Klinik für Hämatologie, Onkologie, Infektiologie und Palliativmedizin
Alb-Fils Kliniken Göppingen

Transplantations-assoziierte Thrombotische Mikroangiopathie (TA-TMA)

2025 Tübingen

Martin Bommer

Interessenskonflikte

1. Arbeitsverhältnis oder Führungsposition
Nein

2. Beratungs- oder Sachverständigentätigkeit
AWMF-Leitlinien Kommision TTP und HUS

3. Eigentum an Aktien, Aktien oder Fonds
Aktien von GSK, Pfizer, Sanofi

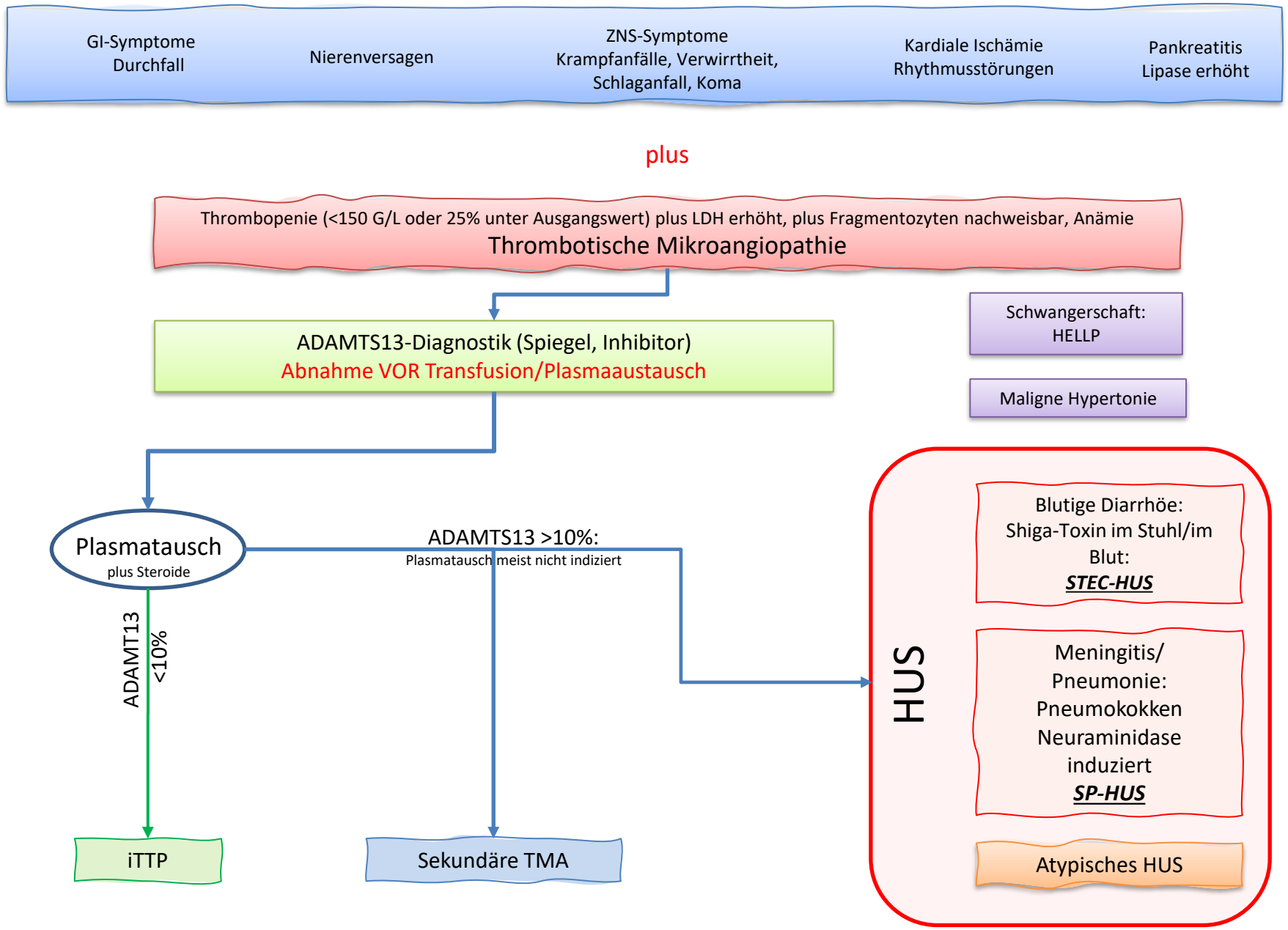
4. Patent, Urheberrecht, Verkaufslizenz
Nein

5. Honorare
Vortragshonorare von Alexion, Vifor, Jazz Pharma, Pfizer, Novartis, Ablynx

6. Finanzierung der wissenschaftlichen Forschung
Ablynx

7. Sonstige finanzielle Beziehungen
Nein

8. Immaterielle Interessenkonflikte
Nein



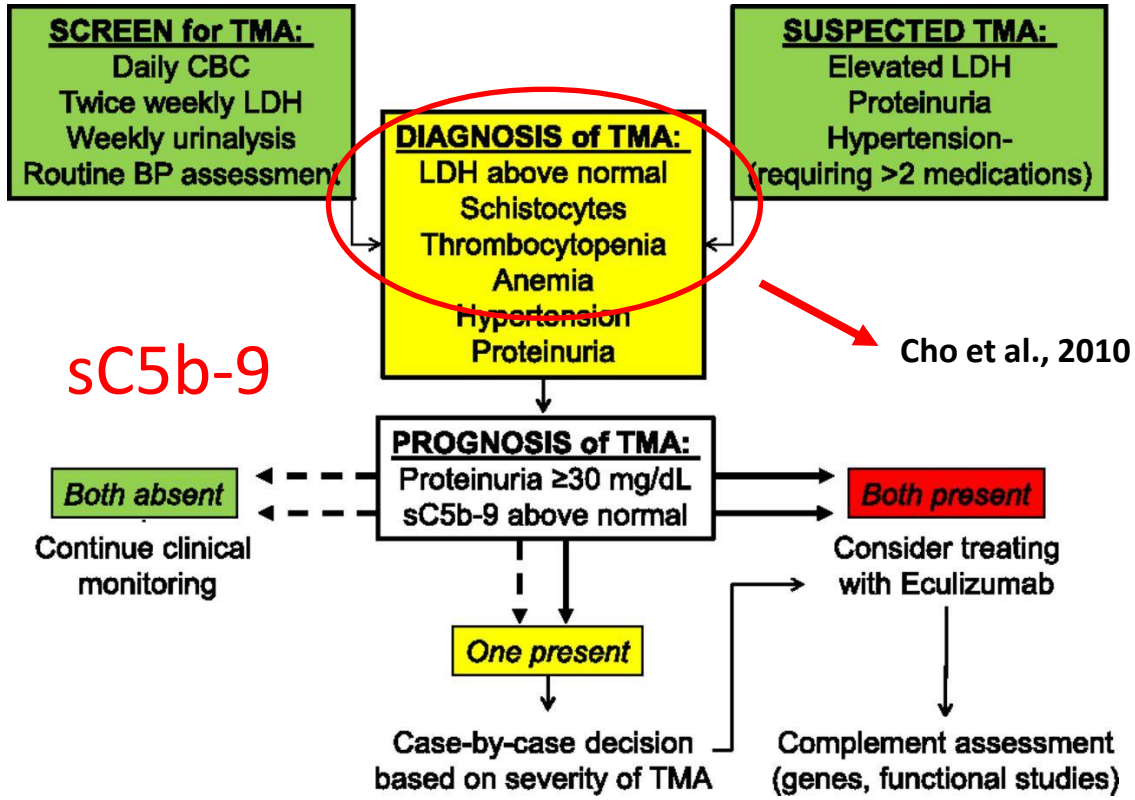
Fakkouri et al., Nature Reviews Nephrology, Volume 17 August 2021

Symptome einer TA-TMA

	Erwachsene	Kinder
Niere		
Akutes Nierenversagen	41%	**61%**
Hypertonie	32%	**Häufig**
Proteinurie >30 mg/dL	68%	**76%**
Neurologie		
Enzephalopathie, Verwirrtheit oder Krampfanfälle	25%	**23%**
Gastrointestinal		
Vorhergehende/gleichzeitige akute GVHDb	49%	**38%**
Gastrointestinale Blutungen	8%	**25%**
Kardiopulmonal		
Diffuse Alveolarblutung	9%	**17%**
Perikarderguss	n.b.	**18%**
Pulmonale Hypertonie	**n.b.**	**7%**

Ang Li and Sarah E. Sartain, Transplant-associated TMA: the conundrum of diagnosis and treatment, ASH Educational 2024

TA-TMA: Diagnose



Jodele et al., Blood rev, 2015

Dvorak, C.C. et al; Frontiers in Pediatrics, April 2019, Volume 7

Labordiagnostik bei V.a. TA-TMA

TEST	INDIKATION	RATIONALE
CBC/diff, Retikulozyten, BMP, LFT, gesamtes/direktes Bilirubin, LDH, Haptoglobin	Alle Patienten	**Bestätigung der Hämolyse, Ausschluss einer Aplasie der roten Blutkörperchen oder einer aplastischen Anämie**
Blutausstrich (Serie)		**Bestätigung des Vorhandenseins und der Persistenz der Schistozytose**
DAT; IAT (Agglutinationsstärke)		**Ausschluss einer autoimmunen oder alloimmunhämolytischen Anämie**
DIC (Quick/PTT/INR, D-Dimere, fibrinogen)		**DIC ausschließen**
Infektions Workup		**Infektion/Sepsis ausschließen**
Vitamin B12		**Ausschluss von Cobalamin-Mangel-bedingter Pseudo-TMA**
Urinanalyse		**Suche nach einer frühen Schädigung der Nierenorgane (Proteinurie)**
sC5b9 assay		**Prognostischer Biomarker für TA-TMA**
ADAMTS13; antinukleärer Antikörper; Lupus-Antikoagulans; Anticardiolipin; Beta-2-Glykoprotein		**Ausschluss von TTP und anderen autoimmunen Ursachen (selten tritt sie zum ersten Mal nach der Transplantation ohne Vorgeschichte auf)**
Stuhlkultur für Shiga-Toxin; Darmbiopsie	Neuer Durchfall	**ST-HUS ausschließen**
KM-Biopsie	Inadäquate Hämatopoese oder zirkulierende Blasten	**Ausschluss eines Rezidivs oder eines Transplantatversagens**
Nierenbiopsie	**Neue Nierenschädigung**	**Bestätigen Sie die Diagnose von TMA in der Biopsie**

Ang Li and Sarah E. Sartain, Transplant-associated TMA: the conundrum of diagnosis and treatment, ASH Educational 2024

TA-TMA Diagnosekriterien

A. TA-TMA harmonization panel consensus–recommended Diagnostic criteria, modified Jodele criteria		B. Supportive tests aiding biomarker Attribution to TA-TMA
(1) Biopsy-proven disease (kidney or GI)		Affected tissue histologic diagnosis (any affected organ)
(2) Clinical criteria: must meet ≥4/7 criteria within 14 days at two consecutive time points		ADAMTS13 activity to rule out TTP
Anemia*	Defined as one of the following: 1. Failure to achieve transfusion independence for pRBCs despite evidence of neutrophil engraftment 2. Hemoglobin decline from patient's baseline by 1 gm/dL 3. New onset of transfusion dependence 4. Rule out other causes as the sole cause of anemia such as AIHA and PRCA	• Haptoglobin. Haptoglobin degradation products • Reticulocytes • Free plasma hemoglobin to confirm hemolysis • Direct Coombs
Thrombocytopenia*	Defined as one of the following: 1. Failure to achieve platelet engraftment 2. Higher-than-expected platelet transfusion needs 3. Refractoriness to platelet transfusions 4. 50% reduction in baseline platelet count after full platelet engraftment	• Antiplatelet antibodies, when applicable • Disseminated intravascular coagulation panel
Increased LDH	Above the upper limit of normal for age	• Free plasma hemoglobin indicates intravascular hemolysis • Increased reticulocyte count can be observed in response to hemolysis • Increased indirect bilirubin supports the diagnosis of hemolysis when associated with LDH • Urinary hemoglobin indicates breakdown of RBCs in association with increased LDH
Schistocytes	Present	• Manual review of peripheral blood smear • Tissue evidence of extravasated schistocytes
Hypertension	>99th percentile for age (<18 years) or systolic BP ≥ 140 or diastolic BP ≥ 90 (≥18 years)	

Jodele S, Gavriilaki E. Translating biomarker insights into practice: a path forward in TA-TMA management. Front Med (Lausanne). 2025 May 8;12:1550365. doi: 10.3389/fmed.2025.1550365. PMID: 40406401; PMCID: PMC12095249.

TA-TMA Biomarker sC5b-9

Increased plasma sC5b-9	Higher than or equal to the upper limit of normal	• Differentiation between physiologic and pathologic sC5b-9 increase **Physiologic** • Mild and transient, most commonly as response infection • Return to baseline with trigger resolution • Lack of severe hemolysis or microangiopathy • Lack of organ dysfunction **Pathologic** • Significant and sustained increase, typically doubling from the baseline • Associated with microangiopathy leading to endothelial injury • Results in organ dysfunction • Prolonged and worsening symptoms • Response to complement blockade
	sC5b-9 doubled from pre-HSCT baseline and sustained increase in sC5b-9	• Persistently increased sC5b-9 levels on serial measurements, particularly when doubled from the baseline or sustained for over 2 weeks, are associated with severe TA-TMA and multiorgan dysfunction
	Response to C5 inhibitors	• Reduction in sC5b-9 levels using C5 inhibitors confirms the role of clinically meaningful complement activation in endothelial injury in TA-TMA

Jodele S, Gavriilaki E. Translating biomarker insights into practice: a path forward in TA-TMA management. Front Med (Lausanne). 2025 May 8;12:1550365. doi: 10.3389/fmed.2025.1550365. PMID: 40406401; PMCID: PMC12095249.

TA-TMA Biomarker rUPCR

rUPCR random urine protein/creatinine ratio

Proteinuria	≥1 mg/mg rUPCR	• Cystatin C GFR • Increased serum creatinine (normal serum creatinine does not rule out AKI in pediatric HSCT recipients) • Urine microalbumin • Urine albumin/creatinine ratio (>30 mg/g) • uPAR (urokinase plasminogen activator receptor)

Clinical criteria plus biomarker: must meet ≥4/7 criteria within 14 days at two consecutive time points

Jodele S, Gavriilaki E. Translating biomarker insights into practice: a path forward in TA-TMA management. Front Med (Lausanne). 2025 May 8;12:1550365. doi: 10.3389/fmed.2025.1550365. PMID: 40406401; PMCID: PMC12095249.

DIFFERENTIALDIAGNOSEN ZUR TMA

ERKRANKUNG	PATHOPHYSIOLOGIE	ABGRENZUNG ZUR TMA	THERAPIE
Vitamin B12-Mangel, Pseudo-TTP	B12-Mangel mit Auftreten von Fragmentozyten und neurologischen Symptomen, hohe Homocystein-Spiegel mit Endotheldefekt	Retikulozyten vermindert, LDH extrem hoch (> 5000 U/L), Methylmalonat erhöht	B12-Substitution
Akute schwangerschaftsinduzierte Fettleber	Hereditäre Defekte des Fettstoffwechsels mit Leberversagen	Übelkeit, Bauchschmerzen Hypoglykämie, Transaminasenerhöhung, Bilirubinerhöhung, ATIII vermindert, Gerinnungsfaktoren vermindert	Entbindung, Supportivtherapie
Hyperfibrinolyse mit DIC	Fibrinverbrauch z.B. bei APL, Prostata-Ca, Magen-Ca	Fibrinogen vermindert, Blasten mit Auerstäbchen im PB (APL), leuko-erythroblastisches Blutbild	Spezifische Therapie
Herzklappeninduzierte Hämolyse	Mechanische Fragmentation von Erythroyzten mit Verbrauch von Blutplättchen	Anamnese! Klappenprothese, Klappenvitium, TEE	Korrektur des Vitiums
Endokarditis	Bakteriämie mit Sepsis bei Klappenvegetationen	Blutkulturen, TEE	Zielgerichtete Antibiose
Evans-Syndrom	Immunthrombopenie mit Coombs-positiver Autoimmunhämolyse	Coombs-Test, keine Fragmentozyten	Immunsuppression
Sepsis mit DIC	Verbrauchskoagulopathie	Blutkulturen, Procalcitonin	Sepsistherapie, Antibiose
Katastrophales Antiphospholipid-Syndrom	Arterielle und venösen Thromben, sekundäre Endothelschädigung	aPTT verlängert, Cardiolipin-AK, aβ2GPI-AK	Heparin, evtl. Plasmapherese, (Eculizumab)
Malaria, Babesiose	Intrazelluläre Parasiten mit Hämolyse und Thrombopenie	Morphologie des peripheren Blutes	Antiparasitäre Therapie
Hämorrhagisches Fieber, Virale Infektionen	Dengue-Virus, Filoviridae, Puumula-Virus (Hanta-Virus)	Keine Hämolyse, Expositionsanamnese	Supportivtherapie
Hämophagozytische Lymphohistiozytose (HLH)	Unkontrollierte Inflammation, hereditär: z.B. Perforin-Defekt	Ferritin↑↑, Triglyceride↑↑	Steroide, Etoposid
HIT Typ 2	PF4 AK nach Heparin Exposition	Keine Hämolyse	

Bommer, M. et al.; Dtsch Arztebl. 2018 Mai 11;115(19):327-334

Medikamenten induzierte TMA

Medikament		Mechanismus	Klinik	Therapie
Mycophenolat		• Direkte Endothelschädigung • Antikörper-vermittelt • Prostacyclin Hemmung	• Dosisabhängig, bis zu 15 Monate nach Beendigung möglich • Komplement-Aktivierung	Rituximab Eculizumab
Ciclosporin A		• Direkte Endothelschädigung	• Dosisabhängig, bis zu 15 Monate nach Beendigung möglich	
Gemcitabine		• Direkte Endothelschädigung • Antikörper-vermittelt	• Dosisabhängig • Verspätetes Auftreten • TMA Niere	Rituximab Eculizumab?
Platinderivate	• Cisplatin • Oxaliplatin	• Direkte Endothelschädigung • Antikörper-vermittelt (ADAMTS13-AK?)	• Systemische TMA • „TTP-like“	Eculizumab? Analog TTP (falls ADAMTS13<10%)
Liposomales Doxorubicin		• Unbekannt		?
Bleomycin		• Direkte Endothelschädigung	• Systemische TMA	Eculizumab?
Taxane		• Unbekannt	• Systemische TMA	?
Pentostatin		• Unbekannt	• Systemische TMA	?
VEGF Inhibitoren		• Indirekter Enothelschaden • VEGF-Inhibition	• TMA Niere • „Prä-Eklampsie-like“	Eculizumab?
TKI		• VEGF-Inhibition	• „Prä-Eklampsie-like“	
Proteasomeninhibitoren	• Bortezomib • Carfilzomib • Ixazomib	• Direkte Endothelzell-Schädigung • ADAMTS13-Autoantikörper	• Dosisabhängig • Systemische TMA	Eculizumab? Analog TTP (falls ADAMTS13<10%)
Check-point Inhibitoren	• Ipilumumab • Nivolumab	• unbekannt	• Hypertonie • TMA Niere	
Antikörper	• Cetuximab	• VEGFR-Inhibition	• „Prä-Eklampsie-like“	

P. Valério, J.P. Barreto, H. Ferreira et al. Translational Oncology 14 (2021)

Stratifikationsmerkmale

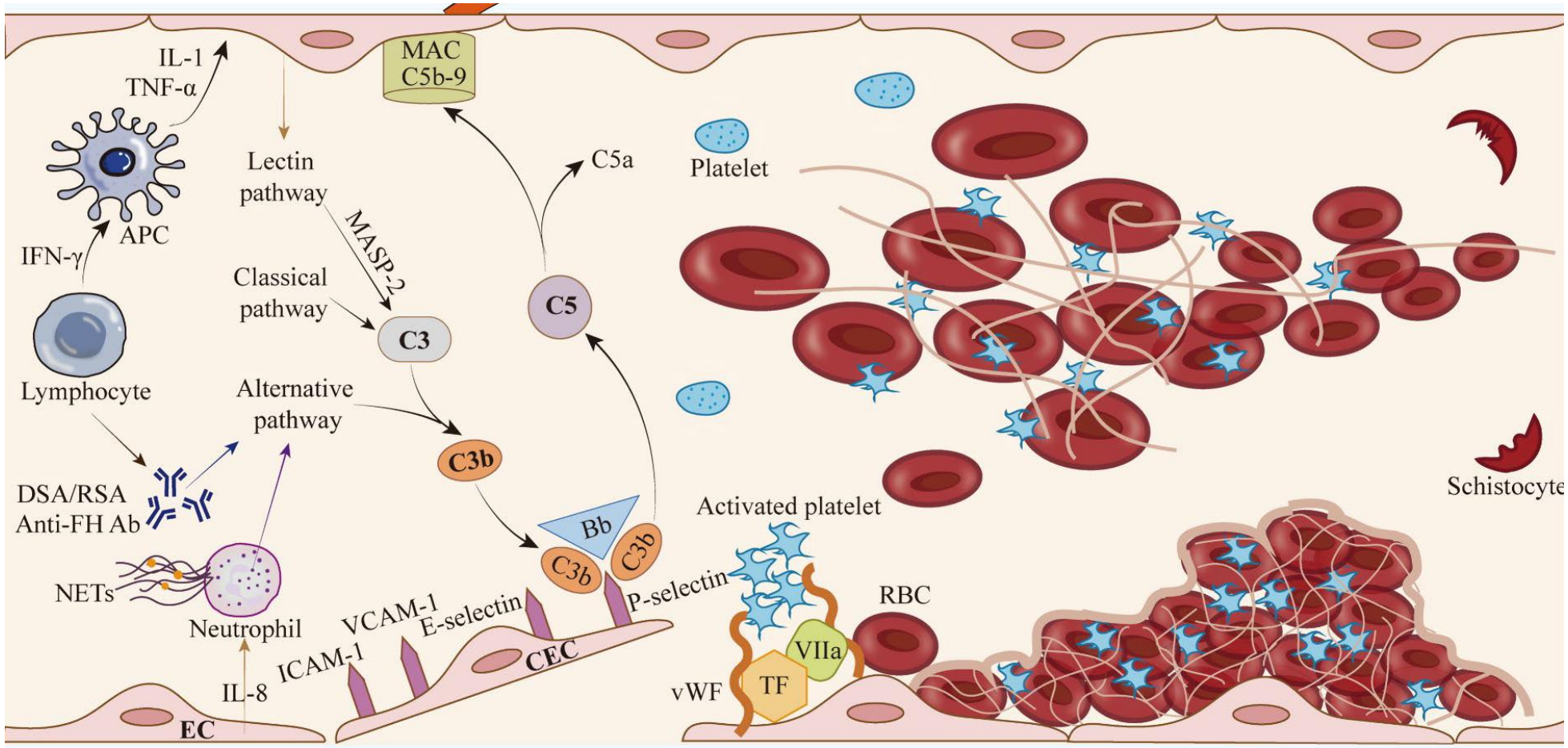
Inherent/ non-modifiable	Transplant-associated	Post-transplant events
Female sex	HLA-mismatched donor	CNI ± Sirolimus
Gene variants	Minor ABO mismatch	Infection (Bacteremia or IFI)
African-American race	Use of PBSC	Infection (DS-DNA Virus, e.g., CMV, HHV-6, BK)
Severe aplastic anemia	Lack of ATG in conditioning regimen	Acute GVHD
CMV seropositive recipient	Myeloablative conditioning	Autoantibody formation (Factor H, others)
Prior HCT	Slow metabolism of conditioning agents?	

HLA, human leukocyte antigen; CNI, calcineurin inhibitor; ABO, blood type antigens; IFI, invasive fungal infection; PBSC, peripheral blood stem cells; GVHD, graft-vs. -host disease; CMV, cytomegalovirus; HHV-6, human herpes virus-6; ATG, anti-thymocyte globulin; HCT, hematopoietic cell transplant.

Dvorak, C.C. et al; Frontiers in Pediatrics, April 2019, Volume 7

TA-TMA Pathophysiologie

1 - Komplement-Aktivierung 2 - Endothelschädigung 3 - Mikrothrombosen



Liu W, Zhu X, Xiao Y. Neurological involvement in hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Ann Hematol. 2024 Sep;103(9):3303-3313. doi: 10.1007/s00277-024-05798-6. Epub 2024 May 20.

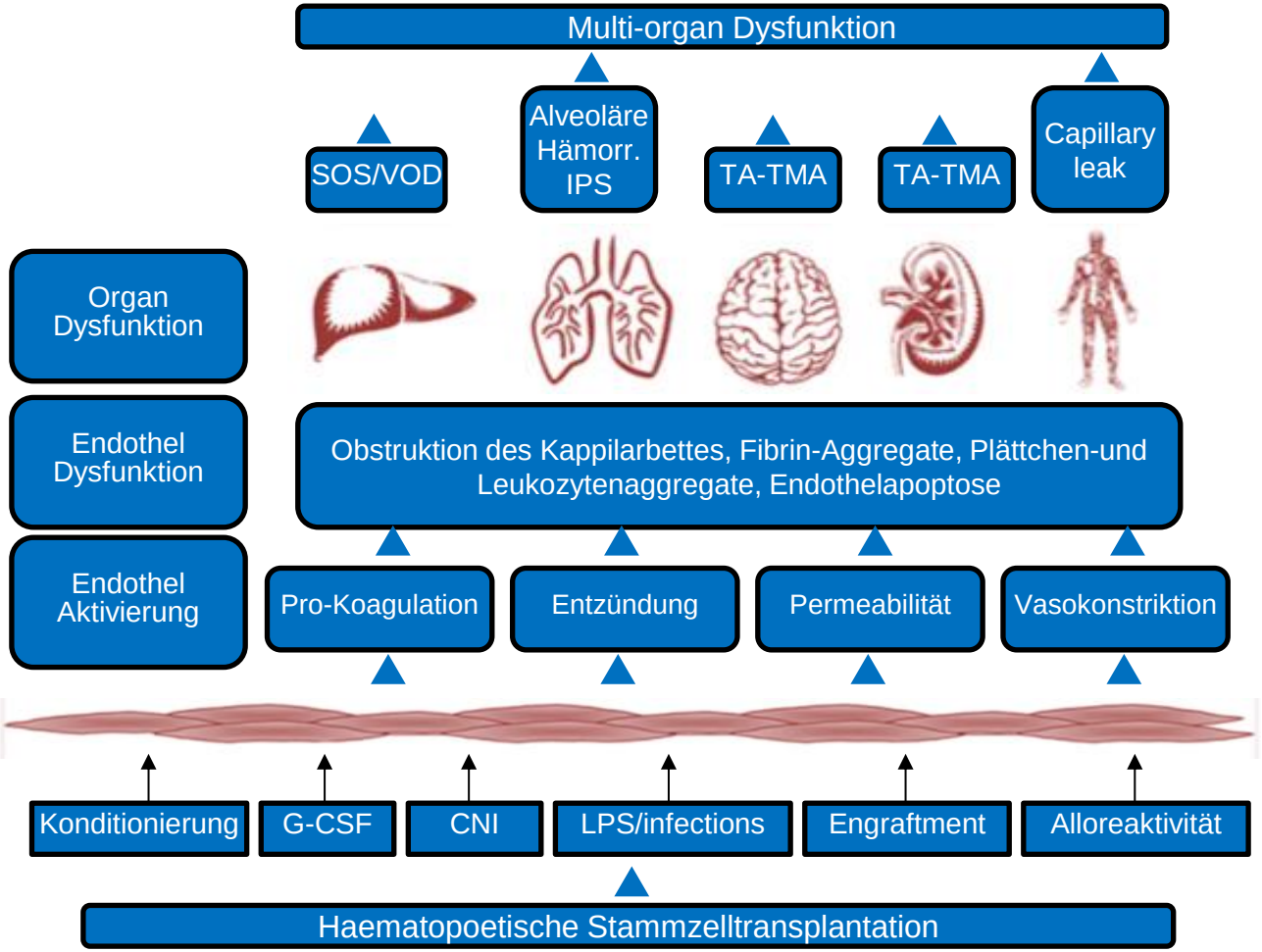
Pathophysiologie der TA-TMA

- **Konditionierung:**
  - MAC > RIC
    - Busulfan, Fludarabin and TBI → Hohe Inzidenz eines Endothelschadens **(Willems E at al 2010; Nakamae et al 2006, Takatsuka et al 2002)**

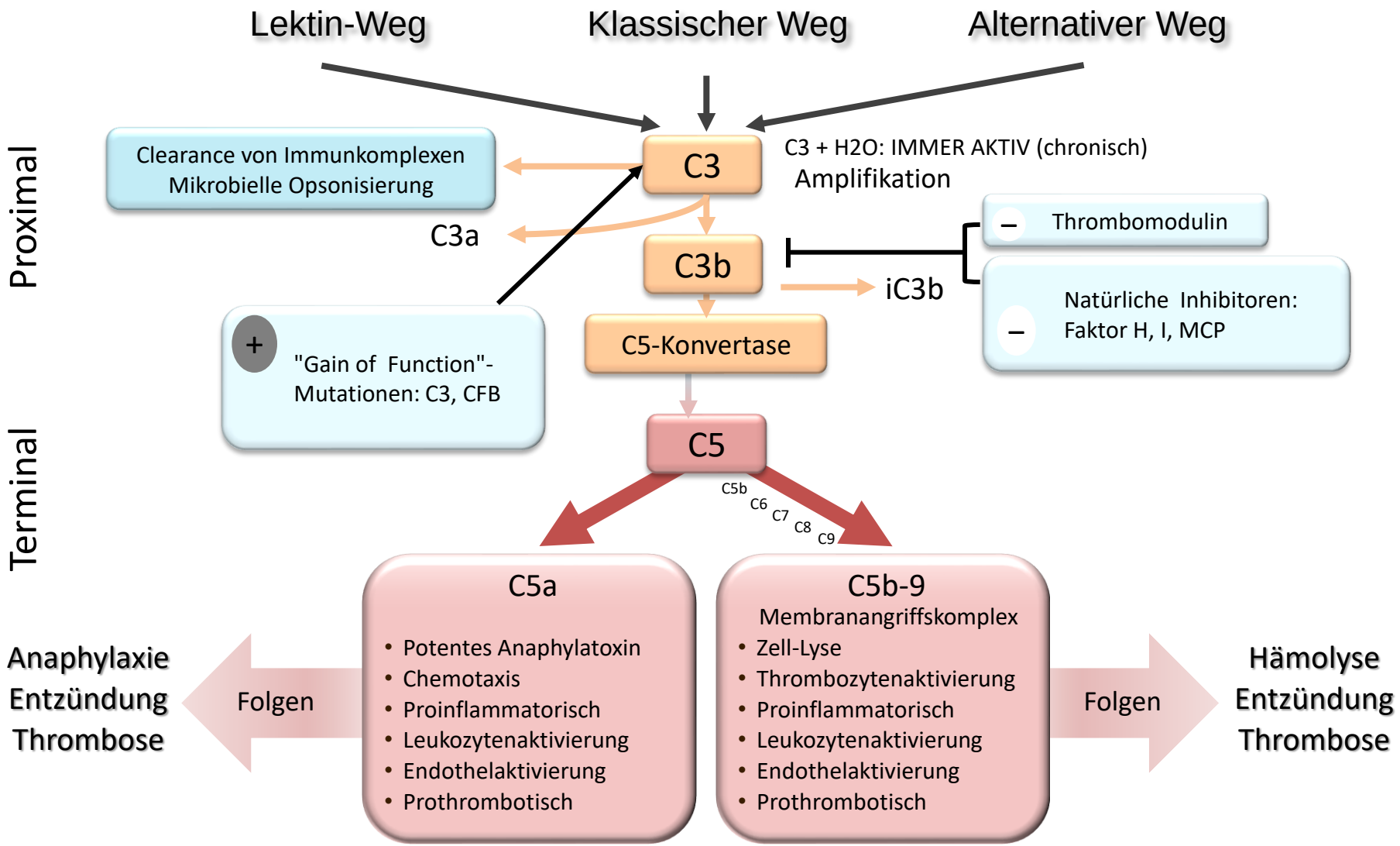
- **CNI (Tacrolimus und Cyclosporin) / mTor inhibitoren (Everolimus)**
  - Endothelschaden durch Reduktion von Prostaglandinen und Stickoxid, Anstieg von Thromboan A2, verminderte Protein C Aktivierung, Reduktion der Faktor H Aktivität ***(Garcia-Maldonado et al 1991; Brown et al 1987; Renner 2013)***

- **GvHD**
  - TMA 4fache Inzidenz bei Pat.mit aGvHD,(Grad III-IV)
  - Endothelschaden durch zytotox. T-Zellen, inflammatorische Zytokine und reduziertes VEGF ***(Changsirikulchai et al 2009; Willems E et al 2010)***
  - GvHD und Komplement-Aktivierung?
- **Infektionen**
  - Aspergillus, CMV, Adenovirus
  - Thrombomodulinfreisetzung, Plasminogen Aktivator Inhibitor und inflammatorische Zytokine **(Obut et al 2015)**

Endothel-assoziierte Komplikationen nach HSCT



Carreras E & Diaz-Ricart M. *Bone Marrow Transplant* 2011;46:1495–1502



- **Erhöhtes sC5b-C9 assoziiert mit schlechtem Outcome (Jodele et al 2014)**

1. Loirat C, Fremeaux-Bacchi V. Orphan J Rare Dis. 2011;6:60. 2. Noris M, Remuzzi G. N Engl J Med. 2009; 361:1676-1687. 3.; Holers MV. Immunol Reviews. 2008; 223:300-316. 4. Hirt-Minkowski P, Dickenmann M, Schifferli JA. Nephron Clin Pract. 2010; 114:c219-c235. 5. Noris M et al. CJASN 2010;10:1844–1859.

Therapie der TA-TMA

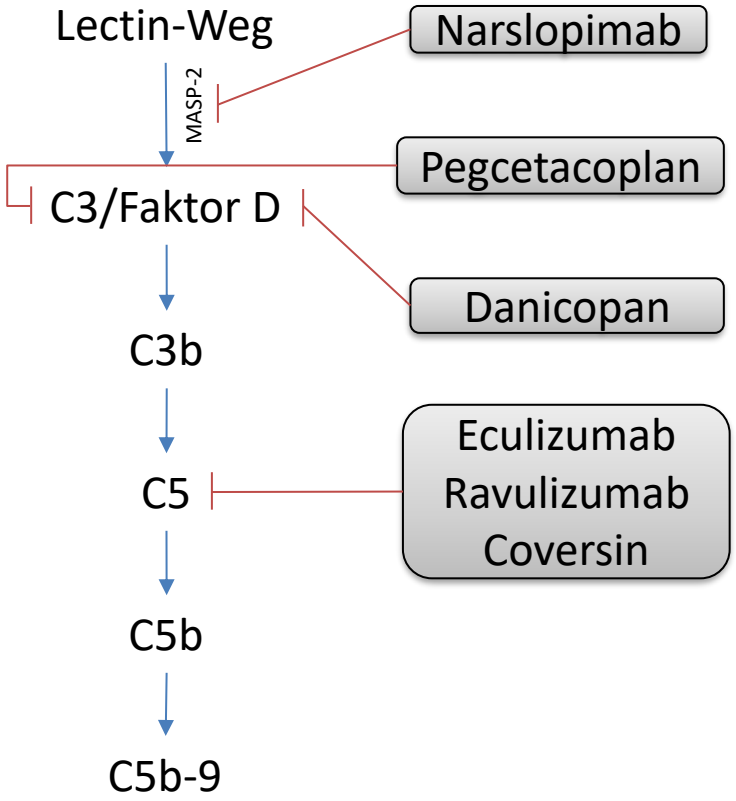
Supportive Maßnahmen

- Absetzen von CNI
- Nierenersatztherapie
- Antiinfektive Therapie
- Antihypertensive Therapie

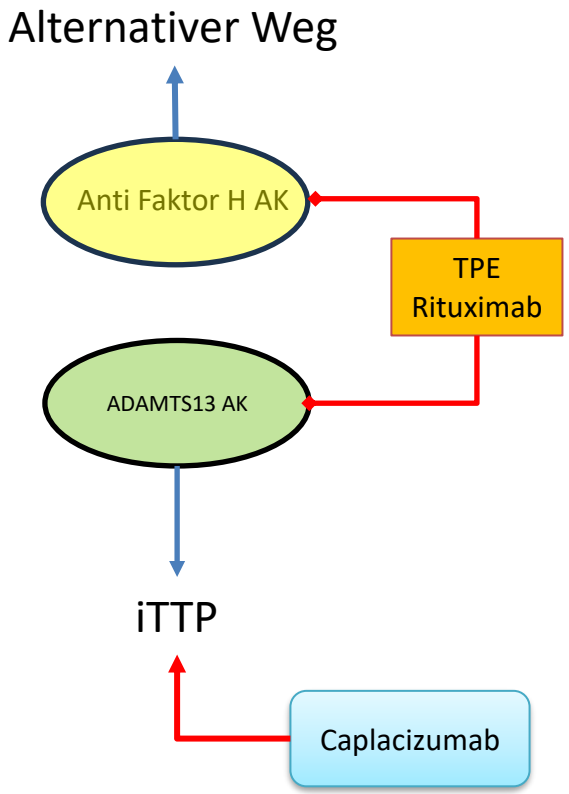
Endothelprotektion

- Defibrotide
- N-Acetyl-Cystein
- Statine

Komplement gerichtete Therapie



Antikörper Elimination



Liu W, Zhu X, Xiao Y. Neurological involvement in hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Ann Hematol. 2024 Sep;103(9):3303-3313. doi: 10.1007/s00277-024-05798-6. Epub 2024 May 20.

Educational: Transplant-associated TMA: the conundrum of diagnosis and treatment

Ang Li1 and Sarah E. Sartain2
1Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX; and 2Section of Hematology, Department of Pediatrics,
Texas Children's Hospital, Baylor College of Medicine, Houston, TX

Therapie

Published studies

Drug	Author	Study type	Number of patients	Inclusion criteria	Response	Survival
Eculizumab	Jodele 2020	Retrospective, single institution	64	Children and young adults with hrTMA (concurrent proteinuria and elevated C5b9) and treated with eculizumab	64% response 56% CR	OS 77% at 6 months
	Zhang 2021	Systemic review with retrospective studies	116 (including 64 from above)	Studies that included patients diagnosed with TA-TMA and eculizumab used first- or second-line	71% response 32% CR	OS 52% at last follow-up of each study
	Svec 2023	Retrospective, multi-institution	82	Allogeneic transplant patients <18 years with TA-TMA diagnosed by the treatment center and treated with eculizumab	48% response	OS 47% at 6 months
	Jodele 2024	Prospective, single-arm, multi-institution (NCT03518203)	21	Children and young adults, at least 5 kg, meeting criteria for hrTMA (concurrent proteinuria and elevated C5b9)	67% response 48% CR	OS 71% at 6 months
Narsoplimab	Khaled 2022	Prospective, single-arm, multi-institution (NCT02222545)	28	Adults 18 or older with persistent TA-TMA	61% response	OS 68% at 100 days
Defibrotide	Yeates 2017	Retrospective, multi-institution	39	Pediatric and adult patients who received defibrotide to treat TA-TMA	77% response	OS 59%-64% at unspecified follow-up
	Marinez-Munoz 2019	Retrospective, single institution	16	Adult patients who underwent allogeneic HCT with a diagnosis of TA-TMA	65% response	OS 59% at unspecified follow-up

Ongoing clinical trials

Drug	Sponsor	Study type	Number of patients	Inclusion criteria	End points to collect	
Ravulizumab	Alexion	Randomized, double-blind, placebo-controlled, multi-institution (NCT04543591)	106 estimated	12 years of age or older, HCT in the last 12 months, TMA diagnosis for at least 72 hours, weighing 30 kg or greater	- TMA response at 26 weeks	- OS at 26 and 52 weeks - nonrelapse mortality at 26 and 52 weeks
Nomacopan	AKARI Therapeutics	Prospective, single-arm, multi-institution (NCT04784455)	50 estimated	6 months to 18 years of age, undergone HCT with a diagnosis of TA-TMA	- Transfusion independence by week 24	- rUPCR 2 mg/mg or less at 24 weeks
Narsoplimab	Omeros	Prospective, single-arm, multi-institution (NCT05855083)	18 estimated	Pediatric patients 28 days to <18 years of age with high-risk TMA	- % clinical response	- OS at 100 days after high-risk TMA diagnosis
Pegcetacoplan	Sobi	Prospective, single-arm, multi-institution (NCT05148299)	12 estimated	Adults 18 years or older, with a diagnosis of TA-TMA, and with rUPCR 1 mg/mg or greater	- % clinical & TMA responses at 12 and 24 weeks	- OS at 100 days - OS 24 days from treatment start

CR, complete response; HCT, hematopoietic cell transplantation; hrTMA, high-risk TMA; OS, overall survival; rUPCR, random urine protein to creatinine ratio.

Hematology 2024 Educational

4778 Genetic Susceptibility in Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease

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[1]Hematology Department-BMT Unit, George Papanikolaou General Hospital, Thessaloniki,

Studientyp	Multinational, multizentrisch, translational, prospektiv
Studienpopulation	30 SOS/VOD-Patienten vs. 30 TA-TMA-Kontrollen
Diagnosekriterien	SOS/VOD: revidierte EBMT-Kriterien; TA-TMA: IWG-Kriterien
Probenahmezeitpunkt	Vor allogener HCT
Analyseverfahren	Next-Generation Sequencing (NGS) mit MiniSeq (Illumina)
Gen-Panel	CFH, CFI, CFB, CFD, C3, CD55, C5, CD46, THBD, ADAMTS13
Erkannte Varianten (SOS/VOD)	20 pathogene Varianten: u.a. ADAMTS13 (z. B. rs28647808), CFH, C3, CFB
Erkannte Varianten (TA-TMA)	Pathogene Varianten in CFH, CFI, C3, ohne Überschneidungen zu SOS/VOD
Häufige Varianten bei SOS/VOD	ADAMTS13: rs28647808 (5 Pat.), CFB: rs12614 (10 Pat.)
Fazit	Genetische Unterschiede zwischen SOS/VOD und TA-TMA weisen auf unterschiedliche Pathogenese hin

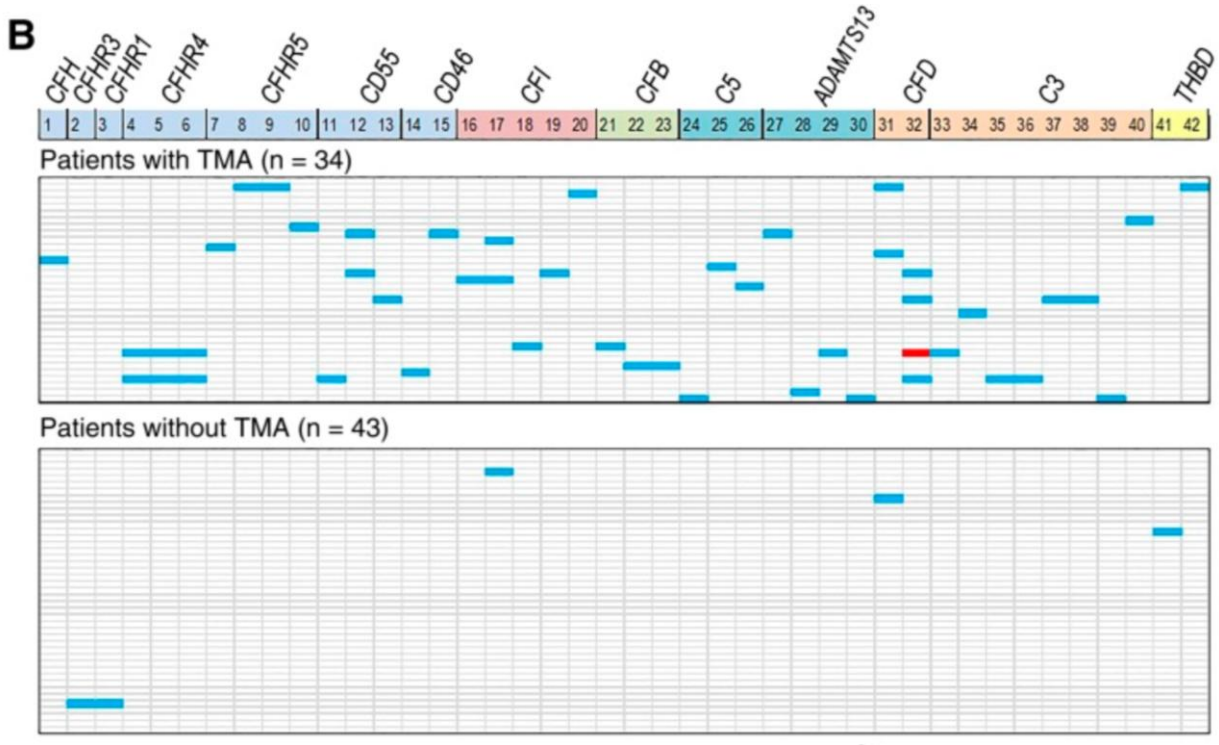
ASH 2024, *Blood* (2024) 144 (Supplement 1): 4778

Genetik und Autoantikörper bei (a)HUS and TTP

ABNORMALITY	GENE (LOCUS)	CASES (%)
aHUS		
Factor H CFH	(RCA: 1q32)	11–29
Membrane cofactor protein (MCP/CD46)	MCP (RCA)	3–17
Factor I CFI	(4q25)	2–17
C3 C3	(19p13)	2–17
Factor B	CFB (6p21)	0–5
Thrombomodulin	THBD (20p11)	0–5
Hybrid gene	CFH-CFHR (RCA)	0-2
Combined mutations		3–17
Factor H autoantibodies		4–13
TTP		
ADAMTS13 mutation	9q34 (90 mutations)	10
ADAMTS13 antibodies		40-50

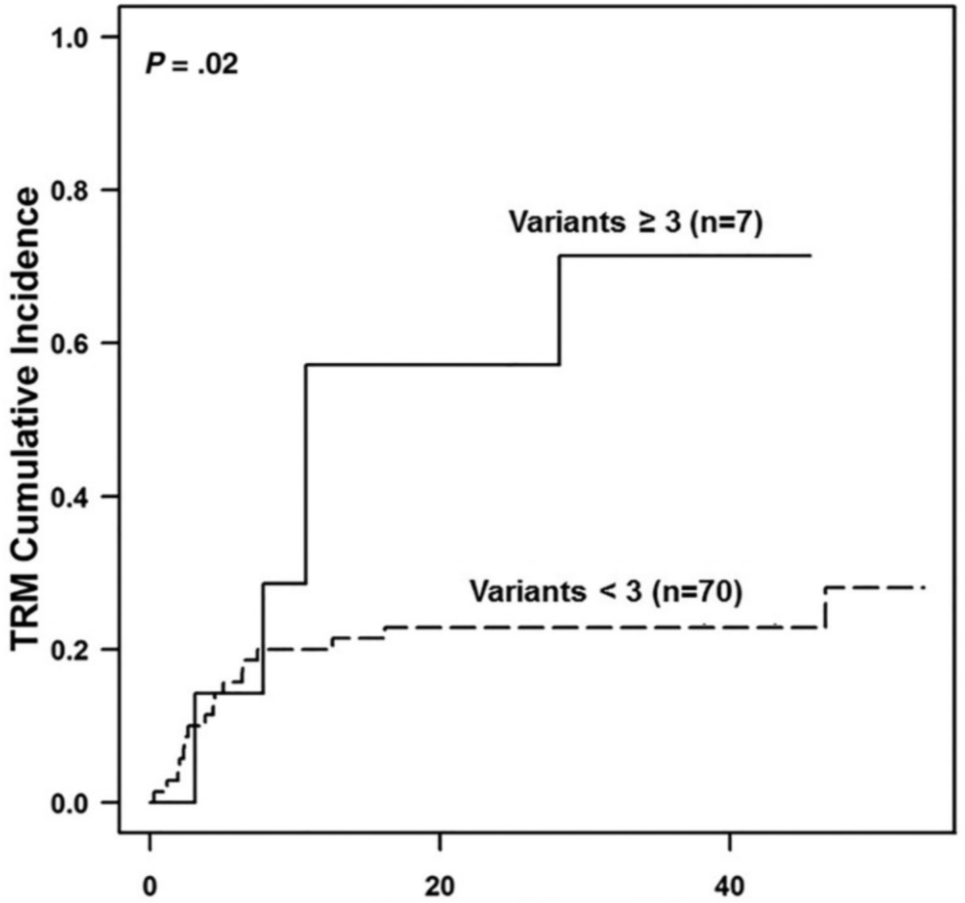
Nephrol Dial Transplant (2012) 27: 2673–2685
Int J Hematol 2010; 91: 1–19.

TA-TMA: Genetik



Jodele S, Zhang K, Zou F, et al. The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy. *Blood*. 2016;127(8):989–996.

TA-TMA: Prognose und Genetik



Jodele S, Zhang K, Zou F, et al. The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy. *Blood*. 2016;127(8):989–996.

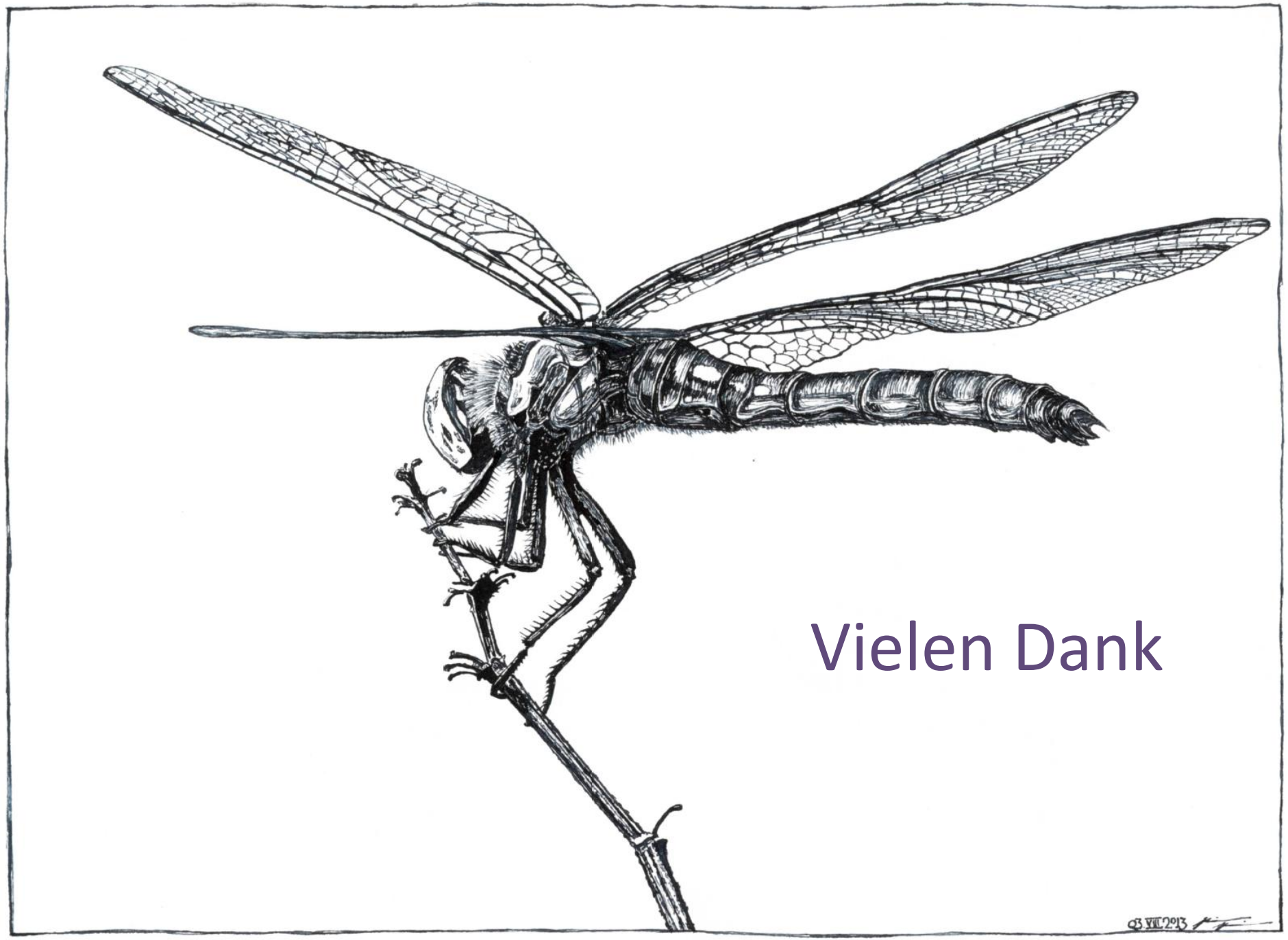
Klinische Studien

Study Title	NCT Number	Status	Conditions	Interventions	Sponsor
Evaluate the PK Efficacy Safety and Tolerability of Pegcetacoplan in Patients With Thrombotic Microangiopathy Added to My Studies	NCT05148299	Completed	• Transplant-Associated Thrombotic Microangiopathy	• Drug: Pegcetacoplan	Swedish Orphan Biovitrum
A Safety and Efficacy Study of NAC in Patients With **TA-TMA** Added to My Studies	NCT03252925	Completed WITH RESULTS	• Thrombotic Microangiopathies • Hematologic Diseases	• Drug: N-Acetylcysteine • Drug: Placebo Oral Tablet	The First Affiliated Hospital of Soochow University
Identification of Plasma Biomarkers for Early Diagnosis of Transplant-associated Thrombotic Microangiopathy Added to My Studies	NCT06102694	Recruiting	• Thrombotic Microangiopathies • Hematopoietic Stem Cell Transplantation		Institute of Hematology & Blood Diseases Hospital, China

Search for: TA-TMA | List Results | ClinicalTrials.gov

TA-TMA: Zusammenfassung

- Verlässliche Labordiagnostik zur Komplementaktivierung (sC5b-9, Proteinurie rUPCR)
- Einheitliches Vorgehen bzgl Screening und diagnostischer Algorithmus wichtig
- Klinische Studien und einheitliche Diagnosekriterien elementar
- Rolle genetischer Prädisposition bei TA-TMA
- Rolle der Komplementinhibition in der Therapie der TMA



Vielen Dank