same parameters, except for MCV (**Table 5**).

Recommendation 8
If ADAMTS13 activity measurements are not available, the clinical diagnosis of iTTP can be made using the French scores or the PLASMIC scores [27, 38]. (2B)

Table 5: PLASMIC score [38] and FRENCH score [27]

Lab test	PLASMIC score	FRENCH score
Platelet count	<30 G/L (+1)	<30 G/L (+1)
Serum creatinine level	<176.84 µmol/L (+1)	<199.83 µmol/L (+1)
Signs of haemolysis (presence of at least 1 of the following) indirect bilirubin >34.2 µmol/L reticulocyte count >2.5% undetectable haptoglobin	(+1)	*
No history of active tumour in recent years	(+1)	*
No history of solid organ or stem cell transplantation	(+1)	*
INR <1.5	(+1)	*
MCV <90 fL	(+1)	NA
Probability of ADAMTS13 activity below 10%:	Score 0-4: 0-4% Score 5: -24% Score 6-7: 62-82%	Score 0: 2% Score 1: 70% Score 2: 94%

Each item is worth 1 point (+1); INR, international normalised ratio; MCV, mean corpuscular volume; SCT, stem cell transplantation;
**The French score can be used in TMA if there is no history of tumour, transplantation and unconfirmed disseminated intravascular coagulation in addition to fragmentation haemolysis. These are basic criteria and no specific points are awarded for them in the French score. The French score originally included the antinuclear factor.*
NA: MCV is not included in the French score.

Secondary TTP
Secondary TTP is discussed in detail along with secondary HUS in a later section (**Table 11**).

Therapy
The objective of therapy in TTP associated with an ADAMTS13 deficiency is the replacement and restoration of enzyme activity. Substitution therapy is indicated in the case of a genetically determined deficiency, plasma exchange to remove the inhibitor and substitute enzyme activity in the presence of antibodies against ADAMTS13, and immunosuppressive therapy to inhibit the reproduction of the inhibitor are indicated.

Treatment of congenital/familial cTTP [1, 11, 31].

Recommendation 9
Both plasma therapy (plasma transfusion or rarely plasma exchange) and, if plasma therapy is unavailable or contraindicated, coagulation factor VIII with ADAMTS13 activity can be used for treatment. The dose and treatment frequency must be determined so that the patient's platelet count remains stable above 150 g/L [1, 11, 31]. (1B)

Recommendation 10
In the case of recurrent plasma-responsive headache, lethargy, abdominal complaints, prophylactic plasma therapy should be considered even if blood count parameters are normal [33]. (2B)

Recommendation 11
During pregnancy, prophylactic plasma therapy is recommended [4]. (1C)

Recommendation 12
The patient should be informed about the possibility, expected benefits and possible adverse side effects of prophylactic plasma therapy [33]. (1D)

Recommendation 13
Treatment and care for USS should be provided in an oncohaematology (paediatric) or haematology (adult) centre experienced in the treatment of TTP [1]**. (1A)**

Treatment can be with FFP or virus inactivated plant plasma (pooled plasma, human, solvent-detergent treated). The dose per session is 10–15 mL/kg, generally every 1–3 weeks. The frequency of administration must be defined individually to keep the platelet count above 150 g/L. Plasma exchange is generally unnecessary. As there is no inhibitor, immunosuppressant treatment is not necessary. In pregnancy, plasma prophylaxis improves the life expectancy of both the mother and the foetus [32]. Even in the absence of haematological symptoms, prophylactic plasma therapy may be recommended if the patient has frequent recurrent headache, lethargy, and abdominal pain that responds well to plasma. Therefore, a normal platelet count in patients does not necessarily mean full clinical remission. In addition to the clinical signs mentioned above, an increase in organ damage markers and urinary protein/creatinine ratio may be indicative of subclinical activity [33]. Prophylactic plasma therapy reduces the incidence of cerebrovascular events, and can therefore be considered for use in completely asymptomatic patients [33].
In the event of plasma intolerance, an intermediate purity factor VIII product containing ADAMTS13 activity [39] may also be used as an alternative therapy, or more recently, an ultra-pure factor VIII product [40]. They have the advantage of being safe against viruses and being of small volume, i.e. no fluid load, but their efficacy can vary due to the fluctuating ADAMTS13 content of the products, and they are therefore less and less recommended [4].

Treatment of autoimmune iTTP [1, 11, 28].

Recommendation 14
iTTP requires emergency treatment [1]. (1A)

Recommendation 15
If iTTP is reasonably suspected, the adult patient must be transferred to the territorially competent hospital with an apheresis centre and haematology ward. If this has not been done for any reason, the haematology ward must be contacted by telephone and the patient's treatment discussed daily until the transfer [6]. (1D)
If iTTP is reasonably suspected (French score 2, see **Table 5**above), the patient must be sent to a haematology centre with a 24-hour apheresis service as soon as possible; if the patient cannot be transported, mobile PEX

must be requested. In this case, daily consultation is necessary with the territorially competent haematology centre.

First-line therapy

Recommendation 16
Plasma exchange must be started within 4–8 hours [1]. (1B)

Recommendation 17
If the plasma exchange fails for any reason, plasma transfusion should be administered [41, 42]. (1C)

Recommendation 18
The plasma exchange must be performed according to the specifications included in Table 6 [1]. (1B)

Table 6: The practice of plasma exchange in TTP [1].
– Volume: 1.5 plasma volumes/day (initially) 1.0 plasma volumes/day (once the patient's condition has stabilised)
– Substitution fluid: FFP (>50%)
– Frequency: daily
– Endpoint: haematological remission*
* *Platelet count >150 g/L on at least two consecutive days, with no signs of haemolysis and rising or normal haemoglobin level.*

Recommendation 19
If the patient's state is critical, or if it deteriorates in spite of starting therapy (e.g. artificial respiration is needed, new neurological or cardiac symptoms develop etc.), it is recommended to increase the intensity of plasma therapy (the volume and/or frequency of plasma exchange) [1, 43, 44].(2B)

If possible, treatment should be started immediately, but no later than within 4–8 hours [1]. A clinical diagnosis or reasonably suspected diagnosis (French score 2, see Table 5) established based on clinical history data, clinical symptoms, the results of the standard physical exam and the results of the laboratory tests specified in Table 2 is sufficient for initiating therapy. Plasma exchange (PEX) is still the first-line treatment to be opted for based on controlled data [41, 42]; its characteristics are summarised in Table 6.
For the plasma exchange, a centrifugal device [1] should be used. Nevertheless, positive experiences have been reported internationally using filtration devices at paediatric dialysis stations [45]. Treatment must be started at an intensity of 1.5 plasma volumes/day and may be decreased to 1 plasma volume/day once the patient's condition stabilises. If the patient's condition deteriorates in spite of starting therapy (e.g. artificial respiration is needed, new neurological or cardiac symptoms develop etc.), PEX can be repeated more frequently, twice daily [1, 43, 44] (currently not funded by NEAK). The latter can be induced by a very slow, almost continuous infusion of FFP (10-15 mL/kg) between PEXs, if the patient's circulation can tolerate it. We have had positive experiences with the latter at the South Pest Central Hospital.
The substitution fluid in the current Hungarian setting is either FFP or cryosupernatant (if available), but according to international guidelines [1, 14, 29] and practice, the use of virus-inactivated plasma would be warranted due to extremely high donor exposure. Virus inactivation can be performed in several ways, for instance with solvent detergent (SD), methylene blue, amotosalen/UVA or riboflavin/UV treatment. The protein S and alpha 2-antiplasmin content of SD plasma is lower, nevertheless it has proven to be equivalent to FFP in clinical studies [46]. Amotosalen/UVA/FFP has also proven just as effective [47], while the effectiveness of methylated blue/UVA/FFP was varied [48]. There is no data to date on the use of riboflavin/UV/FFP. During the first half of the plasma exchange, 5% albumin may also be given in lieu of FFP [49], but the substitution fluid must contain at least 50% FFP.

Recommendation 20
Plasma exchange must be repeated until haematological remission is achieved (platelet count of at least >150 g/L on two consecutive days, no sign of haemolysis, rising or normal haemoglobin level). (1A)

Recommendation 21

When haematological remission is achieved, the gradual reduction (tapering) of the frequency of plasma exchange is not recommended [1, 49]. (2B)

Recommendation 22
Close observation for at least one month following haematological remission is necessary, and the frequency of monitoring should be determined on an individual basis. (1D)

Recommendation 23
In the case of a steadily deteriorating or abnormal platelet count, continuation of plasma exchange is recommended until the condition stabilizes or haematological remission is achieved [1]. (1B)

When the platelet count becomes normalised, non-improving anaemia, reticulocytosis without an increase in haemoglobin, a haptoglobin level that remains low and insufficient ADAMTS13 activity, or a once again decreasing platelet count within the normal range may signal disease activity without symptoms, so the patient requires close monitoring. Residual neurological or renal symptoms upon reaching haematological remission (platelet count >150 g/L on 2 consecutive days or normal haemoglobin level) generally do not warrant the continuation of treatment. When haematological remission is achieved, a gradual decrease in the frequency of PEX (instead of sudden discontinuation) does not decrease the risk of relapse [49].
PEX alone does not decrease, but rather increases the production of the anti-ADAMTS13 antibodies so sustained remission can only be expected with the concomitant use of immunosuppressant treatment (see below).
Treatment should be restarted in the face of deteriorating results (exacerbation within 30 days of suspending or discontinuing treatment) until the patient's condition stabilises. Several months of treatment may be needed at times to achieve sustained remission. As a rule of thumb, if TTP does not respond or does not respond well to the treatment, other reasons for the condition (infection, tumour, autoimmune disease) must be investigated.

Late relapse (following 30 days of maintained haematological remission, i.e. inactive disease) observed in 20–50% of patients [1]; often triggered by pregnancy, surgery or infection, and responds similarly to the first episode, generally well. The time of late relapse is unpredictable. In our own (South-Pest Central Hospital) patient material, the longest asymptomatic period between two episodes was 24 years (!).

Alternative plasma therapy
If plasma exchange cannot be accessed within 4–8 hours, an FFP infusion should be given: its recommended daily dose is 20–30 mL/kg [9]. However, plasma exchange should be strived for, as the effectiveness of plasma infusion therapy is significantly lower according to controlled data [26, 27]. Blood for the specific tests listed in Table 3 must be drawn before the first FFP and stored or forwarded according to the specialist laboratory's instructions.

Immunosuppressant treatment (ISU) [1].
In iTTP of autoimmune (ADAMTS13 inhibitor) mechanism, the use of immunosuppressant therapy is broadly accepted. Data is available in the literature on the use of the following agents:

Recommendation 24
For cases where a platelet count below 30 G/L and the absence of acute renal function impairment (initial serum creatinine level below 200 µmol/L; see also Table 7 for an accurate assessment of renal impairment) are observed at the onset of the condition (or French score ≥2, see Table 5). In addition to plasma exchange, steroid therapy should be initiated as pulse therapy (1 g/day for 3 days in adults) or by giving a standard dose (1 mg/kg/day) [1, 27, 50-52]. (1B)

Recommendation 25
Both platelet count and ADAMTS13 activity should be considered when withdrawing corticosteroid (steroid) therapy [8]. It is recommended to check ADAMTS13 activity at each dose change. If the activity shows a downwards trend (even within the normal range), a review of immunosuppressive therapy is recommended. (1D)
Corticosteroids [50-52]:
The most commonly and longest used agents; their dose can vary between 1 mg/kg/day (iv. or per os) and pulse therapy (1 g/day for 3 consecutive days). If there is no contraindication, administration should be started as soon as possible; if possible, it should always be administered after plasma exchange. When switching to oral dosing, prednisolone is recommended instead of methylprednisolone. Both platelet count and ADAMTS13 activity should be considered during reduction. The initial dose (1 mg/kg/day) is maintained for 2 weeks, followed by a

rapid reduction to 0.5 mg/kg/day, after which the recommended dose should be reduced to 2.5-5 mg/week [8]. Following rituximab treatment, the degradation may be faster if ADAMTS13 activity is stable in the normal range.

Recommendation 26
The administration of rituximab is recommended if there is no haematological response (at least minimal) following 5 plasma exchanges (platelet count <50 g/L), the platelet count decreases following a temporary improvement and/or a new clinical symptom (neurological, cardiac etc.) presents [1]. (1B)

Recommendation 27
Rituximab may also be given as first-line treatment for patients in a critical condition [1, 53]. (1B)

Recommendation 28
The patient should be screened for HBV, HCV prior to starting rituximab treatment. If the patient tests positive for HBV, HCV, an individual treatment protocol must be designed with the involvement of an infectologist[54-56]. (1C)

Despite its off-label use, rituximab is part of standard treatments today. Cannot be administered during pregnancy and conception is not recommended for one year following administration [56]. Virological status must be determined prior to beginning treatment (mandatory: HBV and HBC) as the agent may cause viral reactivation [54-56]. If the patient tests positive, a personalised treatment plan must be designed with the help of an infectologist. The most frequently used dose: 375 mg/m^2, generally given once a week for 4 weeks. Fixed-dose therapy is now used in a very wide dose range (100 mg-1000 mg). The efficacy of low-dose rituximab (100 mg once a week for 4 weeks) has been confirmed in several recent studies [57, 58], and we have been using it successfully for years at the South Pest Central Hospital. If the patient's condition allows it, plasma exchange should not be performed on the day following administration, but an FFP infusion administered instead at a dose of approx. 10–15 mL/kg. If the plasma exchange cannot be omitted, at least 4 hours [59] must elapse before the next plasma exchange and more frequent administration of the agent (every 3–4 days) may be considered. B-cell count should be checked during rituximab treatment. Based on unconfirmed data, if the B cell count falls below the detectable level (≤1%) on Day +14 after Dose 1, an additional dose is probably not needed [60]. Rituximab accelerates the achievement of remission, decreases the need for plasma exchange, the length of hospital treatment and the one-year relapse rate [61]. Rituximab treatment started within 3 days has proved to be more effective compared to treatment started after 3 days [53]. If there is no haematological response (at least minimal) following five plasma exchanges (platelet count remains <50 g/L or the increase in platelet count is less than 2-fold), the platelet count decreases following a temporary improvement or a new clinical symptom (neurological, cardiac etc.) presents despite the treatment, rituximab is recommended. It is also considered as first-line treatment for critically ill patients, alongside plasma exchange and steroid therapy, and its use is generally gaining ground in therapy. It exerts an effect within 1–2 weeks, so it is unable to avert early death in all fulminant cases. B cell depletion lasts approximately 9 months after which production of the inhibitor may return and accordingly, it has no impact on late relapses [61].
Cyclophosphamide, vincristine, azathioprine, cyclosporine, mycophenolatemofetil, etc.:
Case reports and small-scale studies corroborate the efficacy of these agents. Cyclophosphamide is most strongly recommended [62]. The optimal dosing regimen is not known, but the regimens used in systemic autoimmune diseases are recommended or a single dose of 500 mg may be used [8]. Unconfirmed data suggest that up-front cyclophosphamide treatment (400 mg/m^2 6 times every 3 weeks) has similar efficacy to up-front rituximab treatment [63]. Cyclosporine itself may induce TTP, so great care is necessary when using it.
IV immunoglobulin:
Its standard dose is 2 g/kg over 2–5 days. As regards its efficacy, the data found in the literature are highly contradictory.

Inhibition of VWF and platelet interaction
By blocking the GPIbα binding site in the VWF A1 domain, platelet microthrombus formation can be inhibited. Among several experimental molecules (ARC1779:[64], GBR600:[65], ALX-0681:[66]), caplacizumab has recently been registered as an orphan drug for TTP. The efficacy and safety of caplacizumab in adult patients have been established in 2 randomized controlled studies [67, 68].
Caplacizumab:
It is an immediately effective symptomatic agent that does not affect the underlying disease, but stops disseminated microthrombosis formation, which is most often responsible for organ symptoms and death, by suspending VWF-mediated platelet aggregation. It is expected to make a major contribution to reducing

premature mortality and relapse cases. In the laboratory, its effect is indicated by a decrease in RIPA (ristocetin-induced platelet aggregation) and RICO (ristocetin cofactor) levels below 10% and 20%, respectively, and a decrease in VWF and factor VIII antigen levels, which return to baseline within 7 days of treatment discontinuation (INN-caplacizumab, SmPC [69]). In clinical practice, after a 10 mg IV loading dose (before the 1st PEX), a dose of 10 mg daily should be administered subcutaneously (immediately after PEXs). In trials, it reduced the time to remission, the number of days with plasma exchange, hospital and intensive care time, and the incidence of early exacerbation. There were no refractory patients or deaths among the patients treated with this agent. Adverse effects include mainly mild to moderate bleeding and therefore in patients with other coagulopathies or coadministration of anticoagulant/antiplatelet therapy, an individual risk/benefit analysis and very close monitoring are required. It does not affect the underlying autoimmune process, so administration of concomitant immunosuppressive therapy to suppress the production of inhibitors is very important. In the absence of this or if it is not sufficiently effective, exacerbation/relapse may occur after discontinuation of caplacizumab. The summary of product characteristics recommends that caplacizumab should be continued for 30 days after the last PEX. More recent clinical data suggest that monitoring VWF and ADAMTS13 activity in patients allows the therapy to be customized with significant cost savings. After achieving a stable 10% ADAMTS13, discontinuation of caplacizumab therapy before 30 days elapses did not result in relapse and was found to be safe. In some patients, in addition to monitoring VWF activity, the frequency of drug administration could also be reduced during the plasma exchange-free period [70].
More recent data suggest that caplacizumab may be an effective therapy without plasma exchange if plasma exchange cannot be administered for whatever reason [71].

Recommendation 29
Caplacizumab therapy can be initiated if ADAMTS13 activity is confirmed to be deficient or there is a significant clinical suspicion of TTP (thrombocytopenia not otherwise explained, fragmentation haemolysis, platelet count <30 G/L and serum creatinine <200 umol/L, or French score 2, see Table 5) and the result of ADAMTS13 activity is available optimally within 3 days, but no later than 1 week. Continuation of the caplacizumab therapy is recommended if ADAMTS13 deficiency (<10%) is confirmed, with individual decisions required for a baseline activity between 10-20%, while this medicinal product should not be recommended above 20% [3]. (1C)

Recommendation 30
In patients in haematological remission receiving immunosuppressive treatment, discontinuation of caplacizumab therapy may be considered on an individual basis if ADAMTS13 activity above 10% is achieved [70]. (1D)

Platelet function inhibiting agents

Recommendation 31
During the rising platelet count phase (>50 g/L), the administration of a small dose of aspirin is recommended based on an individual assessment [1, 5, 72]. (2B)

During the rising phase of the platelet count (platelet count >50 g/L), many centres use aspirin ± dipyridamole treatment to shield against relapse caused by rapidly rising platelet count. Its effectiveness has been reported in only one study [72], so its use has recently been considered more on an individual basis [5].
Thienopyridines (including ticlopidine, clopidogrel, and prasugrel) alone can cause TTP (incidence for treatments administered for other indications: ticlopidine: 0.01-0.02%; clopidigrel: 0.0001%, prasugrel: no data) [73]. While in the case of ticlopidine TTP most often develops within the first 2-12 weeks of therapy, is usually associated with ADAMTS13 deficiency and responds well to plasma exchange, in the case of clopidogrel it most often develops within 2 weeks, usually without ADAMTS13 deficiency, in the form of TMA refractory to plasma exchange, often with acute renal impairment. So far, only a few cases have been reported related to prasugrel [73, 74]. Thus ticlopidine should definitely be avoided during the active phase of TTP and generally avoided if the patient's medical history includes TTP. In the case of cerebrovascular and/or cardiovascular indications, clopidogrel and prasugrel may be given under close observation after a careful benefit/risk assessment.

Splenectomy [75]

Recommendation 32
Splenectomy may be recommended in patients who relapse frequently despite sustained immunosuppressant treatment [1, 11, 75]. (1C)

It may be used as salvage treatment in fulminant cases or to avert frequent relapses, with particularly good efficacy in the latter case. It is cost-effective and extremely safe with the right preparation, and may significantly decrease the relapse rate, rendering patients asymptomatic for a very long time even if ADAMTS13 remains abnormal. At least 2 weeks prior to surgery, the patient must be vaccinated (against *pneumococcus*, *meningococcus*, *haemophilus influenzae*). If the outcome of the immunisation is uncertain (due to the concomitant use of immunosuppressant agents), antibiotic prophylaxis may be necessary (penicillin, macrolides).

Supportive therapy

Red blood cell transfusion:
Recommendation 33
When giving a red blood cell transfusion, the administration of a white blood cell depleted product is recommended. (1D)

Recommendation 34
When determining the indication, clinical symptoms must also be taken into account alongside the degree of anaemia, particularly if there is cardiac involvement [1]. (1A)

Defining the Rh and Kell phenotype is also suggested prior to the first transfusion. The transfusion must be performed using a leukoreduced product in every case. The use of a radiated product is generally not necessary. Red blood cell replacement is indicated rarely if haemoglobin levels exceed 70 g/L [1].

Platelet transfusion:
Recommendation 35
Platelet transfusion is generally contraindicated unless there is life-threatening haemorrhage [1, 76]. (1A)

Patients with TTP rarely bleed even if they have a single-digit platelet count. Many publications reported progression of the disease and a rise in mortality following a platelet transfusion [76], while other studies did not establish such a correlation [77]. According to the currently widely accepted stance, a platelet transfusion may only be considered in TTP if vitally indicated, if there is a severe haemorrhage [1]. When placing a central intravenous line, the vein should be chosen in a compressible location (or at the periphery in adults) during the acute phase in order to reduce the risk of complications from an intervention performed at a low platelet count.

Thromboprophylaxis:
Recommendation 36
LMWH should be administered for the purpose of thromboprophylaxis above the 50 g/L platelet count threshold. (1B)
LMWH prophylaxis should be given to reduce the risk of thromboembolism caused by immobility.

Folic acid replacement:
Recommendation 37
Folic acid replacement is necessary during the haemolysis phase [1]. (1C)
Folic acid replacement is suggested in all patients due to continuous haemolysis. The recommended daily dose in adults is 6 mg.

Hepatitis vaccination:
The BCSH guideline suggests HBV vaccination in the active phase of the condition at a platelet count of over 50 g/L [1]. As most patients receive high-dose steroid ± rituximab treatment in such cases, the utility of vaccination is currently in question.
Response to therapy (nomenclature) [2, 10]. The nomenclature of the response to therapy has recently been standardised as follows:
Clinical response in TTP: platelet count maintained above 150 G/L, LDH not exceeding one and a half times the upper normal value, without clinical signs of new or progressive ischaemic organ damage.

Clinical remission in TTP: sustained clinical response without plasma exchange and anti-VWF treatment: at least for 30 days or if ADAMTS13 remission (partial or complete) is achieved, whichever occurs first.
Partial ADAMTS13 remission: ADAMTS13 activity is 20% or higher but below the lower limit of the normal range.
Complete ADAMTS13 remission: ADAMTS13 activity exceeds the lower limit of the normal range.
Clinical exacerbation: platelet count falling below 150 G/L (other cause excluded) after achieving a clinical response but before achieving clinical remission, with or without new or progressive ischaemic organ damage, within 30 days of the completion of plasma exchange or anti-VWF therapy.
Clinical relapse: After clinical remission, platelet count again falling below 150 G/L (other causes excluded) with or without new ischaemic organ damage. Clinical relapse should be supported by evidence of severe ADAMTS13 deficiency.
ADAMTS13 relapse: the ADAMTS13 activity falling below 20% again after a partial or complete ADAMTS13 remission.
Refractory TTP: Persistent thrombocytopenia (<50 G/L) and LDH elevation despite 5 plasma exchanges and immunosuppressive therapy.

Outcome

Recommendation 38
Every patient must be admitted to care and regularly checked. The patient must be informed in depth about the nature of the condition, the risk of relapse, its symptoms, the risks of pregnancy and oral contraception, and the related tasks (see the attached 'TTP-HUS Patient Information Sheet') [1]. (1C)

Recommendation 39
Non-oestrogen-containing products are recommended as contraception [1]. (1C)

Recommendation 40
Rituximab may be administered preemptively in the event of ADAMTS13 deficiency coupled with haematological remission [1, 11, 78, 79]. (2C)

Recommendation 41
If there is ADAMTS13 deficiency coupled with haematological remission, a customised decision may be recommended based on clinical history, the severity of the episode(s), the response to treatment, potential residual symptoms and the patient's wishes. (1D)

If a new symptom presents despite the plasma exchange or if there is persistent thrombocytopaenia, we are dealing with a plasma-refractory condition. In such cases, plasma exchange and/or the intensification of pharmacological treatment may still improve the patient's health. Infection, an undiagnosed autoimmune disease or tumour are often the underlying cause of such resistance. Unfortunately, mortality is still between 5–20%.
Patients in remission must be admitted to long-term care, during which ADAMTS13 activity must be checked occasionally. The frequency of late relapse is approximately 20–50% [1]. To prevent them, the French Thrombotic Microangiopathies Reference Centre's study group recommends the preemptive use of rituximab [78] in cases where ADAMTS13 activity remains, or once again becomes, deficient. Although lower than normal ADAMTS13 activity leads to an approximately 3-fold increase in the probability of a relapse [80], its actual occurrence and time of occurrence are completely unpredictable. Unconfirmed data suggest that if ADAMTS13 activity is still deficient at clinical remission, the likelihood of relapse is several times higher than in patients with at least 10% activity [81]. Not everybody agrees with preemptive rituximab treatment [79], as many patients may be asymptomatic for a long period of time even with 0% ADAMTS13 activity, or the activity may improve spontaneously. However, ADAMTS13 activity that remains low or declines in remission, increases the risk of stroke several fold [82]. ADAMTS13 activity is also important in the non-TTP patient population in terms of stroke probability and it has an impact on survival [26].
For this reason, at present a customised decision may be recommended based on clinical history, the severity of the episode(s), the response to treatment, potential residual symptoms and the patient's wishes.
The patient should be informed about the nature of the disease, the risks associated with pregnancy and oral contraceptive use, the possibility of relapse, its most common causes (including infection, pregnancy, and surgery) and the need for increased monitoring (see attached "TTP-HUS Patient Information Leaflet"), the risk of low ADAMTS13 activity and the treatment options. Trigger drugs (such as quinine, oestrogen, ticlopidine, interferon, cyclosporine) should generally be avoided.

Unfortunately, TTP does not always heal without a trace, residual renal [83] and neurological [84] symptoms may remain, which is why the importance of care cannot be overemphasised.

Future therapeutic options

Recombinant ADAMTS13:
The Phase I study using the BAX-930 molecule ended with positive results [85] in the congenital form of TTP. It would primarily make the treatment of USS very simple and safe. Phase III of the trial is currently under way (ClinicalTrials.gov Identifier: NCT03393975). Its use in inhibitor-associated TTP could be considered, but the immunocomplex formation may be an undesirable consequence, and a patient-specific dose, depending on the amount of inhibitors, may be required [86, 87]. It is therefore currently being tested as an adjuvant therapy in addition to the standard treatment in the inhibitor form of TTP. A solution could be to produce a variant of ADAMTS13 to which the inhibitor would bind with less affinity while the enzyme would have been increased proteolytic function [88].

VWF — platelet interaction inhibiting therapies:
VWF plays a central role in primary haemostasis and the pathomechanism of TTP. No wonder it is a prime target for pharmaceutical research. Most medicinal products target the inhibition of the bond between the VWF A1 domain and the platelet GP1b receptor, and less frequently the bond between the A3 domain and collagen [89]. From these, the nanobody ALX-0681 has recently been approved for the treatment of the acquired form of TTP under the name caplacizumab [195, 196]. In addition to antibody molecules (82D6A3, h6B4-Fab, AJW200, GBR600), nucleic acid aptamers are under development as well (ARC1779, TAGX-0004). They have in common that they bind tightly and specifically to the target molecule, are non-toxic, non-immunogenic, chemically easy to produce, and cheap, but have a short half-life [90].
A promising recent development is the GP1b receptor antagonist Anfibatide derived from snake venom, with which human trials are already underway [91].

N-acetylcysteine (NAC)[92]:
NAC is an antioxidant that is a precursor for the synthesis of L-cysteine and glutathione. It reduces the viscosity of airway secretions by breaking down disulfide bridges between mucin monomers and has long been successfully used in obstructive lung diseases. *In vitro and in vivo*, it decreases the number of soluble VWF multimers and decomposes ULVWF thanks to their structural similarity with mucin. Animal data suggest that it will be used mainly for preventive purposes, as it is not able to dissolve developed VWF-rich thrombi in TTP. There is very little human clinical data yet.

Bortezomib [93]:
A proteasome inhibitor used with great success in the treatment of multiple myeloma. The therapy would be aimed at destroying the plasma cells that produce the ADAMTS13 antibody, as they are resistant to traditional immunosuppressant therapy. There is still very little experience with it.

Complement-inhibiting treatment:
Increasing evidence suggests that enhanced complement activation on the alternative activation pathway is also involved in TTP, for the initiation of which ULVWF fibres anchored to the endothelium may serve as an activation surface [94-96]. To date, only sparse clinical data are available on the use of complement-inhibiting treatment in TTP therapy-resistant cases [97].

HAEMOLYTIC URAEMIC SYNDROME (HUS)

The triad characterising the condition is listed in Table 7. The concurrent or the consecutive presence of all three symptoms is necessary for establishing a diagnosis [13, 14, 17, 19, 29, 30].

Clinical forms
HUS is an umbrella term; 2 large groups can be distinguished based on the introductory symptoms, aetiology and clinical course (**Figure 2**). 'Typical' HUS usually refers to clinical forms presenting as a single episode following acute gastroenteritis that responds well to supportive therapy and only rarely leads to severe chronic kidney injury or death. 'Atypical' HUS usually refers to clinical forms where patients do not respond sufficiently to supportive and/or renal replacement treatment, follow a clinical course characterised by relapses and/or exhibit an asynchronous familial nature. The conditions often progress and can lead to the sustained impairment of renal function; fatal outcomes are not rare (see also Table 8). ADAMTS13 activity is characteristically normal or just slightly decreased in HUS.

Table 7: The clinical triad of HUS [13, 14, 17, 19, 29, 30].
Thrombocytopaenia caused by platelet consumption
Microangiopathic haemolytic anaemia
— Confirmed acute kidney injury: proteinuria and/or glomerular haematuria and/or decreased renal function, with the following classification according to RIFLE criteria [98]: — Risk: 1.5x increase in serum creatinine or decrease in GFR >25%, or urine output per hour <0.5 mL/kg/hour for 6 hours, — Injury: 2x increase in serum creatinine or decrease in GFR >50%, or urine output per hour <0.5 mL/kg/hour for 12 hours, — Failure: 3x increase in serum creatinine or decrease in GFR >75% or an acute increase in serum creatinine of >353 micromol/L (>44 micromol/L), or urine output per hour <0.3 mL/kg/hour for 24 hours, or anuria for 12 hours — Loss: protracted acute renal failure = total loss of kidney function for >4 weeks, ESRD End stage kidney disease (>3 months)

HUS forms associated with specific infections

Typical HUS, STEC-HUS [99]
Clearly defined typical or STEC-HUS clinical entity associated with enterohaemorrhagic *E. coli* (EHEC, VTEC/STEC, formerly known in Hungary as *E. coli* 0157:NM) that produces verotoxin/Shiga-like toxin. In certain tropical regions, it may also be associated with *Shigelladysenteriae* and rarely, *Citrobacterfreundii and salmonella*. It is the most common form of childhood acute renal failure, but is also not rare in adulthood. About half of the STEC-HUS cases confirmed in Hungary in recent years occurred in adults. The source of the infection may be food, drink or water contaminated with the toxin-producing bacteria. However, faecal-oral transmission is also possible. The prodromal phase is characterised by runny diarrhoea accompanied by cramps, often followed by bloody diarrhoea which is succeeded by acute renal failure approximately 3–10 days later. The symptoms are caused by the toxin being absorbed in the intestines. Its receptor is globotriaosylceramide (GB3) and the degree of receptor expression plays a role in the localisation and severity of tissue damage. The toxin is directly toxic to the vascular endothelium by inhibiting protein synthesis. In addition, the activation of the white blood cell, platelet and coagulation system, the cytokine (IL-6, IL-8, TNF) effect at the outflow of higher ULVWF from the stimulated endothelium along with secondary ADAMTS13 enzyme consumption also play a role in the pathological consequences. The development of autoantibody cross-reacting with the verotoxin and the CD36 structure has also been described [100].
Approximately 14-33% of EHEC infection cases develop colitis, of which approximately 10% develop typical HUS, with clinical risk factors including dehydration, fever, vomiting, visible blood in the stool, younger or older age, use of intestinal motility inhibitors and some antibiotics. From the laboratory findings, an elevated white blood cell count and a C reactive protein level higher than 12 mg/L may be predictors of HUS. Rarely, typical HUS may be a consequence of a urinary tract infection. In this case, there is no typical diarrhoea and the bacteria producing the toxin is detectable in urine.
Most frequently, renal failure dominates the clinical presentation while the neurological symptom is a rare consequence – in roughly 25% of cases, almost always accompanied by renal failure – of hypertension and metabolic encephalopathy or brain microangiopathy. Clinical cardiac complications (such as ischaemia and arrhythmia) are even rarer (<10%). By and large, it is a relatively benign condition in childhood, with a mortality rate of 3–5%. If significant renal function impairment was observed in the early phase, hypertension, proteinuria and kidney function impairment may present years after full regression of symptoms, so the patient must be monitored periodically. There is no relapse after recovery, but reinfection is possible, and the infection may be a trigger factor for the development of previously asymptomatic atypical HUS. In older age, the condition is far more malignant with a high mortality rate.

Diagnosing typical HUS
Typical HUS is recognisable by the fact that it generally presents 3–10 days after acute gastroenteritis, at which point the patient often no longer has diarrhoea. Microbiological (culture, identification of the pathogen, toxin detection in the stool sample or in the identified pathogen with a biological or serological procedure) or immunological (confirmation of a serological response against LPS typical of the STEC strain) tests can confirm a diagnosis of typical HUS. In Hungary, the above microbiological tests are available at the National Enteral Reference Laboratory of the National Public Health Centre. Typical HUS requires mandatory reporting.

Therapy for typical HUS
In the most recent epidemics of STEC-HUS, best supportive care (BSC) has improved survival statistics compared to earlier outbreaks [101]: this involves maintaining the fluid and electrolyte balance, controlling blood pressure, renal replacement treatment if necessary, parenteral nutrition and transfusion. The use of medicines inhibiting intestinal motility should be avoided. For a long time, the general view was that antibiotic treatment is rather harmful because of the increased toxin production, direct toxin release from decaying bacteria and damage to normal gut flora. The antibiotic effect is toxin-specific and bacterial strain-specific, which explains the conflicting clinical results. In larger epidemics, the exact bacterial strain can be quickly identified by whole genome sequencing, which can also provide information on serotype, virulence and resistance profile. Bioinformatics systems, now available online, can help to select the right, effective antibiotic [197]. In sporadic cases, in the absence of the former, antibiotics can be given only for shiga toxin-1-producing bacteria. Phosphomycin is the most indicated agent (beginning within 2-3 days from the onset of diarrhoea), while beta-lactam and trimethoprim/sulfamethoxazole should be avoided. Fluoroquinolones have been shown to be beneficial in clinical trials, despite failing in in vitro studies. Of the other agents, rifamycin is the most promising. In addition, studies are being conducted with antitoxin monoclonal antibodies and the use of adjuvant zinc therapy [102].

Recommendation 42
The efficacy of plasma exchange has not been confirmed in typical HUS [101, 103, 104]. (2B)

Recommendation 43
Plasma exchange therapy can be attempted in severe childhood STEC HUS with neurological symptoms [45, 101, 105].(2C)

Plasma exchange is generally not recommended in childhood HUS; in practice, it is reserved for severe forms of the disease accompanied by neurological symptoms [106]. Plasma exchange decreased mortality in adults during the Scottish epidemic [103]. By contrast, during the German epidemic of 2011, which mostly affected adult patients, extended plasma exchange had a mostly negative impact on outcome [104].
Dysregulation of the complement system has also been described in typical HUS, so it is not surprising that a Phase III trial is currently underway to assess the clinical efficacy of eculizumab [198], but some results suggest that this treatment is not effective for this disease [107].
Attempts to neutralise the toxin have so far not produced satisfactory results.

HUS associated with neuraminidase-producing pathogens
5-15% of all HUS cases. Recently, the number of cases has been increasing, probably due to better awareness of the disease. Presents after an infection caused by neuraminidase-producing pathogens, most commonly *Streptococcus pneumoniae* [108], generally in children below 2 years of age. The presentation of the disease is characterised by a severe clinical condition (most commonly pneumonia accompanied by empyema or meningitis), and it is often accompanied by DIC. The prognosis for cases with meningitis is significantly worse. Relapse after recovery is not known. The long-term prognosis for the kidney is generally good, with renal function restored in most patients.
Neuraminidase cleaves sialic acid from the surface of red blood cells, platelets and endothelial cells which exposes hidden Thomsen-Friedenreich (T) antigens. The blood stream contains regular anti-T antibodies against these antigens. This process is called T activation, and indicative signs may include polyagglutination detected in blood group serology, autocontrol positivity and Coombs positivity. Recently, the importance of anti-T antibodies has been questioned and T-activation has been considered a marker of the process rather than the cause of pathological events. Neuraminidase-neutralising antibodies develop in the blood of most people until the age of 2 years, which explains the age-specificity of the syndrome. Recent data also suggest that the proteolytic effect of plasmin activated on the bacterial surface is responsible for endothelial damage [109]. In addition, removal of sialic acid from the membrane reduces the binding of factor H to the cell surface and its function, thereby causing the dysregulation of the alternative pathway and complement activation [110].

The diagnosis of *Streptococcus pneumoniae*-associated HUS (SP-HUS)
A firm diagnosis of **SP-HUS** can be made if all three conditions are present:
- the *Streptococcus pneumoniae*infection can be confirmed (using antigen, nucleic acid detection or culture based methods), and
- HUS can be confirmed (see Table 7), and
- DIC can be ruled out (no bleeding can be confirmed, fibrinogen level is not reduced).

Neuraminidase activity has recently become detectable using serum, which may help in therapeutic decision-making.

Therapy for *Streptococcus pneumoniae*-associated HUS (SP-HUS) [108]
As factor H, which plays a central role in the regulation of the alternative complement activation pathway, binds to sialic acid on the cell membrane and there may be an overlap between the neuraminidase-mediated and complement-mediated forms of aHUS [111], it is recommended to extend diagnostic tests to the complement system.

Recommendation 44
The use of FFP should be avoided in *Streptococcus pneumoniae*-mediated HUS. Albumin is recommended for plasmapheresis [112-114]. (2C)

Stopping the infection is decisive in the treatment of *Streptococcus pneumoniae*-mediated HUS; supportive and renal replacement treatment should only be given if necessary. Given its neutralising anti-neuraminidase antibody content, IVIG may be a potentially effective therapy, although extensive clinical validation is still awaited. Given the complement activation promoting effect of neuraminidase, complement-inhibiting treatment is also being tested, with encouraging results so far. No controlled studies are available regarding plasma therapy. Based on the pathogenesis, plasma therapy (FFP infusion or FFP substitution) should be avoided in the acute phase; instead, plasma exchange using albumin substitution may be efficacious [112-114]. Recently, successful treatment with T-antibody-negative plasma has also been reported [115]. The potential benefit and the potential side effects and complications of apheresis require individual assessment.
More recently, HUS has been reported as a complication of influenza virus A infection, with a pathogenesis similar to the one described above due to the viral neuraminidase effect [116]. Therapy is fundamentally based on antiviral and supportive treatment; plasma should not be administered in this form of the disease.

Complement-mediated atypical HUS [14, 19, 117]
A heterogeneous patient group that includes both sporadic and familial forms, which manifest in some disease cases in response to trigger factors (which may include infections or pregnancy). Their common trait is a severe and progressive course, and the tendency for relapses in some cases. Can occur at any age, but mainly affects neonates, children and young adults. Rare; with an estimated incidence of 1–2/1 million [14, 118]. The following subgroups based on aetiology are known:

Atypical HUS caused by complement dysregulation

More than half of all cases of aHUS stem from impaired regulation of the alternative complement pathway. Spontaneous activation due to the continuous cleavage of C3 and amplification are characteristic of the alternative pathway of the complement system. Complement regulation proteins are responsible for keeping this process in check.
Impaired alternative pathway regulation may stem from loss-of-function or gain-of-function mutations or an antibody inhibiting the factor H regulator. So far, mutations in factor H (FH), factor I (FI), membrane cofactor protein (MCP, CD46), factor B (FB) and C3, and thrombomodulin genes have been described in the background of aHUS. FH, FI, MCP and thrombomodulin mutations are typically loss-of-function mutations, in other words the regulatory protein affected is not produced or does not function. FB and C3 are gain-of-function mutations which do not allow the physiological regulation to prevail. Whichever underlying mechanism is at play, the end result is the amplification of the alternative pathway, the excessive activation of the terminal response pathway with consequential tissue damage (resulting from inflammation causing anaphylatoxins and a cell-damaging complex).
Complement-mediated aHUSis clinically characterised by an insidious onset, express hypertension, fluctuating clinical symptoms and laboratory results. In most cases, the onset of the disease is caused by indirect trigger factors, such as infection or pregnancy. It exhibits numerous similarities to TTP. It is not only a childhood disease, as approximately 60% of cases manifest in young adulthood, and a case has also been reported in an 85-year-old patient. In childhood, 50% of cases manifest before the age of 2 years. In children, the male/female ratio is nearly identical while a slight female predominance can be observed among adults. In more than half of patients (children: 58%, adults: 73%) the platelet count is over 50 g/L and normal (>150 g/L) in 15% of cases. 59% of children and 81% of adults require dialysis treatment at the beginning of the process [118]. Although the clinical presentation is mostly predominated by acute renal failure, 10–30% of patients present with extrarenal symptoms (neurological, cardiac, other) [119]. The prognosis is worse in adults and in cases with familial accumulation. The majority of relapses occur within one year. The outcome is significantly influenced by genetic background [118, 119].

Genetic predisposition can be identified in approx. 50–60% of confirmed complement-mediated aHUS patients and is mostly complex: it consists of the cumulative effect of one or more rare variations (mutations) and one or more risk polymorphisms or haplotypes. Due to complex genetic predisposition, mutation penetrance is low, approximately 40–50%. The most commonly affected genes are [120]:

Factor H and factor I mutations

Factor H is the most common (30%) mutation, while factor I is far rarer (5-10%). Numerous mutations are known for both factors. Both proteins are predominantly produced by the liver. Factor H inhibits C3 convertase and helps factor I as a cofactor. Factor I plays a role in the regulation of both the alternative and classic pathway, and cleaves the C3b and C4b alpha chain in the presence of a cofactor. The factor H gene is located on chromosome 1 at location q32 while the factor I gene is located on chromosome 4 at location q25. If a patient carries a factor H or combined factor I mutation, without treatment the prognosis is poor, with a 60–70% likelihood of developing irreversible renal failure. Relapse following a kidney transplant is approximately 80% in factor H mutations and nearly 100% in factor I mutations within two years [121] of the transplant.

MCP mutations

Membrane cofactor protein (MCP or CD46) is a transmembrane glycoprotein that is expressed on all cells with the exception of red blood cells. It is a cell surface cofactor necessary for FI functioning; MCP mutations can be detected in approximately 10% of aHUS patients. Its penetrance is also low. In carriers of the MCP mutation, aHUSmanifests most often following an infection. It is a benign form of the condition in terms of clinical course, with 20–30% of patients developing irreversible renal failure. The frequency relapse following transplantation is low (the donor organ does not carry the mutation), approximately 10%. The treatment of post-transplantation ISU and the endothelial microchimerism may both play a role. As it is a non-soluble protein, plasma exchange is not expected to yield any results.

Other mutations

The gain-of-function mutations in factors **C3 and B** have an adverse clinical course, often presenting as aHUS accompanied by sustained hypocomplementaemia, in which the disease has a high likelihood of recurring in the graft following the kidney transplant.

Thrombomodulin mutations (which also plays a complement regulation role) are identified in the lowest ratio among aHUS patients (roughly 5%), and if there are multiple mutations, the functional relevance of the variation cannot be confirmed. There is insufficient clinical experience on thrombomodulin mutations [122].

Plasminogen mutations were confirmed in aHUS patients in the US in 2014 with tests performed using a new generation sequencing method. They found that variations that had an adverse effect on plasminogen/plasmin function accumulated in aHUS patients, thereby preventing the breakdown of thrombi [123]. No new data have been published in recent years to support a role for plasminogen in aHUS.

Autoimmune (anti-factor H autoantibody positive) aHUS [124]

aHUS developing based on the autoimmune mechanism can be confirmed in 6–56% of patients according to geographic location. It is characterised by the presence of autoantibodies produced against the alternative pathway regulator factor H, which shows a close correlation with the homozygous deletion of complement factor H-like genes 1 and 3 (*CFHR1, 3*). It has been confirmed that anti-FH autoantibodies bind to the factor H C-terminal domain and have the functional effect of inhibiting factor H from binding to the cell surface and neutralising the regulator function of factor H.

Table 8: Signs suggestive of atypical HUS [29].
— Absence of diarrhoea prior to the onset of HUS
or
— Diarrhoea + presence of any of the following:
- Age <6 months or >5 years
- Insidious onset
- HUS relapse
- Presumed earlier HUS
- Prior unexplained anaemia or thrombocytopaenia
- HUS following any organ transplant
- Asynchronous HUS occurring in the family

Other atypical HUS forms
Other mechanisms not based on the defective functioning of the complement system may explain HUS exhibiting a clinically atypical course.

HUS caused by defective cobalamin C metabolism
May be expressed in the form of HUS with an autosomal recessive inheritance pattern. Fulminant forms already presenting at birth, or milder forms only manifesting later [125, 126, 127] are both known. Feeding difficulties, stunted growth, hypotension, lethargy, leukopenia, megaloblastic anaemia require major attention to the condition. Its characteristic symptoms are hyperhomocysteinaemia and methylmalonic acidemia. Presence of the disease can be confirmed with the sequencing of the MMACHC gene, the mutations of which were described in the most recently affected case. Renal biopsy is pathognomonic. Therapy: hydroxocobalamin administered daily. aHUS associated with cobalamin E and G disease has also been reported.
Very rarely, pernicious anaemia [128] may also result in a microangiopathic blood count. However, the clinical presentation corresponds most closely to TTP, disproportionately high LDH may draw attention to it, and a low serum B12 vitamin level and normal ADAMTS13 activity may help distinguish the condition.

HUS associated with diacylglycerol kinase epsilon (DGKE) mutation
Loss-of-function mutations of the DGKE gene were described in 2013 in the background of early-onset HUS typically manifesting with severe hypertension and proteinuria [129]. By analysing the disease course in additional patients, it has been recognised that there may be an overlap between TMA and membranoproliferative glomerulonephritis in affected individuals [130]. Impaired DGKE function does not affect the functioning of the complement system, but it does cause prothrombotic changes in endothelial cells. It was reported in 2014 that in certain patients, impaired regulation of the alternative complement pathway and DGKE mutation are present and the complement abnormality largely determines the time and severity of the presentation of HUS [131]. For this reason, genetic tests should be extended to DGKE for all cases of early-onset HUS.

The diagnosis of atypical HUS [12]

Recommendation 45
aHUS must always be considered as a possibility in the event of acute renal failure. The clinical diagnosis must be based on the clinical history, the clinical symptoms (Tables 7 and 8) and routine laboratory test results (Table 2) [17, 29] (1A)

Recommendation 46
The tests needed to clarify aetiology (Table 3) must be performed prior to starting plasma therapy [17]. (1B)

Recommendation 47
If aHUSis clinically suspected, an in-depth complement diagnostic examination (complement C3, C4, alternative total complement, FH, FB, FI, MCP expression, anti-FH antibody ± genetic test) and ADAMTS13 (activity, inhibitor ± genetic test) must be performed for every patient [12, 13, 17, 132]. (1B)

The diagnosis of atypical HUS is a multiple step process. There is currently no method of investigation to confirm aHUS with the requisite diagnostic sensitivity and specificity in a short amount of time. Therefore, aHUSis diagnosed using the exclusion method and requires complex verification.

Step 1:
The basis of the clinical diagnosis of HUS is the recognition of acute thrombocytopaenia, acute non-immune (Coombs negative) microangiopathic haemolytic anaemia and kidney injury (Table 7). Table 2 sums up the early diagnostic steps, while Table 8 sums up the clinical symptoms to be regarded as “atypical” signs [29]. If HUS does not present with accompanying acute gastroenteritis (diarrhoea), severe purulent pneumonia or meningitis or alongside an unequivocal comorbidity, it should be clinically regarded as atypical.
Step 2:
Confirming the diagnosis of aHUS. If atypical HUS is suspected, before potentially necessary supportive therapy (red blood cell or rarely, platelet transfusion) or plasma therapy is started, a blood sample must be drawn for in-depth complement diagnostics (classical and alternative pathway activity, C3, C4, FH, FI, FB level, MCP expression, anti-FH antibody screening and complement genetic testing), ADAMTS13 (enzyme activity, inhibitors and genetic testing) and cobalamin metabolism testing [17]. The normal range of C3 and C4 tests

generally available in larger laboratories does not rule out the possibility of complement defect, so the blood sample must be sent to a special laboratory (such as: Semmelweis University, Clinic of Internal Medicine and Haematology, Research Laboratory [133] [134] or frozen until transportation according to the laboratory's instructions (see: [194]).
Obviously, it is generally not possible to wait for the results; therapy must be started within 24 hours and may be modified based on the results (intensification, suspension, supplementation, see below). A diagnosis of aHUS can also be established if alternative pathway deregulation or hypocomplementaemia cannot be confirmed. At the same time, in the vast majority of cases of aHUS, a positive result confirms the diagnosis and is suitable for guiding therapy and monitoring its efficacy (particularly in anti-FH autoantibody positive patients).
If the patient's clinical condition allows a kidney biopsy, the typical abnormalities detected in the histological sample both clarify the diagnosis and provide a prognosis for assessing the outcome of the renal process/renal failure.
Step 3:
Critical assessment of the results of the differential diagnosis and the clinical response to initial therapy. In the 2–4 days following the onset of HUS, if verotoxin positivity, ADAMTS13 deficiency, cobalamin metabolism disorder or primary disease warranting HUS as a complication (see Figure 3 and Table 11) cannot be confirmed, a diagnosis of aHUS can be established. In cases of atypical HUS, the clinical response (increase in platelet count, degree of haemolysis, severity of renal impairment, resolution of oliguria, improvement of renal function, other organ damage) to initial (supportive, infection control, plasma treatment) therapy is often partial, slow or completely absent.
Step 4:
The need for and results of genetic tests in aHUS. Genetic tests (*CFH, CFI, CD46, CFB, C3, THBD2, CFHR1-5, DGKE, PLG* genes DNA sequence analysis for identifying rare and common variations and defining copy number) are warranted for every new aHUS patient during the first episode of the disease. Likewise, an in-depth genetic test is warranted in the event of HUS relapse (confirmed or suspected), in the event of an asynchronous family history of HUS (in healthy family members for screening purposes and for assessing subsequent risk of the disease) and if aHUSpresents during or after pregnancy or if HUS presents *de novo* following a transplant. A kidney transplant in patients with sustained kidney injury due to earlier HUS can only be authorised following in-depth genetic testing. The above genetic tests are warranted in patients with aHUS for the following reasons: to confirm the complement-mediated form of the disease (possible in approximately 50–60% of patients); to assess prognosis and the risk of relapse; for genetic counselling and family screening; for designing the transplantation protocol if necessary (see below); for choosing effective and safe treatment protocols and determining the required length of treatment.
Great care is necessary when evaluating the results of the above genetic tests. Only mutations that have previously been described in aHUS patients (but not in healthy individuals) with a confirmed harmful functional effect can be declared as having an aetiological effect on aHUS with a high degree of certitude. Likewise, mutations that have not been described in either patients or healthy individuals but which have an experimentally proven harmful effect on complement regulation are also to be regarded as aetiological factors. In all other cases, careful *in silico* experimental and family analysis, etc. are necessary for assessing the functional relevance and aetiological nature of the specific variation. The potential role of common aHUS risk polymorphisms and haplotypes should also be carefully evaluated.

Therapy for typical HUS [12, 15, 135]
Figure 2 shows the diagnostic and therapeutic algorithm for HUS.
As the incidence of secondary HUS/TTP cases in adulthood is far higher compared to childhood (due to the possibility of cancer, autoimmune disease, pregnancy, malignant hypertension and other trigger factors), investigating the aetiological background and establishing a final diagnosis generally takes longer.

Recommendation 48
If atypical HUS is suspected, child patients should be immediately transferred to a paediatric nephrology centre experienced in treating HUS that has the facilities for paediatric dialysis and paediatric ICU care [14]. (1D)

Recommendation 49
If atypical HUS is suspected, adult patients must immediately be transferred to a hospital experienced in the treatment of TTP-HUS that has facilities for dialysis, 24-hour apheresis service and intensive care unit, nephrological and haematological care. (1D)

Recommendation 50
A clinical diagnosis of aHUS in children should be followed by first-line treatment with complement-inhibiting treatment, which should be started within 24-48 hours [12, 14, 15, 18].(1B)

Recommendation 51
In the absence of complement-inhibiting treatment, initiation of plasma exchange therapy in paediatric aHUS patients is recommended within 24 hours (Table 9) [29]**. (1B)**

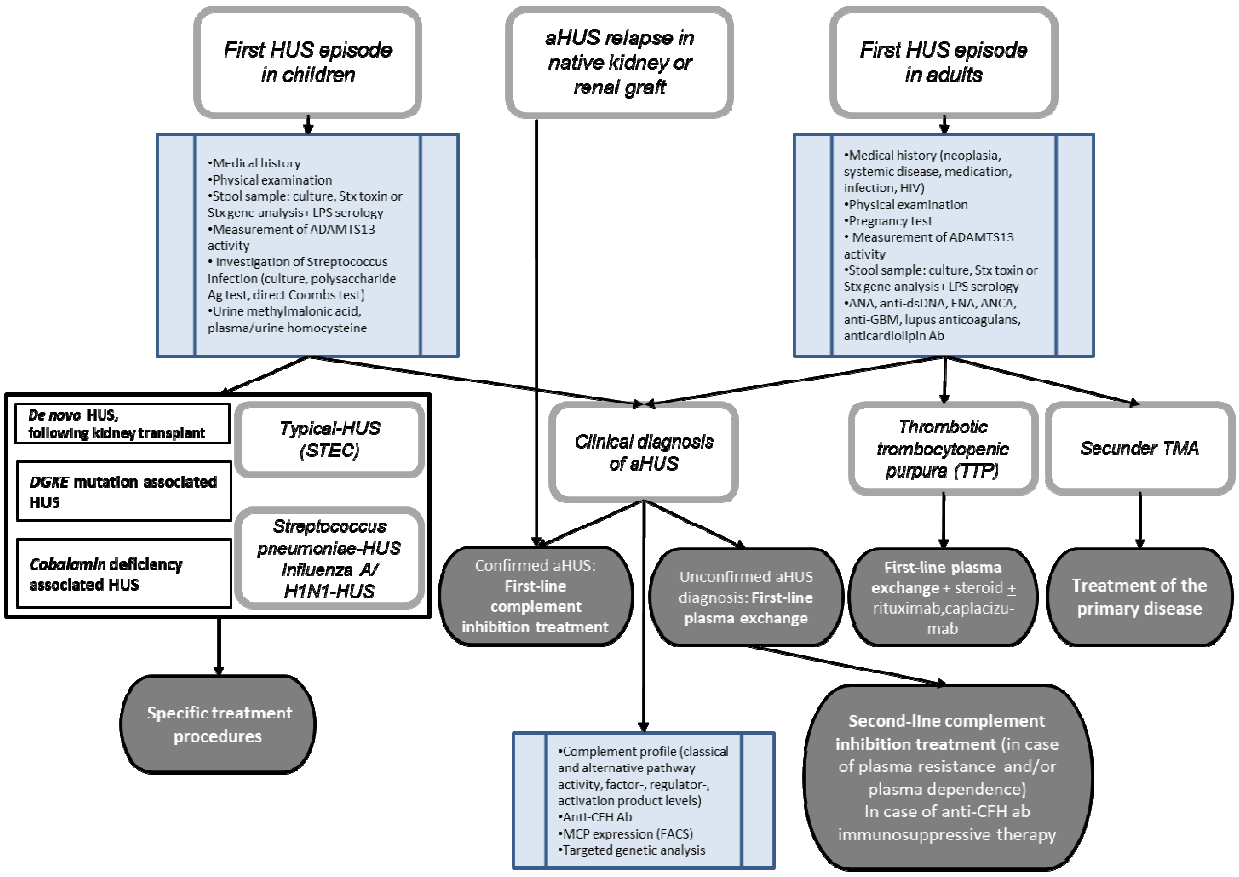
Table 9: Plasma exchange in childhood atypical HUS (The recommendation of the European Paediatric Study Group for HUS) [29]
— Starting plasma exchange within 24 hours, except:
- if an alternative diagnosis requiring different treatment is reasonably suspected
- in small children if placing the line in the vein causes technical difficulties
- if renal involvement is mild, if the risk/benefit balance is negative
— Substitution: FFP or pooled plasma, human, solvent-detergent treated
— Volume: 1.5 plasma volumes (60–75 mL/kg/session)
— Frequency:
- 1x daily for 5 days
- 5x weekly for 2 weeks
- 3x weekly for 2 weeks
- on day 33 of the evaluation of therapeutic effect
— Endpoint:
- Confirmation of an alternative diagnosis that is not treatable with plasma exchange
- Severe complication requiring the discontinuation of plasma exchange
- Haematological remission*
* *Aetiology must be clarified in order to continue plasma exchange*

Recommendation 52
If aHUSis clinically diagnosed in adult patients, plasma exchange is recommended as first-line treatment according to the plasma exchange protocol for TTP (Table 6). However, the endpoint of treatment must be determined individually [15, 17, 30, 136]. (1B)

Recommendation 53
A switch to complement-inhibiting treatment must also be deployed for adult patients if the serum creatinine level does not show at least a 25% improvement following 5 plasma exchanges, irrespective of the change in haematological symptoms and parameters, if the secondary causes can be ruled out with great likelihood [15]. (1B)

Recommendation 54
In adults, in case of aHUS relapse or renal graft-related aHUS, first-line complement-inhibiting treatment is also recommended [15]. (1B)

Figure 3: Summary of the diagnostic algorithm and possible modes of therapy for HUS [132]. See the text for detailed explanations. Based on Reference no. [15], as amended. Only the most common forms are indicated in the figure.



Plasma therapy

Table 9 contains the standardised 2009 plasma exchange recommendation of the European Paediatric Study Group for HUS for children [29]. A higher volume of treatment compared to the plasma exchange protocol for TTP, with gradually decreasing frequency, is recommended. The daily plasma exchange protocol described for TTP may still be used in adults [17].

In case of mutations resulting only in factor deficiency, plasma transfusion (10–20 mL/kg, 2–3 times per week) may also be effective instead of plasma exchange if the patient tolerates fluid overload well. In mutations resulting in abnormal protein, particularly gain-of-function forms, the abnormal protein must also be removed, so plasma exchange should definitely be chosen in these cases. In the case of thrombomodulin mutations, 80% of patients responded to plasma therapy [119]. In MCP mutations, plasma therapy must be decided as a function of the condition's severity [119], and no significant result can be expected in DGKE mutations.

Experience drawn from the high-volume plasma exchange protocol recommended by the European Paediatric Study Group for HUS guidelines shows that the effect of intense plasma exchange is sub optimal: 17% of children still required dialysis on day 33 of treatment, 11% did not achieve haematological remission and 31% presented with some kind of central cannula complication [18]. As a result, the most recent International Consensus now recommends first-line complement-inhibiting treatment for children, to be initiated within 24–48 hours; plasma exchange is only considered in the absence of the former [12].

Based on the recommendation of the French Study Group for aHUS/C3G, complement inhibitor treatment must also be used in adults if the serum creatinine level dips below 25% after 5 plasma exchanges, irrespective of the status of haematological parameters [15]. This amount of time is generally sufficient to rule out ADAMTS13 deficiency, verotoxin, autoimmune mechanism, cancer, pharmacological effects and infections. A histological exam may confirm the diagnosis if a kidney biopsy can be performed safely given the current platelet count and haemostasis parameters. In adults with proven aHUS relapse or aHUS in case of kidney graft, first-line complement-inhibiting treatment should be chosen, and plasma exchange is an option only until this is started.

If no complement-inhibiting treatment is available, plasma exchange should be continued until complete remission or until maximum improvement is achieved, but for at least 1 month. The exception is if it is

discovered in the meantime that the process is plasma-refractory or requires other specific therapy, or if an adverse reaction occurs that prevents the continuation of treatment [29].
Once maximum improvement has been achieved, maintenance therapy can be started, carefully decreasing the frequency of treatments. The method (plasma infusion or plasma exchange), dose, frequency and duration of such treatment must be determined individually [19].
If a complement-inhibiting medicinal product is not available, bilateral nephrectomy may also be considered in the event of end-stage renal failure in severe, uncontrollable active thrombotic microangiopathy and/or malignant hypertension [13, 17].

Targeted complement-inhibiting treatment

Recommendation 55
Patients should be vaccinated against meningococcal disease (conjugate vaccine against serogroup A, C, Y, W135 and conjugate vaccine against serogroup B) at least 2 weeks before the scheduled administration of the complement-inhibiting treatment. Antibiotic prophylaxis (methyl penicillin or macrolides) must be used within two weeks of treatment. Patients below 18 years of age must also be vaccinated against *meningococcus* and *Haemophilus influenzae* [12, 14, 137]. (1A)

Recommendation 56
Before starting complement-inhibiting treatment, a patient information brochure and patient safety card must be given to patients. Patients must be given in depth information about the fact that the vaccine does not provide comprehensive protection (see attached information brochure) against meningococcus infection. If the patient presents with fever accompanied by headaches and/or nuchal rigidity, medical attention must be sought immediately as these may be signs of *meningococcus* infection [12, 137]. (1A)

Recommendation 57
Prior to starting complement-inhibiting therapy, a kidney biopsy is recommended in adult patients to specify the diagnosis and assess prognosis if it is feasibly safe given the haematological parameters and other circumstances [14]. (1D)

Recommendation 58
If dialysis treatment lasts for more than three months, the indication for starting or continuing complement-inhibiting therapy should be decided based on a kidney histological report [12]. (1C)

Recommendation 59
Complement-inhibiting therapy can also be recommended to treat severe extrarenal symptoms if renal failure is not reversible [12]. (2C)

Recommendation 60
When initiating complement-inhibiting treatment, we recommend checking complement inhibition from a blood sample drawn prior to the second dose in a specialised laboratory, see: [194]). A subsequent verification is also recommended if the absence or a decrease in effectiveness is clinically suspected [12]. (1C)

Recommendation 61
A minimum of 3 months of ineffective treatment is required for the complement-inhibiting treatment to be deemed ineffective [12]. (1C)

Recommendation 62
The decision to suspend complement-inhibiting treatment can only be taken after receiving the results of a complement genetic test, in which case very close monitoring is required. In the case of a relapse (in the absence of a contraindication), treatment must be reinitiated [12]. (1B)

Both eculizumab [137] and ravulizumab are registered for the treatment of aHUS and are available to patients in Hungary on the basis of individual compassionate use. The availability of eculizumab for emergency use has improved significantly in recent years. Ravulizumab [138, 139] is a structurally modified eculizumab. The aim of the modification was to improve binding to endosomal neonatal Fc receptors (FcRN), thereby increasing the half-life. Both drugs are humanized IgG2/4 kappa monoclonal antibodies, which prevent the cleavage of the C5 complement protein by binding to it with a high affinity, thus creating the C5b-9 complex (membrane attack

complex). It thereby stops the new activation of the complement terminal pathway without substantially influencing the activation of the alternative pathway at the level of C3. None of the drugs inhibits complement activation at the level of C3, which is essential for the opsonisation of microorganisms, antigen presentation and clearance of immune complexes. The clinical efficacy and adverse effect spectrum of the two agents are similar, the difference lies in the dosing: while for eculizumab, maintenance treatment should be provided every 2 weeks, for ravulizumab this is enough every 8 weeks. More stable blood levels with less frequent dosing create more favourable therapeutic conditions [140].

According to international recommendations [12, 15] and the SmPCs of eculizumab and ravulizumab [137], patients should be vaccinated against meningococcal disease (conjugate vaccine against serogroup A, C, Y, W135 and conjugate vaccine against serogroup B) at least 2 weeks before starting treatment. Antibiotic prophylaxis (penicillin V or macrolides) must be used within two weeks of treatment. In some countries, this is mandatory throughout the entire duration of treatment and for an additional 60 days after its completion. If vaccination is not feasible at least two weeks before the start of complement-inhibiting treatment, the administration of antibiotic prophylaxis should be considered until the end of the complement-inhibiting treatment. A patient information brochure and patient safety card must be given to patients, and they must be given in-depth information about the fact that the vaccine does not provide 100% protection. If the patient presents with fever, fever accompanied by headaches and/or nuchal rigidity, or sensitivity to light, medical attention must be sought immediately as these may be signs of *meningococcus* infection. Patients below 18 years of age must also be vaccinated against *Haemophilus influenzae* and *pneumococcus*.

Importantly, vaccination can increase complement activation, so the patients need close monitoring.

The use of eculizumab during pregnancy has been shown to be safe and to have no effect on the complement system in newborns [141], although more recent data have shown that it can be detected in the blood of newborns [142]. There are no data yet on ravulizumab in pregnancy. Eculizumab may be given during pregnancy on the basis of an individual assessment and stricter monitoring if the indication is clear.

It is administered as an infusion, eculizumab is given once weekly initially for 4 weeks, then at fixed doses every 2 weeks [137]. Several studies have shown that the dosing interval can be extended safely in a significant proportion of patients with monitoring of eculizumab blood levels, complement activation and haemolysis biomarkers [143, 144]. Higher body weight and male sex did not decrease the elimination half-life of the medicinal product and increased the possibility of interval extension. Personalisation of therapy resulted in significant cost savings and improved quality of life for patients [143].

In the case of ravulizumab, we switch to maintenance treatment every 8 weeks after 2 weeks following the first loading dose. In the case of ravulizumab, a dose adjusted for body weight should be administered [138]. The emergence of complement inhibition must be checked in a specialised laboratory before administering the second dose, and in every case where its effect is clinically suspected to have decreased or stopped. If inhibition is not complete, the cause must be clarified. Underlying causes may be complement-activating states (infection, pregnancy, surgical intervention, trauma, ischaemia/reperfusion), massive proteinuria or protein-losing conditions (e.g. active IBD), incorrect dose and – very rarely – genetic resistance (resistant C5 variant in Asian and Japanese patients)[12]. After starting treatment, plasma therapy can generally be discontinued, but if this is not possible, the dosage must be modified according to pharmacopoeial requirements. Its effect in aHUS is identical in cases with or without complement mutation. If extrarenal symptoms occur, its administration is indicated irrespective of the reversibility of renal failure [12]. If treatment is initiated early (<28 days after the onset of HUS), there is a greater likelihood of restoring kidney function [15, 145]. Three months after dialysis treatment, a kidney biopsy may decide on the indication for giving or continuing the medicinal product [12].

Treatment should theoretically be lifelong with eculizumab, except if the product proves ineffective. Treatment of at least 3 months is necessary to determine this [146]. In the case of ravulizumab, treatment is recommended for at least 6 months, after which further treatment can be customised [138]. Successful attempts are being made to achieve stable remission in children and in adults by suspending administration of the product in order to avoid the huge cost of treatment, the potential complications and the discomfort caused by regular infusion [147]. A recent prospective multicentre study found that relapse was less than 5% in patients without a complement gene variant, compared to a rate of 50% in those carrying a complement gene variant. The risk of relapse was also increased by female sex and higher sC5b-9 levels at the time of treatment discontinuation. After restarting treatment, pre-relapse levels of renal function were achieved in 11/13 cases [148]. In retrospective studies, both the frequency of recurrence and the significance of genetic differences vary [135, 149].

The question is not yet definitively settled, but the available data tend to favour the safety of discontinuation [148]. If the complement-inhibiting treatment is discontinued, very close monitoring (home monitoring of proteinuria with urine dipsticks twice a week, blood pressure measurement, monitoring of petechiae) is required, [147, 150] and treatment should be resumed at the first sign of reactivation. However, even with factor H, gain-of-function C3 and factor B, *CFH:CFHR1* gene rearrangements, combined mutations and low residual GFR, the risk is still substantial. The decision not to use complement-inhibiting treatment can only be made on the basis

ofa careful assessment of genetic and other predisposing factors [151]. In aHUS related to isolated heterozygous MCP mutations, long-term treatment with eculizumab to prevent relapse does not appear to be justified [152].
In aHUS due to DGKE mutations, no results can be expected from eculizumab treatment, so complement-inhibiting treatment is not indicated in this disease, or if it is already in progress, treatment should be stopped [153].

Complement-inhibiting agents under development
At the time of writing these guidelines, promising clinical trials are underway with other complement-inhibiting agents. Their testing, approval in Europe and placement on the domestic market is ongoing or is expected in the near future. A summary of what is known about the complement inhibitors that are expected to be introduced in the coming years:

Crovalimab [154]
Crovalimab (RO7112689 or SKY59) is a novel anti-C5 monoclonal antibody-based medicinal product with an isoelectric point, binding to the neonatal Fc receptor and pH-dependent affinity designed so that the antibody recirculates from the endothelial cells in addition to an efficient C5 degradation. Thanks to this technology, crovalimab has a long half-life, binds to C5 on the beta chain, and the bond is not sensitive to the C5 c.2654G → A polymorphism. Crovalimab inhibits the activation of the terminal reaction pathway by reducing C5 levels and inhibits the formation of a membrane-damaging complex. Currently, crovalimab is approved for the treatment of paroxysmal nocturnal haemoglobinuria, and two clinical trials are ongoing in 2021 to assess the efficacy and safety of crovalimab in adolescent and adult aHUS patients (NCT04958265 and NCT04861259).

Pegcetacoplan [155]
Pegcetacoplan is a PEGylated C3-binding pentadecapeptide that belongs to a group of complement inhibitors not yet used as drugs. Members of this group have been developed as structural analogues of the complement inhibitor compstatin, which, upon binding to the C3 molecule (its C3b part), prevents enzymatic cleavage, i.e. the formation of active C3 and C5 convertase enzymes. The medicinal product can be administered subcutaneously and has inhibitory effects at both the C3-convertase level (alternative, lectin and classical pathways) and the C5-convertase level (terminal pathway). The first marketing authorisation was granted in 2021 for PNH, and clinical trials are ongoing in several other complement-mediated diseases, including transplant-associated thrombotic microangiopathy (EudraCT Number: 2021-003157-27).

Iptacopan [156]
Iptacopan (LNP023) is the first oral, small molecule protease inhibitor with reversible effects capable of inhibiting the serine protease B-factor of the alternative pathway C3 convertase enzyme complex. As a result of the inhibitory effect, the function of the alternative pathway C3 convertase complex (C3bBb*) is reduced, the amplification loop is inhibited, but the classical/lectin pathway C3 convertase (C4b2a) is not inhibited. Currently, clinical trials are ongoing in PNH and several complement-mediated diseases, including adult aHUS (EudraCT Number: 2020-005186-13).

Treatment of autoimmune aHUS

Recommendation 63
In the autoimmune form of aHUS, plasma exchange and immunosuppressant therapy constitute first-line treatment. (1B)

Recommendation 64
In case of life-threatening extrarenal symptoms in the autoimmune form of aHUS, complement-inhibiting treatment may be given as first-line treatment in addition to immunosuppressive therapy [12]. (1C)

Traditional treatment consists of intensive plasma exchange and immunosuppressant (induction: steroids, cyclophosphamide or rituximab; maintenance treatment: steroids, mycophenolate mofetil or azathioprine) treatment. Treatment must be performed so that the antibody titre dips below 1000 AU/mL, if possible. A baseline titre of over 8000 AU/mL is indicative of a poor prognosis [157] In case of severe extrarenal symptoms, first-line complement-inhibitor (due to its immediate effect) + immunosuppressant treatment may be the optimal choice [158].

Supportive therapy

Recommendation 65
When giving a red blood cell transfusion, the administration of a white blood cell depleted product is recommended. (1D)

Recommendation 66
When determining the indication, clinical symptoms must also be taken into account alongside the degree of anaemia, particularly if there is cardiac involvement. (1A)

Recommendation 67
In renal anaemia, erythropoietin is recommended to reduce the need for transfusion [159]. (1B)

Recommendation 68
Platelet transfusion is generally contraindicated unless there is life-threatening haemorrhage [13, 19]. (1A)

Recommendation 69
Folic acid replacement is necessary during the haemolysis phase [1]. (1C)

Recommendation 70
The patients should be vaccinated against influenza A and SARS-CoV-2 [15, 19]. (1C)

Recommendation 71
Every patient must be admitted to care and regularly checked. The patient must be given in depth information (see the attached 'TTP-HUS patient information brochure') about the nature of the condition, the risk of relapse, its symptoms, the risks of pregnancy and the related tasks. (1D)

Besides the elements described under supportive therapy for TTP, particular attention must be given to resolving electrolyte, acid-base and fluid balance, and treating hypertension. Administering erythropoietin is recommended in renal anaemia to reduce the need for red blood cell transfusion. As influenza is one of the most common triggers, immunising patients against influenza A is recommended [15, 19].

The indication of kidney transplantation in patients with aHUS [17]

Recommendation 72
Kidney transplantation due to atypical HUS cannot be performed without clarifying the genetic background [12, 14, 17]. (1B)

Recommendation 73
In case of a kidney transplant, the risk of relapse and prophylactic therapy to prevent relapse must be determined based on genetic testing of the complement and the condition's biological behaviour. [12]. (1B)

Recommendation 74
In the event of a relapse following a kidney transplant, first-line complement-inhibiting treatment is necessary as plasma exchange is ineffective with regard to the kidney based on the literature and local experience [12, 160]. (1B)

Recommendation 75
As a prophylactic treatment for kidney transplantation, complement-inhibiting treatment is recommended for patients at high risk, and complement-inhibiting treatment or plasma exchange for patients at intermediate risk [15]. (1C)

For a long time, a basic diagnosis of atypical HUS was a contraindication for kidney transplant in end-stage renal disease, mainly due to the particularly poor graft survival data. When performing a kidney transplant in atypical HUS, the main reason for graft loss was a recurrence of the primary disease according to historical data [160]. This may occur immediately after transplantation. In the cited study, graft loss generally occurred 6 months after transplantation and affected ~60–90% of patients according to the data of the various case series reports [161, 162]. Confirmed complement mutation has proven to be the most important predicting factor of the post-transplantation recurrence of aHUS. The mutations that correlate with a low, moderate or high increase in the

risk of recurrence were identified by summing up the features of genetic mutations (affected gene, type of mutation, functional effect of the mutation) [15]. In accordance with the recommendations of the French study group, prophylactic therapy is necessary during the peritransplantation period if there is a moderate or high risk of relapse, currently in the form of plasma exchange or targeted complement-inhibiting treatment (Table 10).

Table 10: Prophylaxis preceding kidney transplantation [12, 121]

Risk of recurrence	**Mode of prophylaxis**
High — FH and gain-of-function mutations: FB, C3 — Combined mutations, with the exception of MCP combinations — Due to the recurrence of earlier graft loss, irrespective of the genetic test results	Complement-inhibiting treatment
Moderate — Isolated FI mutation — Combined MCP mutation — Mutation of unknown functional effect	Complement-inhibiting treatment or plasma exchange
Low — DGKE mutation — Isolated MCP mutation — No detectable mutation — Low anti-FH antibody titre	prophylaxis is not necessary

In 2019, the French Working Group validated the practical usefulness of this recommendation with new data [121]. It was demonstrated that transplantation in aHUS patients is possible, that complement-inhibiting treatment improves graft survival, and that the therapy chosen based on genetic differences did indeed improve outcome. Based on the new results and the experience gained during the earlier treatment of patients in Hungary (all patients currently awaiting a transplant have previously proven to be plasma-resistant) and the previous literary data (when the disease relapsed during the post-transplantation period, graft loss could not be avoided with plasma exchange [160]), prophylactic complement-inhibiting treatment is indicated if there is a moderate or high risk of recurrence (see Table 10). If complement-inhibiting treatment is not available, prophylactic plasma therapy may be allowed on a case-by-case basis.

Peritransplantational plasma treatment must be started 12–24 hours prior to transplantation and continued for at least 24–48 hours following transplantation. Decreasing the frequency and discontinuing plasma treatment may be planned according to the complement profile and ADAMTS13 activity parameters. Substitution is recommended during the peritransplantational period: 100% FFP or pooled plasma, human, solvent-detergent treated. More recent results have supported the utility of preemptive plasma therapy, showing that even in the high genetic risk subgroup, graft survival can be improved with preemptive plasma therapy [163].

The duration of prophylactic peritransplantational eculizumab treatment should be at least 12–18 months according to the experiences of the French study group (the risk ratio of the primary aHUS recurring in the graft decreases significantly in months 15–20 after transplantation [160]). The guidance provided by the Summary of Product Characteristics and the protocol described in the French study group's paper [164] must be adhered to if the complement-inhibiting treatment uses eculizumab, and if the patient is given a full dose of eculizumab on day 0 and 1 (for enhanced protection against complement activation due to operative stress and cold ischaemic injury to the graft) and on day 7, and then every two weeks thereafter (for at least 12–18 months). The duration of treatment must be planned according to the type of mutation [165], medical history and family medical history, the results of the complement profile and ADAMTS13 activity during the post-transplantation period [166]. Treatment may be suspended if the patient is in full remission (haematological and renal), TMA inactivity can be confirmed with laboratory measurements (e.g. haptoglobin, complement profile, ADAMTS13) and eculizumab is continuously available for treating a potential relapse after the suspension of therapy.

A HUS episode following a transplantation should be considered aHUS and calls for targeted complement-inhibiting therapy (e.g. eculizumab) as first-line treatment (see Figure 3)

In case of dialysis-dependent renal failure presenting against a backdrop of aHUS, a kidney transplant can only be planned after investigating the patient's genetic background and molecular aetiology.

Kidney transplantation from a living, unrelated donor can be performed in aHUS with good outcomes, with unconfirmed results suggesting that it can be performed without prophylactic use of complement-inhibiting treatment [167].

In the case of a living, related donor (for the protection of both the donor and the graft), transplantation in aHUS should only be allowed if pathogenic or potentially pathogenic mutations in the complement genes can be identified and the donor does not carry any of the risk variants identified in the patient [168].
If aHUS relapse occurs after transplantation in a patient with known genetic predisposition, continuation and long-term use of complement inhibitors is justified, whereas treatment of *de novo* aHUS in graft after renal transplantation with complement inhibitors is only necessary until remission if no genetic risk factor can be confirmed [169].

Combined liver and kidney transplant in HUS
As complement regulator proteins are produced by the liver, a combined liver and kidney transplant is currently the only curative therapy [170] but this is chosen increasingly less in the age of eculizumab treatment due to its potential complications.

TTP AND ATYPICAL HUS A IN PREGNANCY
During pregnancy and the postpartum period, it is difficult to distinguish TTP and aHUS from each other and from severe pre-eclampsia and HELLP syndrome [171, 172]. Accurate differentiation of these pathologies during and after pregnancy is often very difficult due to overlapping symptoms and abnormalities (including hypertension, glomerular impairment, renal failure, elevated LDH, and thrombocytopaenia), especially at the beginning of the process. The timing of and changes in symptoms, the presence of underlying or concomitant diseases/triggers/complications, laboratory abnormalities before (plasma) therapy and probabilistic estimation all play a role in clarifying the exact aetiology and pathology.

Recommendation 76
If atypical peripartum HUS/TTP is suspected, the patient should be transferred immediately to a centre with expertise in the treatment of HUS/TTP, where tertiary obstetrics and intensive care units are available [171]. (1D)

Recommendation 77
If peripartum HUS/TTP is suspected, investigations and therapeutic decisions should be made according to the recommendations of the International Working Group [171]. (1C)

In practice, three practical regularities can also be used to detect TTP and aHUS [172]: Signs of microangiopathy and persistent, deepening thrombocytopenia after delivery raise the suspicion of TTP; elevated serum creatinine after delivery raises the suspicion of aHUS; both thrombocytopenia and creatinine improve after delivery: suspicion of PE/HELLP syndrome.

TTP
About 5% of all episodes of TTP occur during pregnancy. 46% of these present after week 30 of the pregnancy or postpartum, while 54% present prior to week 30 (weeks 20–29: 38%; before week 20: 15%) [173].
In approximately two thirds of first TTP episodes presenting during pregnancy, the ADAMTS13 enzyme genetic defect (late-onset-USS, incidence: 1:200,000 pregnancies) manifests, most often in the third trimester. Foetal survival is just 58% in pregnancies where the disease is unnoticed; this can be increased to 100% in pregnancies where the disease has already been diagnosed and is given the right care from the start of pregnancy, with regular plasma therapy started on week 8–10 (10 mL/kg FFP every two weeks, then every week from week 20 + aspirin after week 12). Plasma therapy must be customised so that the pregnant platelet count remains within the normal range the entire time. The optimal time of birth is in week 36–38 of pregnancy. The patient must continue to be checked after this, as 20% of cases still require regular plasma replacement [173].
The inhibitor form of the condition generally presents during the second trimester or the postpartum period. Foetal survival is 65%. Foetal death in both types of TTP is most common during the second trimester, caused by microthromboses in the placenta. Abnormal ADAMTS13 activity at the beginning of the pregnancy increases the probability of relapse [173]. However, normal activity does not guarantee a relapse-free pregnancy either. If the patient is known to have inhibitor TTP, ADAMTS13 activity should be checked regularly (monthly). If ADAMTS13 activity dips below 20%, prophylactic plasma therapy (± steroids, + 100 mg acetylsalicylic acid after week 12) is recommended. Treatment must be given so that the patient's platelet count remains within the normal range.
In the event of clinical relapse of TTP, daily plasma exchange (+ steroids, acetylsalicylic acid after week 12 if platelet count >50 g/L) should be performed (Table 6) until remission.
Based on our own experiences (at South-Pest Central Hospital), birth may activate the microangiopathic process even if total remission was achieved with treatment during pregnancy. This must be factored in and the patient

monitored closely for at least six weeks following birth, particularly if ADAMTS13 activity is abnormal. If laboratory results are deteriorating continuously, therapy must be restarted as described for TTP.

Atypical HUS
About 20% of new-onset aHUS episodes occur during or immediately after pregnancy. 79% of pregnancy-associated aHUS cases (estimated incidence: 1:25,000 pregnancies) begin during the postpartum period (from day 3 until month 6 following birth), but they may begin earlier (as early as in the first trimester) in response to complement activation factors (such as infection) [174]. According to French data [174], the risk is the greatest during the second pregnancy (nearly 30%), for unknown reasons. Some type of complement mutation can be confirmed in 86% of aHUS cases presenting during pregnancy (FH: 48%, FI: 9%, C3: 9%, MCP: 5%, >1 mutation: 14%, no mutation: 14%) and homozygous aHUS risk haplotype verifiable in 57% of cases (MCP_{ggaac}: 22%, CFHH3: 45%). It is a highly malignant form that causes irreversible renal failure within 1 month in 62% of cases and in 76% of cases in the long term if not managed with the right treatment. By contrast, thrombocytopaenia is mild in 40% of patients (>100 g/L) [174]. Therapy should include immediate plasma exchange and a prompt switch to complement-inhibiting treatment (when PE/HELLP and TTP have been ruled out).

HELLP syndrome
HELLP syndrome (**h**aemolysis, **e**levated **l**iver enzymes, **l**ow **p**latelet count) occurs in about 0.2-0.9% of all pregnancies and in 10-20% of severe eclampsia. Its incidence is approximately 1:1,000 pregnancies. It begins antepartum (weeks 28–36) in 70% of cases and postpartum in 30% of cases, within 48 hours of birth. The latter is not preceded by (pre)eclampsia in 80% of cases. It is more common in Caucasian women over the age of 25 that have given birth several times [175]. It currently constitutes an independent subgroup of TMA (Figure 2) — endothelial dysfunction, of which abnormal placenta development forms the pathological basis. More recently, it has also been linked to abnormal complement regulation [176, 177]. The complement regulation disorder in and of itself leads to a 1.5 to 2-fold increase in the risk of foetal death and eclampsia [174]. It should be differentiated from TTP during pregnancy, and ADAMTS13 deficiency and a LDH/SGOT ratio of over 22 during the third trimester [178] also suggest TTP. The only treatment for HELLP syndrome during pregnancy proven to be effective is termination of the pregnancy and removal of the placenta. The platelet count reaches its trough 23–29 hours after birth before normalising in 6–11 days. Plasma exchange may be effective in the postpartum form of the condition [179]. In cases that do not improve at a satisfactory rate, tests must be extended to investigate aHUS.

SECONDARY FORMS OF TTP-HUS
Table 11 sums up the most common causes of secondary thrombotic microangiopathies. Their common trait is underlying endothelial damage, however the exact molecular mechanism of this is not yet, or not sufficiently, clarified. The pathogenic complement differences underlying atypical HUS do not appear to be dominant in this pathotype [180]. The clinical presentation is most often HUS, but may also be TTP. Silent presentation is also possible, dominated by progressive renal failure alongside mild haematological symptoms. It is also referred to as secondary TTP-HUS/HUS-TTP/TMA or HUS-like/TTP-like in the literature. The outcome depends on the cause; treatment is fundamental and ability to treat also often defines the outcome. ADAMTS13 activity is normal or only slightly reduced in most conditions. However, severe activity deficiency or consumption do rarely occur. In some forms, ADAMTS13 inhibitor (e.g. ticlopidine, interferon, pregnancy, SLE, antiphospholipid syndrome, lymphoma, HIV infection and so on) may also occur. Clarifying this is essential for deciding on treatment. In cases featuring insufficient and inhibition, besides treating the primary disease, plasma exchange and immunosuppressant therapy are also indicated, to be performed as described for TTP. If there is sufficient ADAMTS13 activity, plasma exchange is generally not considered, however eculizumab may be effective in some cases (e.g. mitomycin [181], gemcitabine-[182] associated HUS). There is no reliable data on the efficacy of plasma transfusion in case of severely decreased but not insufficient activity. Some results have shown that short-term complement-inhibiting treatment (4-12 weeks) has shown beneficial results in patients with secondary HUS/TTP in whom treatment of the underlying disease did not result in improved renal function [183-185], but the issue is still controversial [186, 187]. In cancer-associated forms of the condition, significant progress is expected in the future from agents affecting platelet-VWF interaction.

Significant progress has been made recently in the analysis of the relationship between **malignant hypertension** (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥120 mm Hg (as per regular measurement), together with signs of organ damage such as renal, cardiac, neurological or ophthalmological complications [188]) and TMA, particularly with regard to the site of complement-inhibiting treatment. It has been shown that malignant hypertension is particularly common in patients with aHUS, its presence is a poor

prognostic factor for renal impairment in the absence of pathogenic genetic variation in complement genes, while the efficacy of complement-inhibiting treatment has been demonstrated independently of the presence of malignant hypertension [189]. In another study of 55 and 110 patients with malignant hypertension related to aHUS and other diseases, respectively, Spanish researchers found that patients with aHUS had a better outcome with the complement inhibiting treatment than with plasmapheresis, an effect that was independent of the degree of hypertension [190]. It was also found that TMA as a complication in patients with malignant hypertension from other causes is very rare. This suggests that in malignant hypertension, TMA activity markers should be monitored regularly (see Table 2), and if complete resolution of TMA cannot be achieved with adequate blood pressure control, plasmapheresis or complement-inhibiting treatment may be indicated due to the possibility of aHUS.

Recommendation 78
In the differential diagnosis of hypertensive crisis, aHUS should be considered as an etiological factor and a therapeutic target. (1C)

Recommendation 79
If signs of microangiopathy and acute kidney injury are confirmed during a hypertensive crisis, a nephrologist should be consulted to develop a further investigation and treatment plan. (1D)

Recommendation 80
If signs of microangiopathy and acute kidney injury are confirmed during a hypertensive crisis and the process is expected to be reversed (e.g. based on renal or fundus examination), then initiation of complement-inhibiting treatment is warranted. The length of treatment should be judged on an individual basis (such as verifiability of genetic background and the extent of improvement on antihypertensive treatment, etc.) and should be continued until a maximum clinical response is achieved, with a recommended minimum of 2 months. (1C)

Table 11: Underlying diseases, conditions and treatments in which the development of secondary thrombotic microangiopathies has been described [1, 11-14, 28-30, 191, 192]
— Pharmacological treatments:
- Quinine
- Thienopyridines: ticlopidine, clopidogrel
- Calcineurin inhibitors: cyclosporine, tacrolimus
- mTOR inhibitors: sirolimus, everolimus
- Chemotherapy agents: mitomycin B, cisplatin, bleomycin, gemcitabine, etc.
- Angiogenesis inhibitors: bevacizumab
- Tyrosine kinase inhibitors: sunitinib
- Other agents: oral contraceptives, interferon, etc.
— Malignant hypertension (often against a background of silent IgA nephropathy)
— Disseminated cancers, often mucin-producing adenocarcinomas
— Infections:
- viral infections (e.g. HIV, CMV, etc.)
- sepsis: bacteria, fungus
— Allogeneic stem cell transplantation: graft-versus-host disease; solid organ transplantation
— Autoimmune conditions:
- SLE
- antiphospholipid syndrome
- SSC renal crisis
— Surgeries (e.g. motor heart surgery); protein-losing conditions (e.g. diarrhoea); pancreatitis
— Extracorporeal membrane oxygenator treatment
— Adeno-associated virus 9 vector-based gene therapy (such as Onasemnogeneabeparvovec)

Algorithms for the medical care process (Figures)

Figure 2: Classification of thrombotic microangiopathies[12]

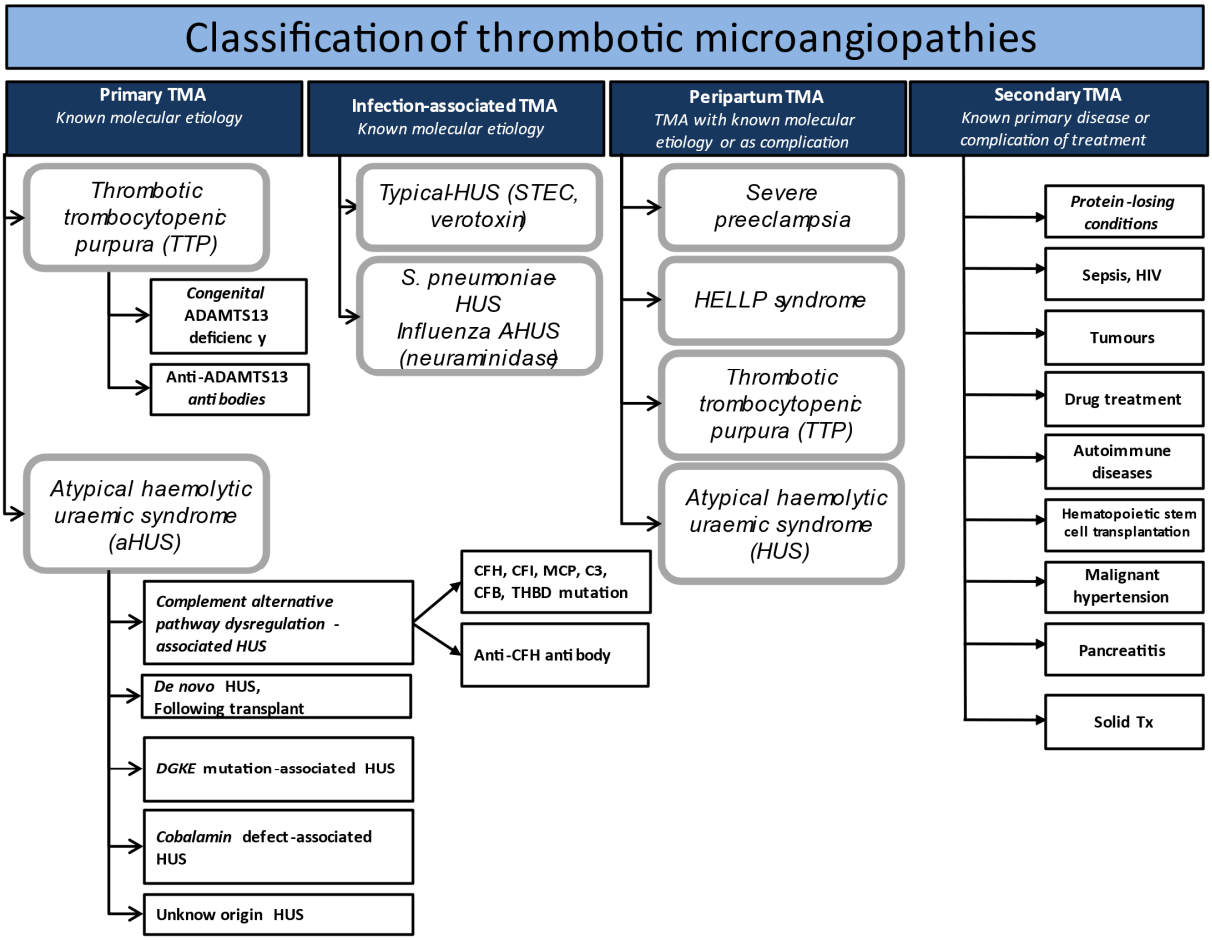


Figure 3: Summary of the diagnostic algorithm and possible modes of therapy for HUS. See the text for detailed explanations. Based on Reference no. [15], as amended.

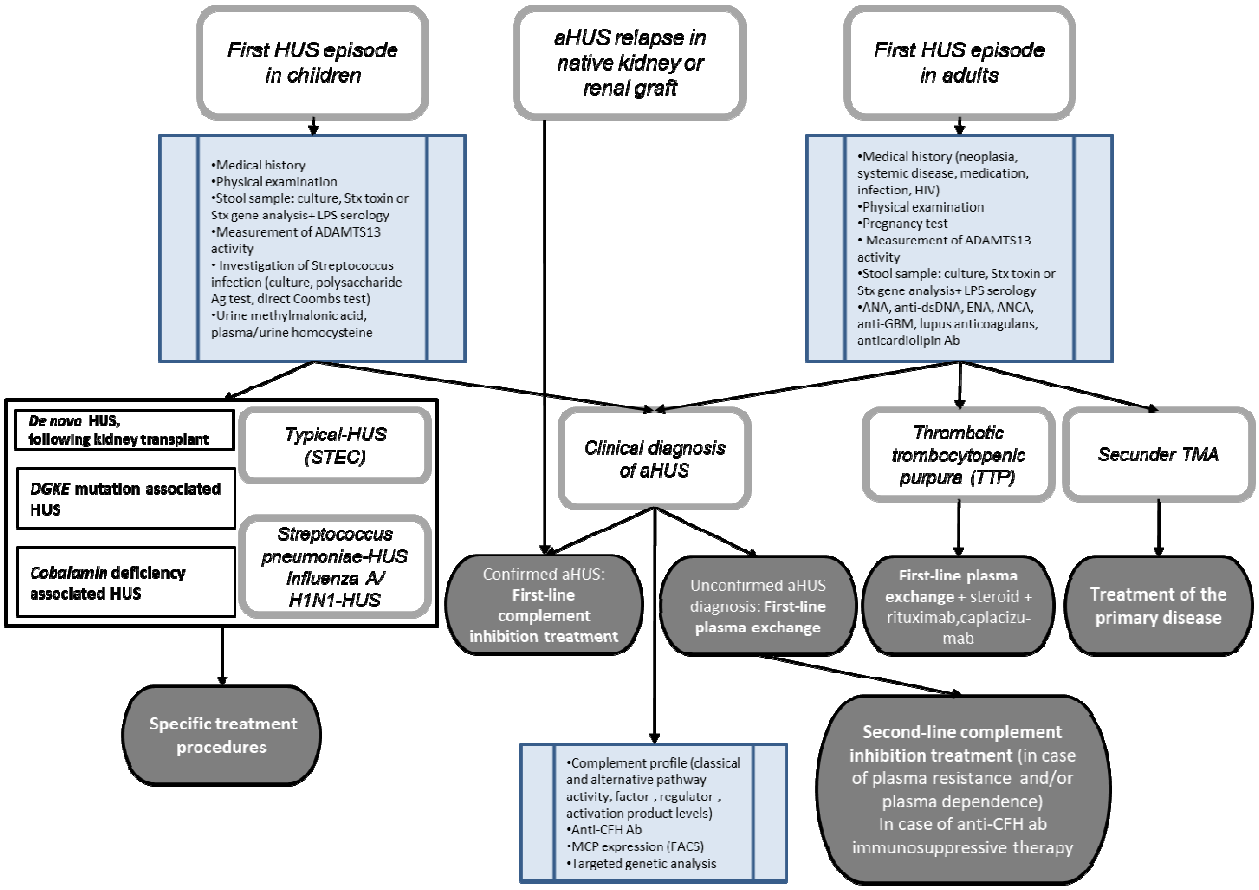


Figure 4: Recommended care algorithm for adult patients

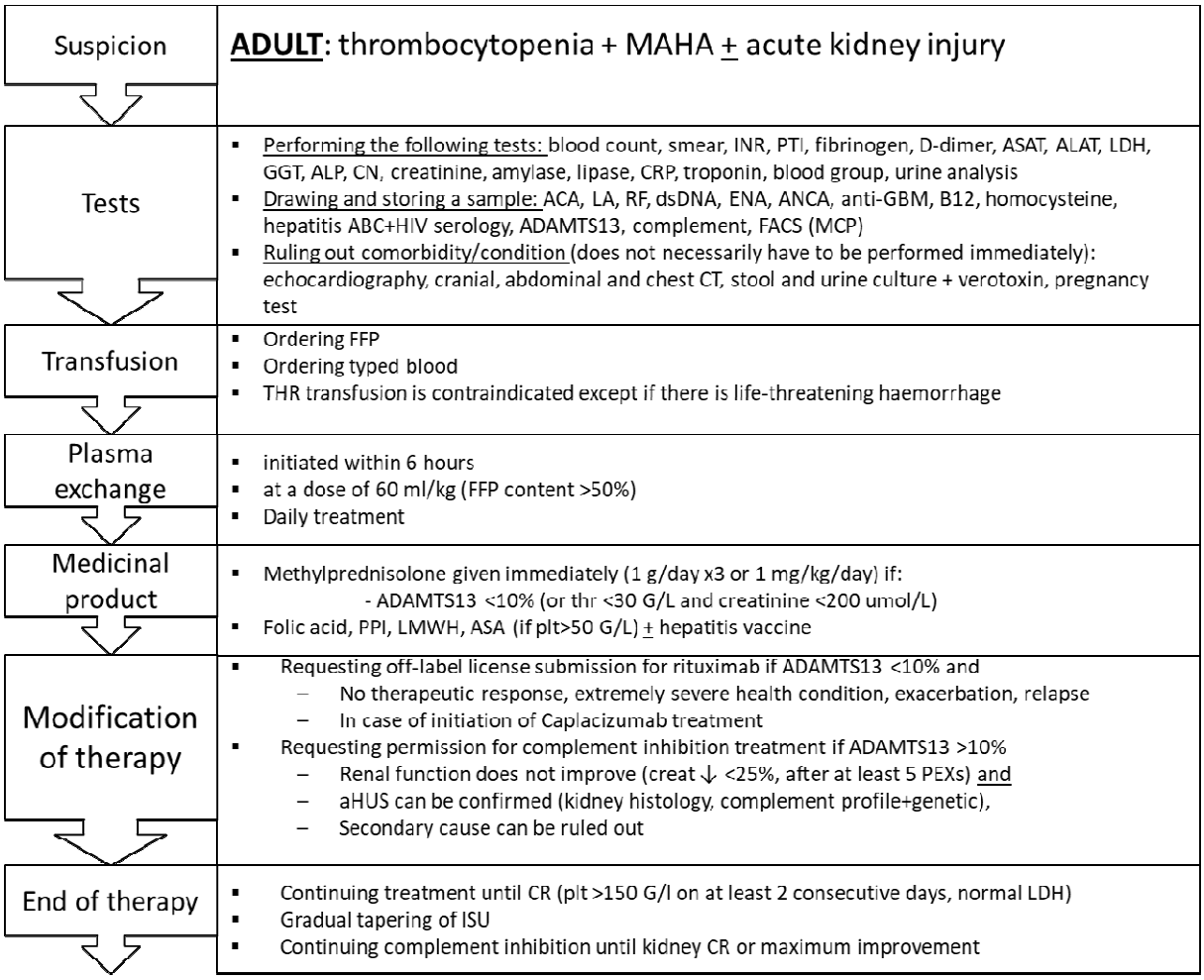
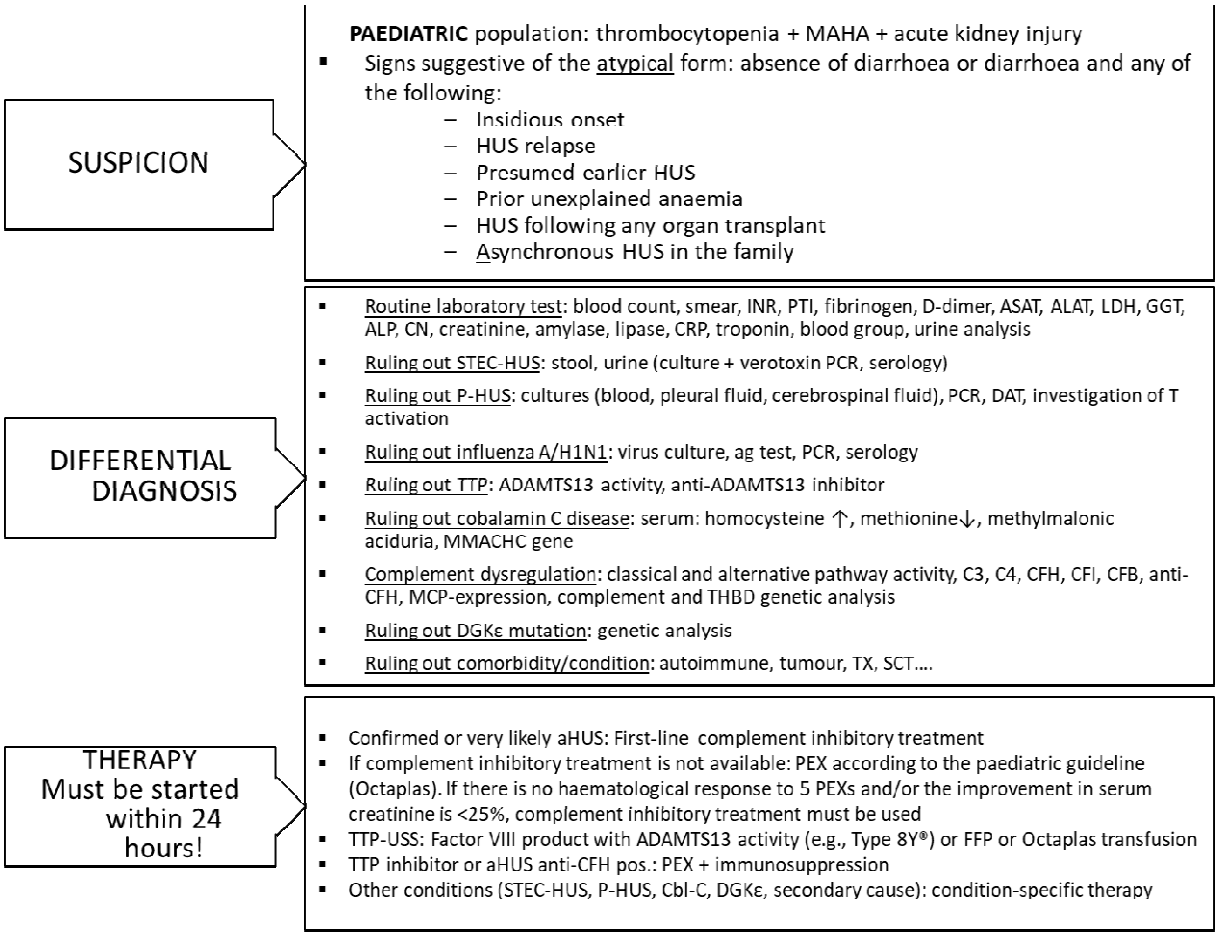


Figure 5: Recommended care algorithm for paediatric patients



VII. SUGGESTIONS FOR APPLYING THE RECOMMENDATIONS

1. Conditions of application in Hungarian practice

— Application of the medical guideline and acute care for patients with TTP and HUS may only be performed at accredited healthcare providers with sufficient experience in managing these conditions.

1.1. Competence (e.g. licence, accreditation, etc.) and capacity of careproviders

— In TTP, treatment should be managed by a haematologist experienced in TTP, while in paediatric aHUS, treatment should be managed by a nephrologist experienced in treating HUS. In adult aHUS, treatment should be managed by a haematologist and/or nephrologist experienced in treating the condition.
— Care for patients with prior TTP or HUS and assessment of potential changes in therapy is the responsibility of specialist doctors.
— Treating and providing care for TMA patients is recommended in tertiary centres.

1.2. Special material conditions and organisational matters (obstacles and facilitating factors, the resolution of these factors)

— Application of the medical guideline and acute care for patients with TTP and HUS may only be performed at accredited healthcare providers with sufficient experience in managing these conditions.

1.3. Patient information, social and cultural circumstances, and individual requirements of patients

— In the course of providing treatment and care for patients with TTP and HUS, continuous patient information, prognosis and risk analysis is necessary (based on the accurate diagnosis, classification and aetiology), which is the responsibility of specialist doctors, with the involvement of a multidisciplinary team if necessary. When providing information to patients, their social and cultural background and individual expectations should be taken into account to the greatest extent possible.

1.4. Other conditions

— List of diagnostic centres
— List of apheresis centres offering continuous care
— List of service providers offering mobile apheresis (for temporary care for ventilated and/or non-transportable patients)
— List of acute dialysis centres
— The funding algorithms for diagnostic tests, specific immunosuppressant and complement-inhibiting therapies and haemosupportivetreatments

2. List of documents to help administration

2.1. Patient information sheet, education materials

1. TTP-HUS patient information sheet
2. Alexion - aHUS patient and parent information booklet.

2.2 Verification questionnaires and data sheets to be used when completing the series of activities

None.

2.3 Tables

Table 1: TTP and HUS: age-related onset of clinical conditions with a known pathomechanism
Table 2: Tests necessary to determine and begin immediate treatment of thrombotic microangiopathies (TTP and HUS) to be performed urgently
Table 3: Tests required for differential diagnosis and the selection of targeted therapy for thrombotic microangiopathies (TTP and HUS)
Table 4: Main clinical conditions to be excluded in the differential diagnosis of TTP and HUS
Table 5: PLASMIC score [38] and FRENCH score [27]
Table 6: The practice of plasma exchange in TTP
Table 7: Clinical triad characteristic of HUS
Table 8: Signs suggestive of atypical HUS
Table 9: Plasma exchange in atypical childhood HUS (The recommendation of the European Paediatric Study Group for HUS)
Table 10: Prophylaxis preceding kidney transplantation
Table 11: Underlying diseases, conditions and treatments in which the developmentofsecondary thrombotic microangiopathies has been described

2.4 Algorithms

Figure 1: Annual trends in the number of patients diagnosed with aHUS and TTP at the FüstGyörgy Complement Diagnostic Laboratory of the Department of Internal Medicine and Haematologyof Semmelweis University
Figure 2: Classification of thrombotic microangiopathies
Figure 3: Summary of the diagnostic algorithm and possible modes of therapy for HUS [132]. See the text for detailed explanations. Based on reference no. [15], with modifications. Only the most common forms are indicated in the figure.
Figure 4: Recommended care algorithm for adult patients
Figure 5: Recommended care algorithm for paediatric patients

2.5 Other document

None.

3. Guidelines for practical application, audit criteria

- Changes in the incidence data for confirmed congenital TTP, immune TTP, typical and atypical HUS
- Evolution of morbidity (development of known complications [e.g. stroke], permanent organ damage [e.g. dialysis] or change in work capacity) and mortality in patients with proven congenital TTP, immune TTP, typical and atypical HUS.
- Developments in the kidney transplant of aHUS patients, changes in the average survival time of kidney grafts.
- Changes in the incidence of peripartum thrombotic microangiopathy and how many investigations have been conducted in this regard per year
- Changes in the data for confirmed congenital TTP, immune TTP, typical and atypical HUS relapses
- How many applications for targeted biologics for iTTP and aHUS diagnoses were made, and how long did the approval take

VIII. GUIDELINES REVIEW PLAN

The scheduled medical guideline review process will begin six months prior to its expiry. The experts appointed by the heads of the co-author sections and the working group developing the guideline will jointly review new findings in the literature and changes in the Hungarian healthcare system. Aspects covered by the review include (but are not limited to):

- Review and assessment of the literature on the pathogenesis, symptoms, diagnosis, classification, complications and therapy of TTP and HUS
- Review and assessment of new international guidelines on the treatment of TTP and HUS
- Special questions: Treatment of TTP and HUS during pregnancy, kidney transplantation and HUS
- Review and assessment of changes in specific treatment procedures (plasma therapy, targeted immunosuppressant or complement-inhibiting treatment, additional targeted therapeutic procedures for the treatment of TTP and HUS) and their availability Hungary.

The working group developing the medical guideline may initiate an extraordinary review if a major new fact, evidence or data related to the medical guideline is published in the literature, or if a major change affecting the medical guideline's application occurs in the Hungarian healthcare environment.

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X. DEVELOPMENT METHOD

1.Formation of the development group, the development method and the documentation of tasks
The chairperson of the National Advisory Board of Healthcare asked the delegated members of the sections affected by the topic to begin developing the guideline. After its creation, the development group defined a list of tasks to be completed. The medical guideline was created with the individual effort of members and following multiple rounds of consultation.

2. Literary search and selection
The literature was primarily reviewed using the PubMed (ncbi.nlm.nih.gov) database based on the following keywords: HUS, TTP, USS, TMA, HELLP, preeclampsia. Analysing the list of references included in the published international guidelines identified during the search was also part of the literary review.

3. Describing the strength and shortcomings of the evidence used (critical assessment, 'evidence or recommendation matrix'), method for determining the level of evidence
The classification system used for the level of evidence is based on the GRADE nomenclature. [193]
In the text, the development group rated scientific evidence and its credibility and scientific support in parentheses following the text description, for instance: (A).

4. Method for drafting the recommendations
The recommendations included in the guideline were rated based on the evidence background.
The system used for ranking recommendations was elaborated by the development group based on the GRADE nomenclature [193]. In the text, the development group classified recommendations in parentheses following the text description, for instance: (1).
When the adapted guidelines used a different classification system, the Hungarian development group adopted the classification used by the BCSH Guideline and classified recommendations from other adapted guidelines using this system. If adapted guidelines assigned a different grade to a specific recommendation, the development group applied the lower recommendation classification grade.
The recommendations of this medical guideline, applicable within its scope, have been adapted to the pertaining Hungarian medical care environment (characteristics, preferences, health culture and cost-bearing capacity of the treated population, legal environment).

5. **Consultation method**
Once the medical guideline's medical content was compiled, the document was sent to the Sections of the National Advisory Board of Healthcare that had requested consultative rights and accepted the development group's request to provide consultation. The recommendations received were incorporated into the medical guideline, or the document's structure was amended based on the recommendations if the medical guideline developers agreed with them.

6. **Independent expert consultation method**
No independent expert consultation took place.

XI. ANNEX

1. Documents to help administration
1.1. Patient information sheet, education materials
1.1.1 TTP-HUS patient information sheet

TTP-HUS PATIENT INFORMATION SHEET

THROMBOTIC MICROANGIOPATHIES (TMA)
An umbrella term for conditions characterised by similar symptoms and abnormalities in laboratory results. The pathological basis is abnormal platelet activation and aggregation that results in thrombosis in the small blood vessels, disrupting blood supply to the affected areas with consequential organ function impairment. The extent and location of organ injury and the underlying molecular mechanism differs in the various conditions.

1. THE MOST COMMON LABORATORY ABNORMALITIES:
- *Thrombocytopaenia* (low platelet count): continuous activation and aggregation lead to the utilisation of platelets. If bone marrow production is unable to keep up, thrombocytopaenia develops. The degree of thrombocytopaenia may differ among the various conditions.
- *Microangiopathic haemolytic anaemia*: clot formation in the small blood vessels causes mechanical damage to red blood cells, which are fragmented (schistocytes) and rupture and dissolve within the bloodstream (haemolysis). If production is unable to keep up, anaemia develops.
- *Elevated LDH* (lactate dehydrogenase): its level increases significantly in processes that result in haemolysis (breakdown of red blood cells) and tissue breakdown.
- *Low serum haptoglobin*: a protein that is used up in the bloodstream during haemolysis with the physiological function of binding the haemoglobin from the fragmented red blood cells. Low haptoglobin levels indicate the presence of haemolysis.
- *Elevated creatinine*: the creatinine level increases in kidney injury, to different degrees in various conditions.
- *Abnormalities in urine*: white and red blood cells and free haemoglobin often appear in the urine. A sign of impaired kidney function.

2. MOST COMMON CLINICAL SYMPTOMS
- *Haemorrhage caused by thrombocytopaenia*: petechiae or small bruising on the skin and mucosa. Sometimes there are no symptoms of haemophilia at all despite very severe thrombocytopaenia. Although severe haemorrhage can sometimes occur, it is generally rare.
- *Haemolytic anaemia*: the mechanical destruction of red blood cells leads to anaemia if red blood cell generation is unable to keep up. The degree of anaemia may vary, and may even be absent initially.
- *Neurological symptoms*: headache, disturbance of consciousness, speech disorders, sensory disorders, paralysis, and seizures may occur in the most diverse combinations. They are mainly seen in thrombotic thrombocytopenic purpura (TTP), but are not compulsory symptoms. The symptoms often 'shift', improving or deteriorating spontaneously.
- *Renal impairment*: a decrease in the kidney's detoxification function characterised by a decrease in the quantity of urine. May require dialysis treatment. Is most often seen in haemolytic uraemic syndrome (HUS) and HELLP syndrome.
- *Fever*: may present without infection (mainly in TTP), but may also signal an accompanying infection.
- *Other symptoms*: besides the nervous system and the kidney, the most commonly affected organ is the heart, manifesting in the form of arrhythmia, myocardial infarction and heart failure. As microthromboses affect the entire body, other symptoms may also occur: intestinal perforation, pancreatitis, etc.

3. KEY CLINICAL FORMS

a. Thrombotic thrombocytopaenic purpura (Moschcowitz syndrome, TTP)

It is a rare disease that mainly affects women, occurring most frequently in young adulthood, but may occur at any age. It is most often caused by a deficiency in an acquired or congenital factor circulating in blood plasma (the ADAMTS13 enzyme) and is characterised by enzyme activity of under 10%. The enzyme physiologically breaks down the von Willebrand factor (VWF). VWF is a coagulation factor with a complex structure, a huge molecule (ultra-large VWF, ULVWF) that enters the circulation when the cells covering the internal surface of blood vessel walls (endothelium) are exposed to damaging or stimulating stimuli. Its physiological role is to anchor platelets, creating a so-called "platelet-dense" seal at the site of damage to the vessel wall. The ADAMTS13 enzyme's function is to cleave excess VWF into smaller parts that do not bind platelets as much. If

ADAMTS13 enzyme function is lacking for any reason, platelet plugs are formed in the small blood vessels and flood the body, are carried away and disrupt blood supply to distant organs (most often the brain, kidney and heart). The process uses up platelets, decreasing the platelet count (thrombocytopaenia) and haemophilia may occur. While passing through clotted red blood cells, the red blood cells are mechanically damaged and ruptured (haemolysis), which may manifest in the form of anaemia. Acquired and congenital forms of the condition are both known:

— *The congenital form*: It is also known as *Upshaw-Schulman syndrome* and is very rare. It stems from a *genetic enzyme disorder*. It may typically present during the neonatal period or later on, mainly during pregnancy. Diagnosis is often delayed in its milder forms. The condition may be hereditary.

— *Acquired form*: stems from an enzyme function disorder, *the autoantibody (inhibitor) inhibiting enzyme function*. The mortality rate is over 90% without treatment, while a sustained asymptomatic state can be achieved in nearly 80–95% of patients with adequate treatment started on time. The condition may return later on (see also section 6/a). It is not hereditary.

b. Haemolytic uraemic syndrome (HUS)

Umbrella term that includes several clearly defined conditions:

— ***Typical HUS (STEC-HUS):*** *caused by infection with verotoxin-producing bacteria* (*Escherichiacoli*, *Shigella dysenteriae*, *Citrobacter freundii*), usually from food or drink. It is the most common cause of paediatric renal failure. Mainly affects children between 2–5 years of age, but may also occur in adulthood. Its typical symptom is acute renal failure, haemolysis and thrombocytopaenia following bloody diarrhoea, which is why it was formerly called diarrhoea-associated 'D+' HUS. Neurological and other symptoms may also occur. Generally responds well to treatment, resolving most of the time without permanent injury, and relapse and family history (except in cases occurring simultaneously in several family members) are not characteristic. Prospects are less positive in adults. A huge epidemic caused by a previously unknown strain of E. coli broke out in Germany in 2011 which uncharacteristically predominantly affected adult women, causing a high number of severe neurological symptoms and high mortality. The condition is not hereditary.

— ***Pneumococcus-associated HUS (P-HUS)*****:** very severe disease in children under 2 years of age. The symptoms are caused by the neuraminidase enzyme produced by the *Streptococcus pneumoniae* bacteria, which exposes hidden antigens by cleaving off sialic acid on cell membranes. The antibodies normally present in plasma react with these hidden antigens and cause cell damage. The condition is generally not hereditary.

— ***Atypical HUS (aHUS)*****:** is usually caused by deregulation of the alternative activation pathway of the complement system. The complement system is found in blood plasma and is a vital part of the congenital immune system. The alternative activation pathway plays an important role in shielding against pathogens. Under normal circumstances, this system exhibits continuous spontaneous activation. The role of regulatory proteins is to keep this smouldering activity at bay and to prevent complement activation from damaging the body's own cells. Its defective functioning damages the endothelium (the layer of cells lining the inside of blood vessels) and forms tiny blood clots that flood the body and result in the dysfunction of many different organs. The most pronounced abnormalities manifest in the kidney, the heart and the nervous system. Haematological abnormalities (haemolysis, anaemia, thrombocytopaenia) are generally milder than in TTP. It may occur at any age, but mainly affects newborns, children over the age of five years and young adults. It does not have a distinctive introductory phase (no bloody diarrhoea) and the process is generally chronic, characterised by relapses and may have a family history. Without proper treatment, it often leads to end-stage renal failure, has high mortality, and generally recurs in transplanted kidney grafts. Several forms are known:

- *Congenital form*: the regulatory factors of the alternative activation pathway of the complement system do not function correctly or are not produced for genetic reasons. It is a hereditary condition.
- *Acquired form*: the autoantibody impedes the functioning of regulatory proteins (e.g.: factor H). It is not a hereditary condition.

— ***Secondary TTP-HUS***

Clinical symptoms and laboratory abnormalities reminiscent of TTP and HUS may manifest alongside various medications, infections, tumours and autoimmune diseases. The underlying cause and mechanism of these is very diverse, and often not precisely known. It is not a hereditary condition.

4. THE EXAMINATION PROCESS

The examination is a complex time-consuming process that is quite costly. Today, establishing an accurate diagnosis is essential for choosing the right therapy. The following examinations may be performed:

- full blood count, peripheral blood smear
- blood chemistry and immunology tests
- blood coagulation tests
- ADAMTS13 tests (and genetic tests if warranted)
- complement tests (and genetic tests if warranted)
- blood type serological tests
- virology (including HIV)
- urine test (chemistry, culture, pregnancy test)
- stool test (culture, and alsoverotoxin)
- imaging examinations (chest x-ray, abdominal/heart ultrasound, cranial CT/MTI)
- other tests (crista biopsy, kidney biopsy)

Genetic tests may be performed to identify hereditary factors; a family examination may also be necessary if the result is positive. The genetic tests can only be performed with your consent.

5. THERAPEUTIC OPTIONS

The time factor may be so crucial in certain conditions that there is no time to wait for the results of every test. In such cases, a reasonable suspicion of the condition is sufficient for starting treatment.

a. ***Plasma exchange:*** a blood cleaning procedure performed outside the body using a cell or plasma separator specifically developed for this purpose, where approximately 40–60 mL/kg of plasma is removed from the patient and primarily replaced with fresh plasma from blood donors in case of TTP and HUS. The procedure is aimed at removing the abnormal substance responsible for the condition (autoantibody, abnormal regulatory factor) and replacing the lacking or dysfunctional substance (enzymes, normal regulatory factors) in large volume. A central cannula may be necessary for the treatment. (For details, see the institutional patient information sheet and informed consent form for plasma exchange). It currently constitutes first-line treatment for TTP. It is currently only recommended in the short term in atypical HUS (for up to 5–10 days), with longer treatment only considered if complement-inhibiting treatment is not available or the diagnosis is unclear.

b. ***Plasma transfusion:*** administration of fresh plasma from blood donors using a transfusion set, at a dose of 10–30 mL/kg. It is the basic therapy for the genetic form of TTP. It can also be used in some cases of atypical HUS (if the regulator protein is not abnormal but absent), particularly if complement-inhibiting treatment is not available.

c. ***Immunosuppressant treatment:*** Therapy used in the acquired forms of TTP and atypical HUS caused by autoantibodies. Steroids and/or rituximab are most commonly used. The latter is an off-label use and therefore requires OGYÉI and NEAK financing authorisation. Rituximab must not be given during pregnancy and is not recommended for one year after pregnancy. It is not without risks, and may entail fatal complications (see the patient information leaflet for rituximab). More rarely, other agents (cyclophosphamide, cyclosporine, mycophenolate-mofetil etc.) may also be considered.

d. ***Inhibition of VWF and platelet bounding:*** the recently registered caplacizumab prevents the bounding of Willebrand factor and platelets. It blocks platelet microthrombus formation without affecting the autoimmune process. It should therefore be combined with immunosuppressive treatment. Very effective, but symptomatic therapy. Mainly mild to moderate bleeding complications can be expected as adverse effects. Its availability is currently limited due to its extreme cost.

e. ***Complement-inhibiting treatment (eculizumab, ravulizumab):*** the treatment of choice in confirmed atypical HUS (also in children in case there is a strong suspicion). Given the huge costs of treatment, its use is always subject to NEAK funding authorisation. It constitutes symptomatic therapy that stops complement activation without affecting the underlying process. It requires long-term treatment spanning several months or years, or lifelong treatment in many patients. At least 2 weeks prior to starting therapy, patients must be vaccinated against *Neisseria meningitis* (and paediatric patients against *Haemophilus influenza* and *pneumococcus* as well), in some cases with the temporary or sustained use of antibiotics.

f. ***Removal of the spleen, splenectomy:*** A procedure that is still used today to prevent frequent relapses in the acquired inhibitor form of TTP. Decreases the frequency of relapse. Vaccination against encapsulated bacteria is necessary beforehand.

g. ***Platelet aggregation inhibition, thrombosis prophylaxis, thrombosis prevention:*** If the platelet count is above 50 g/L, low-dose aspirin and low molecular weight heparin are also used during treatment.

h. ***Transfusion treatment:*** platelet transfusion can generally only be given for serious clinical haemorrhage, otherwise it is not warranted by a low platelet count alone. Red blood cell transfusion is necessary in the

majority of patients using a typed and screened, filtered (leukoreduced) product. Fresh frozen plasma may also be given outside plasma exchange, particularly in TTP. As blood preparations in Hungary are not virus-inactivated, there is a small chance of virus transmission.

i. ***Other supportive therapy:*** some patients require treatment in an intensive care unit, parenteral nutrition, artificial respiration and dialysis. Adequately managing the ion balance, the acid-base balance and hypertension, and detecting and treating any potential infections are important.

6. PROSPECTS FOR REMISSION

a. ***In TTP:*** if plasma exchange is started on time (supplemented with immunosuppressant treatment if necessary), 80–95% of patients achieve a sustained asymptomatic state. In a small proportion of patients, some degree of mainly neurological residual symptoms may remain: memory problems, personality disorders, paralysis or other symptoms. The disease returns in 20–50% of patients (relapse). The time of relapse is extremely variable and cannot be predicted. Relapse is most often triggered by pregnancy, infection or surgery. If ADAMTS13 activity remains abnormal or becomes abnormal once again during the asymptomatic phase, there is a greater chance of relapse. In such cases, repeated immunosuppressant treatment may normalise enzyme activity in some patients. That being said, many patients may remain asymptomatic for years with low or even zero activity.

b. ***In atypical HUS:*** the sooner we start complement-inhibiting treatment, the greater the chance of restoring kidney function: Treatment started within 28 days yields the best results. After three months of dialysis, a kidney biopsy may help decide whether to give or continue giving the medicinal product. Successful attempts are being made to achieve stable remission by suspending administration of the product in order to avoid the huge cost of treatment, the potential complications and the discomfort caused by regular infusion. In such cases, very close patient control is necessary (testing urine twice weekly with a test strip) and treatment must be continued upon the first sign of relapse.
Haematological remission is easily achieved with plasma exchange, but the improvement in renal function is only seen rarely, with most patients developing end-stage renal failure.
If a kidney transplant is performed due to atypical HUS, the results of the complement genetic test are essential for choosing the optimal therapy.

c. ***Typical HUS:*** usually cured with supportive treatment. Residual symptoms are rare and the mortality rate is low.

d. ***Secondary TTP in HUS:*** the treatability of the primary disease determines the outcome, and the prognosis is unfortunately often poor.

7. PREGNANCY AFTER TTP-HUS

a. In the inhibitor form of ***TTP***, the condition often returns after pregnancy, which requires plasma exchange (supplemented with steroid therapy if needed) (rituximab cannot be given during pregnancy). Pregnancy generally further activates the process. Therefore, pregnancy later must be considered very carefully. An effective method of birth control is necessary and oestrogen-based contraceptives should be avoided. If the patient nevertheless chooses pregnancy, it should only be permitted with regular (weekly) control in a tertiary care centre with joint obstetric and haematological care. A positive, complication-free outcome can nevertheless not be guaranteed.
In the hereditary form of TTP, regular plasma transfusion during pregnancy decreases the risk of complications for the foetus and the mother, but does not rule them out completely.
In both forms, ADAMTS13 activity and platelet count must be regularly checked during and after pregnancy.

b. In ***atypical HUS***, the administration of complement-inhibiting treatment during pregnancy is currently not recommended by the manufacturer in the absence of sufficient clinical data. For this reason, treatment can only be performed subject to off-label funding approval from OGYI and NEAK.

c. ***Typical HUS*** in the patient's clinical history does not pose a risk to pregnancy if the condition resolves without residual symptoms.

1.2. Data sheets used when completing series of activities

None.

1.3. Tables

Table 1: TTP and HUS: age-related onset of clinical conditions with a known pathomechanism [19].

Typical age-related onset	Probable diagnosis	Clinical presentation	Tests confirming the diagnosis
From neonate to adult age	Congenital TTP (Upshaw-Schulman sy)	severe jaundice, 'burgundy' urine without any significant haematuria, similar symptoms in blood relatives or siblings, neonatal death	ADAMTS13 activity <10% absence of ADAMTS13 inhibitor ADAMTS13 genetic mutation
Pregnancy	'Late-onset' USS	absence of foetal development or foetal death (42%), or clinical TTP in the third trimester	
Neonates – <6 months of age	Methylmalonic aciduria-HUS (Cobalamin-C defect)	feeding difficulties, stunted growth and development, hypotension	hyperhomocysteinaemia, hypomethionaemia, methylmalonic aciduria, MMACHC mutation
Neonate <1–2 years of age	Diacylglycerol kinase epsilon (DGKE) mutation	hypertension, haematuria, proteinuria, renal failure	DGKE genetic mutation
< 2 years	Pneumococcal-associated HUS (neuraminidase-associated HUS)	fever, invasive S. pneumoniae infection: pneumonia, meningitis, septicaemia (empyema, subdural abscess)	positive direct Coombs, T antigen activation, positive culture (blood, cerebrospinal fluid), PCR
>6 months – <5 years	STEC-HUS (formerly D+HUS)	Acute gastroenteritis, (bloody) diarrhoea in the past two weeks in a STEC or Shigelladysenteriae endemic region	stool culture: MacConkey agar: 0157:H7, PCR: Shiga toxin serum: anti-LPS antibodies
From adolescence to adult age	Autoimmune TTP	haematological symptoms neurological symptoms + renal involvement of varying degree fever	ADAMTS13 activity <10% ADAMTS13 inhibitor
From birth to adulthood	Complement-mediated aHUS	haematological symptoms symptoms of acute kidney injury symptoms suggestive of atypicality (Table 8)	complement C3, C4 alternative total complement FH, FB, FI, MCP expression anti-FH antibody complement genetic test

HUS: haemolytic uraemic syndrome; TTP: thrombotic thrombocytopaenic purpura; ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; MMACHC: methylmalonic aciduria and homocystinuria; PCR: polymerase chain reaction; STEC: Shiga toxin-producing Escherichia coli; LPS: lipopolysaccharide; FH: complement factor H; FI: complement factor I; FB: complement factor B; MCP: membrane cofactor protein (CD46)

Table 2: Tests necessary to determine and begin immediate treatment of thrombotic microangiopathies (TTP and HUS) to be performed urgently [1]. and see **Table 5** too.

The diagnosis requires	**Typical value**
direct Coombs test	negative
complete blood count	thrombocytopenia (TTP<30 G/l; HUS <150 G/l), anaemia, reticulocytosis
peripheral blood smear	schistocytosis+ nucleated red blood cells, spherocytes, polychromasia basophilic stippling
serum haptoglobin	low/unmeasurably low
serum indirect bilirubin	normal/slightly abnormal/rarely elevated
Lactate dehydrogenase (LDH)	high (most often 1000–5000 IU/L)
transaminases	normal/slightly abnormal
screening coagulogram (PT, APTI, fibrinogen)	normal/slightly abnormal
Increased creatinine	TTP: often moderate, creatinine remains below 200 micromol/L HUS: often significant, for an accurate assessment of the degree of acute kidney injury, see Table 7
troponin	normal/varying degrees of increase
C-reactive protein (CRP)	normal/slightly abnormal
procalcitonin	normal/slightly abnormal (renal failure: high)
complete urine	varying degrees of haemoglobinuria, proteinuria, (micro)haematuria

Table 3: Tests required for differential diagnosis and the selection of targeted therapy for thrombotic microangiopathies (TTP and HUS). [1, 12-14, 17, 28-30].

Tests required for differential diagnosis and the selection of therapy	**Comment**
pregnancy test	for women of childbearing age
eye exam, ocular fundus exam	If malignant hypertension is suspected
kidney biopsy if feasible, histological exam	To confirm the final diagnosis of TMA, to assess the reversibility of kidney damage
virology (HIV, hepatitis A/B/C/E, CMV, EBV, +/- other)	the blood sample must be drawn and sent to the laboratory prior to starting therapy
screening test for autoimmune disease (RF, ANA, dsDNA, ENA screening, C3, C4, lupus anticoagulant, antiphospholipid antibodies, In the event of acute kidney injury: ANCA, anti-GBM as well	the blood sample must be drawn and sent to the laboratory prior to starting therapy
ADAMTS13 activity, antigen, inhibitor, genetic test	prior to starting therapy, the blood sample must be drawn and stored according to the specialist laboratory's requirements or sent to the laboratory
complement screening test + complement genetic test + flow cytometry (CD46)	prior to starting therapy, the blood sample must be drawn and stored according to the specialist laboratory's requirements or sent to the laboratory
stool culture + verotoxin PCR	diarrhoea at the onset of the condition or in the 1–2 weeks directly preceding onset
Examination of cobalamin metabolism (plasma, homocysteine, plasma + urine methylmalonic acid, vitamin B12 level, genetic test)	it is recommended in all paediatric cases and in the event of hyperhomocysteinaemia in young adults

Table 4: Main clinical conditions to be excluded in the differential diagnosis of TTP and HUS [1, 12-14, 17, 28-30].

Immune thrombocytopenia
Autoimmune haemolytic anaemia
Evans syndrome (autoimmune haemolytic anaemia and thrombocytopaenia)
Disseminated intravascular coagulation
(Pre)eclampsia, HELLP syndrome
Cobalamin C deficiency (children, young adults), vitamin B_{12} deficiency (adults)
Secondary thrombotic microangiopathies (see **Table 11**)
Thrombocytopaenia and/or other causes of haemolysis

Table 5: PLASMIC score [38] and FRENCH score [27]

Lab test	PLASMIC score	FRENCH score
Platelet count	<30 G/L (+1)	<30 G/L (+1)
Serum creatinine level	<176.84 µmol/L (+1)	<199.83 µmol/L (+1)
Signs of haemolysis (presence of at least 1 of the following) indirect bilirubin >34.2 µmol/L reticulocyte count >2.5% undetectable haptoglobin	(+1)	*
No history of active tumour in recent years	(+1)	*
No history of solid organ or stem cell transplantation	(+1)	*
INR <1.5	(+1)	*
MCV <90 fL	(+1)	NA
Probability of ADAMTS13 activity below 10%:	Score 0-4: 0-4% Score 5: -24% Score 6-7: 62-82%	Score 0: 2% Score 1: 70% Score 2: 94%

Each item is worth 1 point (+1); INR, international normalised ratio; MCV, mean corpuscular volume; SCT, stem cell transplantation;
**The French score can be used in TMA if there is no history of tumour, transplantation and unconfirmed disseminated intravascular coagulation in addition to fragmentation haemolysis. These are basic criteria and no specific points are awarded for them in the French score. The French score originally included the antinuclear factor.*
NA: MCV is not included in the French score.

Table 6: The practice of plasma exchange in TTP [1].

- Volume: 1.5 plasma volumes/day (initially)
  1.0 plasma volumes/day (once the patient's condition has stabilised)
- Substitution fluid: FFP (>50%)
- Frequency: daily
- Endpoint: haematological remission*

* *Platelet count >150 g/L on at least two consecutive days, with no signs of haemolysis and rising or normal haemoglobin level.*

Table 7: The clinical triad of HUS [13, 14, 17, 19, 29, 30].
Thrombocytopaenia caused by platelet consumption
Microangiopathic haemolytic anaemia
— Confirmed acute kidney injury: proteinuria and/or glomerular haematuria and/or decreased renal function, with the following classification according to RIFLE criteria [98]: — Risk: 1.5x increase in serum creatinine or decrease in GFR >25%, or urine output per hour <0.5 mL/kg/hour for 6 hours, — Injury: 2x increase in serum creatinine or decrease in GFR >50%, or urine output per hour <0.5 mL/kg/hour for 12 hours, — Failure: 3x increase in serum creatinine or decrease in GFR >75% or an acute increase in serum creatinine of >353 micromol/L (>44 micromol/L), or urine output per hour <0.3 mL/kg/hour for 24 hours, or anuria for 12 hours — Loss: protracted acute renal failure = total loss of kidney function for >4 weeks, ESRD End stage kidney disease (>3 months)

Table 8: Signs suggestive of atypical HUS [29].
— Absence of diarrhoea prior to the onset of HUS
or
— Diarrhoea + presence of any of the following:
- Age <6 months or >5 years
- Insidious onset
- HUS relapse
- Presumed earlier HUS
- Prior unexplained anaemia or thrombocytopaenia
- HUS following any organ transplant
- Asynchronous HUS occurring in the family

Table 9: Plasma exchange in childhood atypical HUS (The recommendation of the European Paediatric Study Group for HUS) [29]
— Start plasma exchange within 24 hours, except:
- if an alternative diagnosis requiring different treatment is reasonably suspected
- in small children if placing the line in the vein causes technical difficulties
- if renal involvement is mild, if the risk/benefit balance is negative
— Substitution: FFP or pooled plasma, human, solvent-detergent treated
— Volume: 1.5 plasma volumes (60–75 mL/kg/session)
— Frequency:
- 1x daily for 5 days
- 5x weekly for 2 weeks
- 3x weekly for 2 weeks
- on day 33 of the evaluation of therapeutic effect
— Endpoint:
- Confirmation of alternative diagnosis not treatable by plasma exchange
- Severe complication requiring abandonment of plasma exchange
- Haematological remission*
* *Aetiology must be clarified in order to continue plasma exchange*

Table 10: Prophylaxis preceding kidney transplantation [12, 121]

Risk of recurrence	**Mode of prophylaxis**
High — FH and gain-of-function mutations: FB, C3 — Combined mutations, with the exception of MCP combinations — Due to the recurrence of earlier graft loss, irrespective of the genetic test results	Complement-inhibiting treatment
Moderate — Isolated FI mutation — Combine MCP mutation — Mutation of unknown functional effect	Complement-inhibiting treatment or plasma exchange
Low — DGKE mutation — Isolated MCP mutation — No detectable mutation — Low anti-FH antibody titre	prophylaxis is not necessary

Table 11: Underlying diseases, conditions and treatments in which the development of secondary thrombotic microangiopathies has been described [1, 11-14, 28-30, 191, 192]
— Pharmacological treatments:
- Quinine
- Thienopyridines: ticlopidine, clopidogrel
- Calcineurin inhibitors: cyclosporine, tacrolimus
- mTOR inhibitors: sirolimus, everolimus
- Chemotherapy agents: mitomycin B, cisplatin, bleomycin, gemcitabine, etc.
- Angiogenesis inhibitors: bevacizumab
- Tyrosine kinase inhibitors: sunitinib
- Other agents: oral contraceptives, interferon, etc.
— Malignant hypertension (often against a background of silent IgA nephropathy)
— Disseminated cancers, often mucin-producing adenocarcinomas
— Infections:
- viral infections (e.g. HIV, CMV, etc.)
- sepsis: bacteria, fungus
— Allogeneic stem cell transplantation: graft-versus-host disease; solid organ transplantation
— Autoimmune conditions:
- SLE
- antiphospholipid syndrome
- SSC renal crisis
— Surgeries (e.g. motor heart surgery); protein-losing conditions (e.g. diarrhoea); pancreatitis
— Extracorporeal membrane oxygenator treatment
— Adeno-associated virus 9 vector-based gene therapy (such as Onasemnogeneabeparvovec)

1.4. Algorithms

Figure 1. Annual trends in the number of patients diagnosed with aHUS and TTP at the FüstGyörgy Complement Diagnostic Laboratory of the Department of Internal Medicine and Haematology of Semmelweis University. The curve shows the cumulative number of cases, and the numbers above the curve show the number of cases diagnosed in a given year.

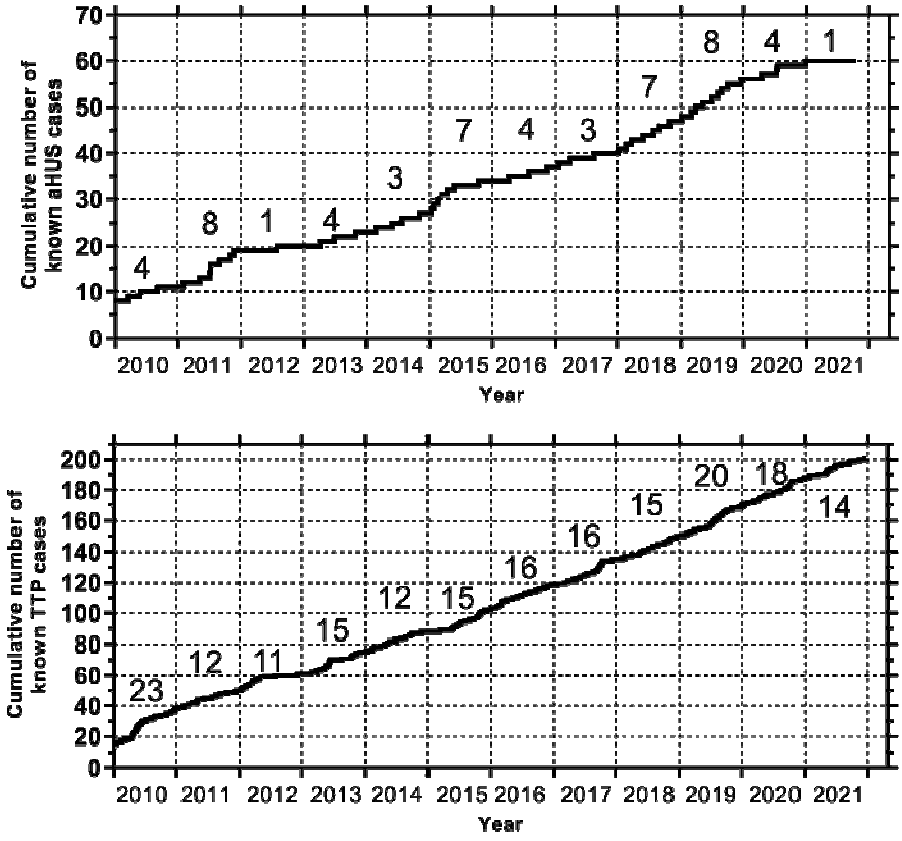


Figure 2: Classification of thrombotic microangiopathies [12]

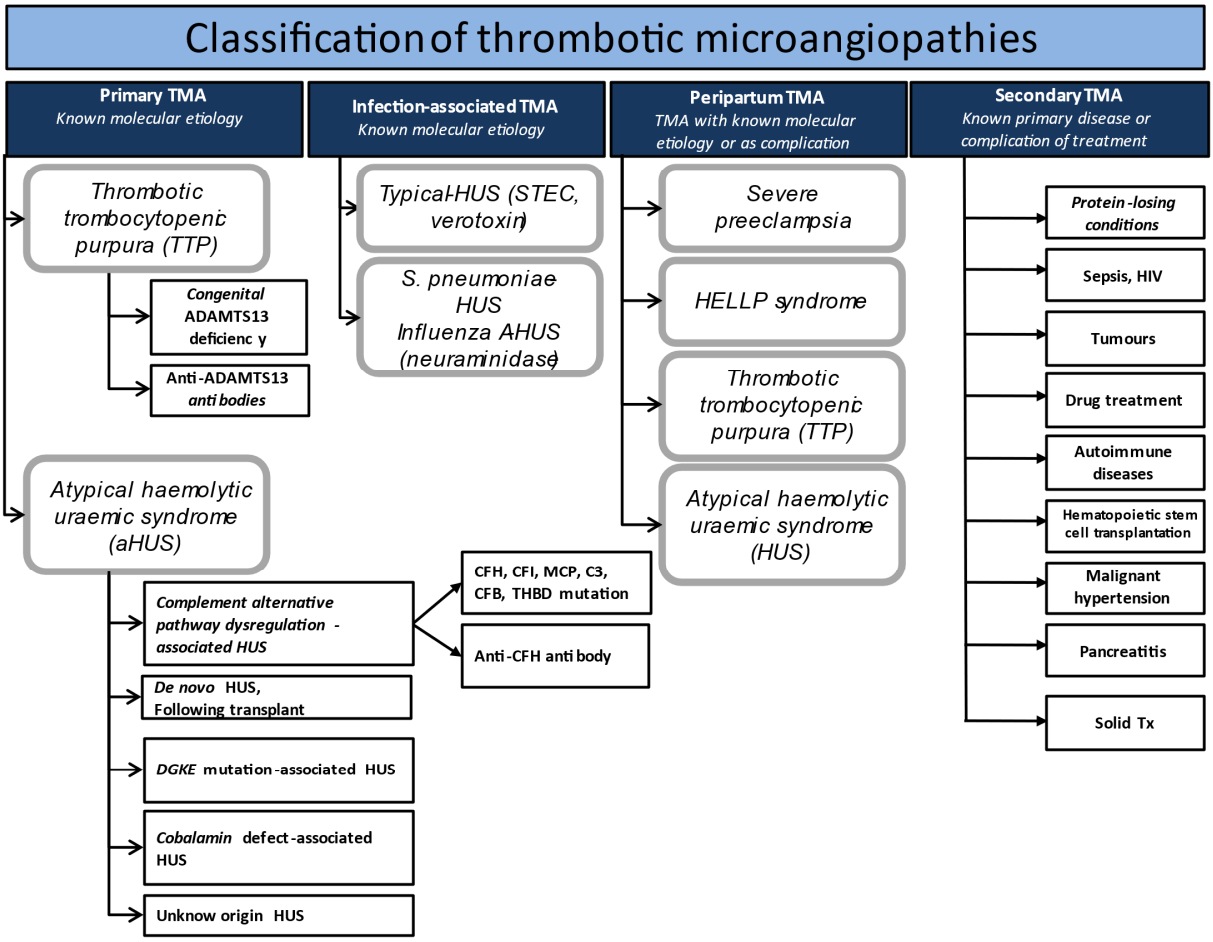


Figure 3: Summary of the diagnostic algorithm and possible modes of therapy for HUS [132]. See the text for detailed explanations. Based on reference no. [15], with modifications. Only the most common forms are indicated in the figure.

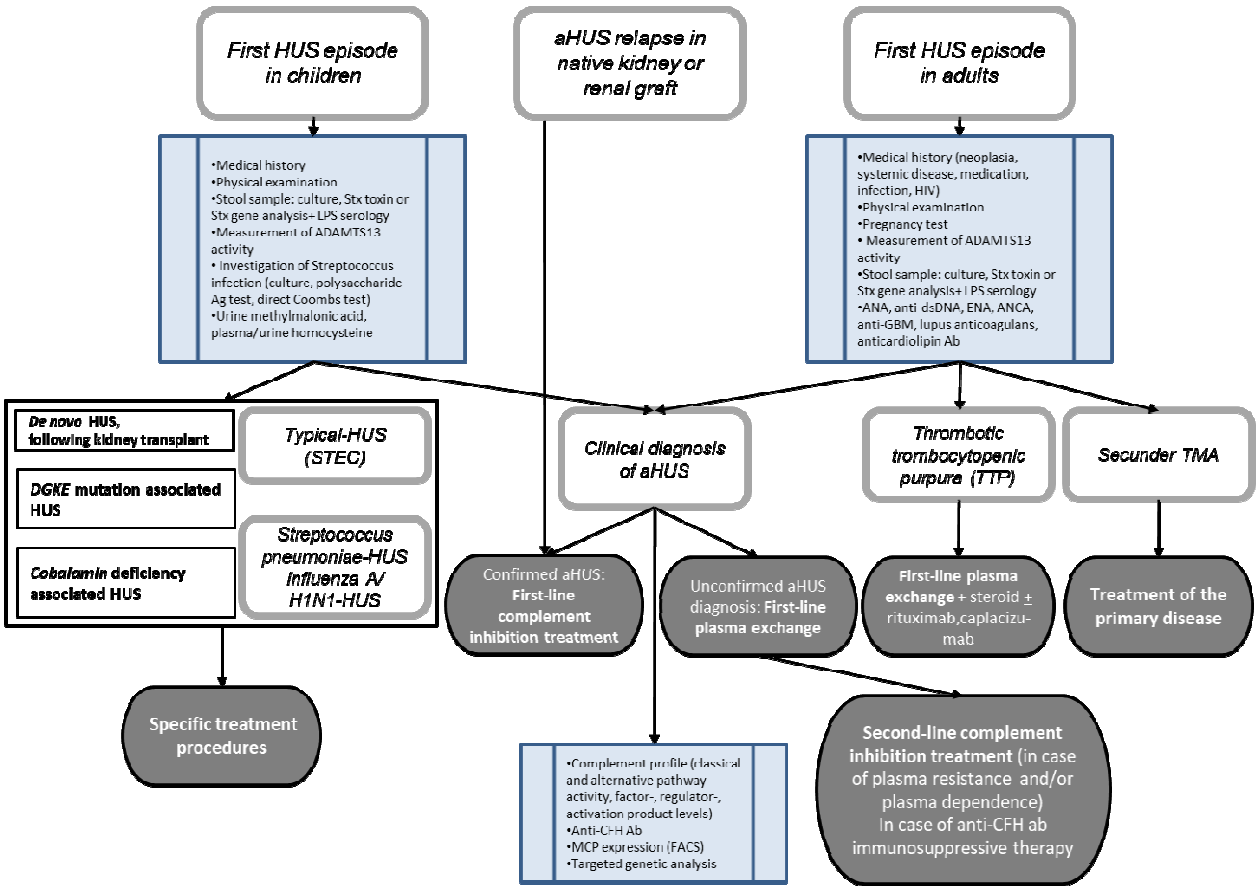


Figure 4: Recommended care algorithm for adult patients

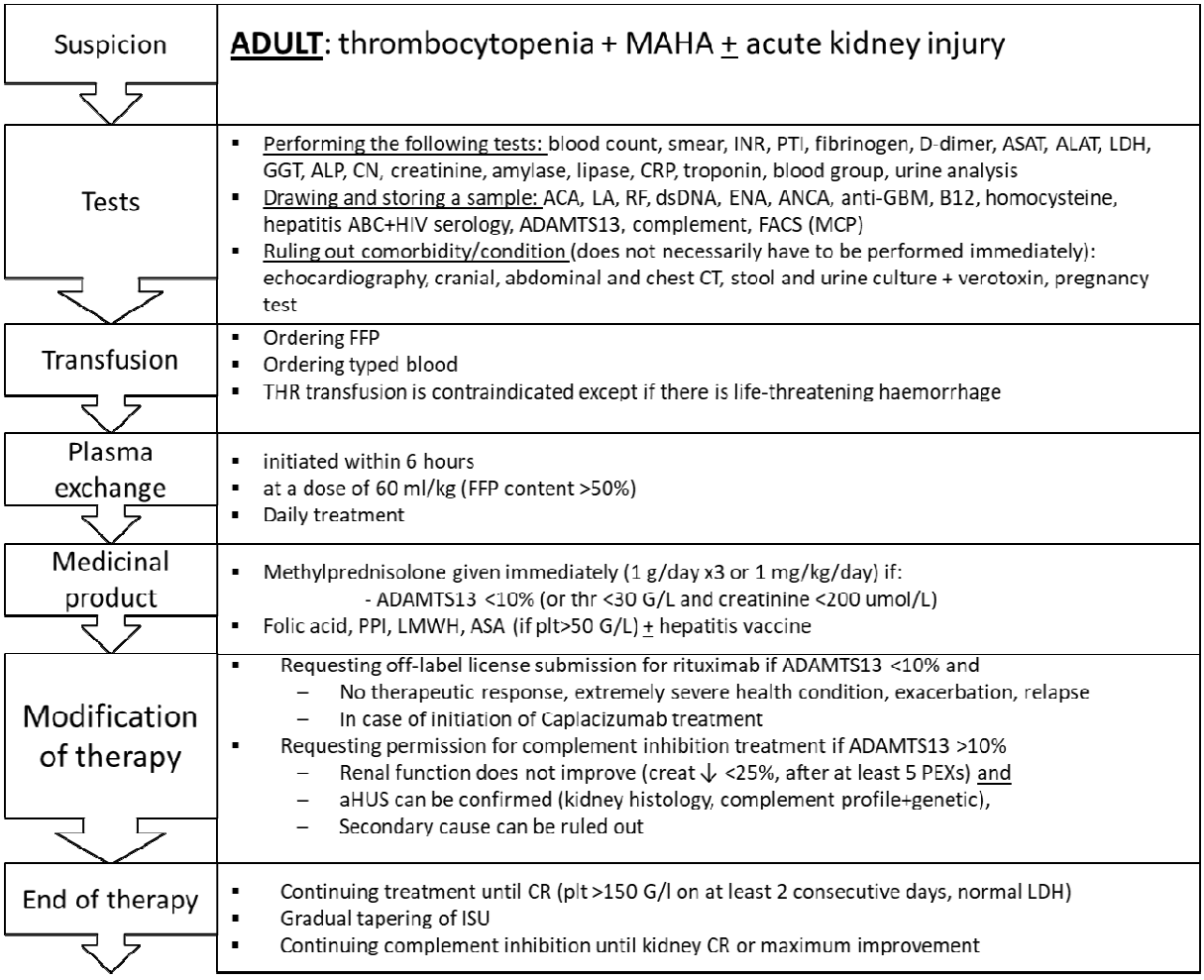
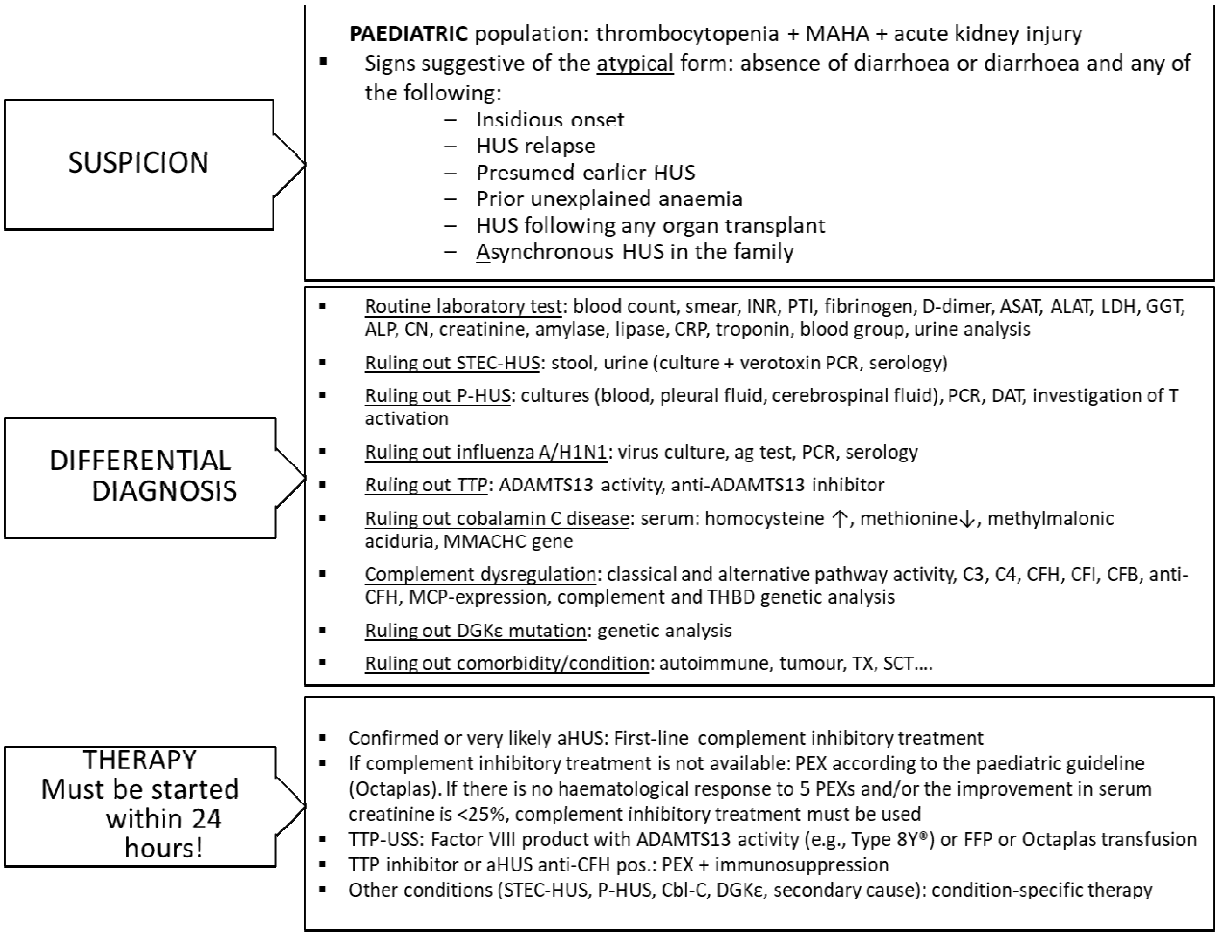


Figure 5: Recommended care algorithm for paediatric patients



1.5. Other documents

None.