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TTP Registry
Hereditary Thrombotic Thrombocytopenic Purpura
Upshaw-Schulman Syndrome

Why always at 2 a.m?
Differential diagnosis & therapy of TTP, HUS & aHUS

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Disclosures

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Advisory boards	Takeda – rADAMTS13 Ablynx/Sanofi – Caplacizumab CSL-Behring, NovoNordisk, Sobi, Roche – Hemophilia
Consultancy	Federal Office of Public Health
Speakers bureau	Roche, Sobi, Takeda
Other	Interprofessional hemophilia care EHCCC Inselspital: CSL Behring, NovoNordisk, Sobi, Roche

Funding of the International Hereditary TTP Registry:

SCHWEIZERISCHER NATIONALFONDS ZUR FÖRDERUNG DER WISSENSCHAFTLICHEN FORSCHUNG

ISTH 2007

Answering T.T.P. Thrombotic Thrombocytopenic Purpura Foundation

BLOODCENTER of WISCONSIN PART OF VERSITI

Takeda

Baxter

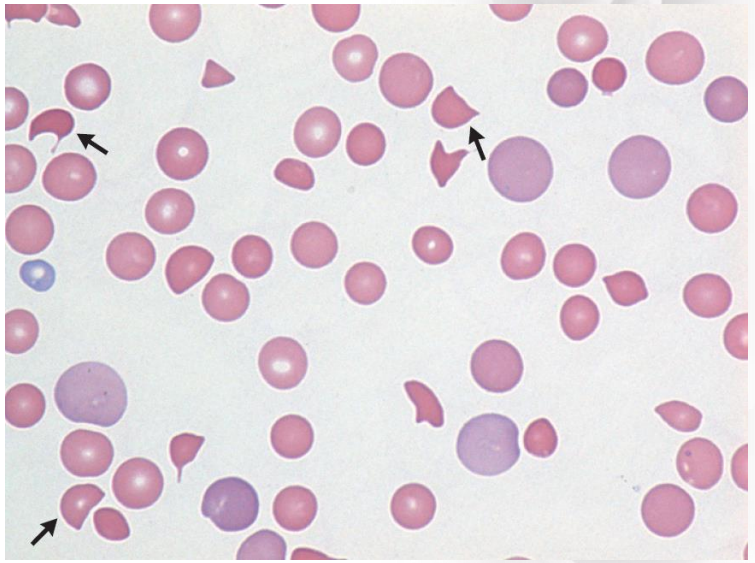
Baxalta

GÜNTER LANDBECK EXCELLENCE AWARD

Mach-Gaensslen Stiftung Schweiz

Patient case

- 35j male, so far healthy
- History of abdominal pain and head ache, and beer-brown urine since 2 days
- Emergency consultation: Temp. 37.5°,
  no abnormal neurological findings,
  no hematoma nor petechia
- Lab
  - Hb 86g/L; platelets 6x10e9/L; numerous schistocytes on smear
  - Bilirubin & LDH increased; haptoglobin < LLD
  - Creatinine 1mg/dl (88µmol)
  - HIV negative



Bhandari S & Kumar R. NEJM 2019;380;16:e23

Agenda

- Introduction
- Why always at 2 a.m ?
- Treatment of:
  - ✓ Immune-mediated TTP (iTTP)
  - ✓ Congenital / hereditary TTP (cTTP)
  - ✓ Atypical / complement-mediated HUS (aHUS / cm-TMA)

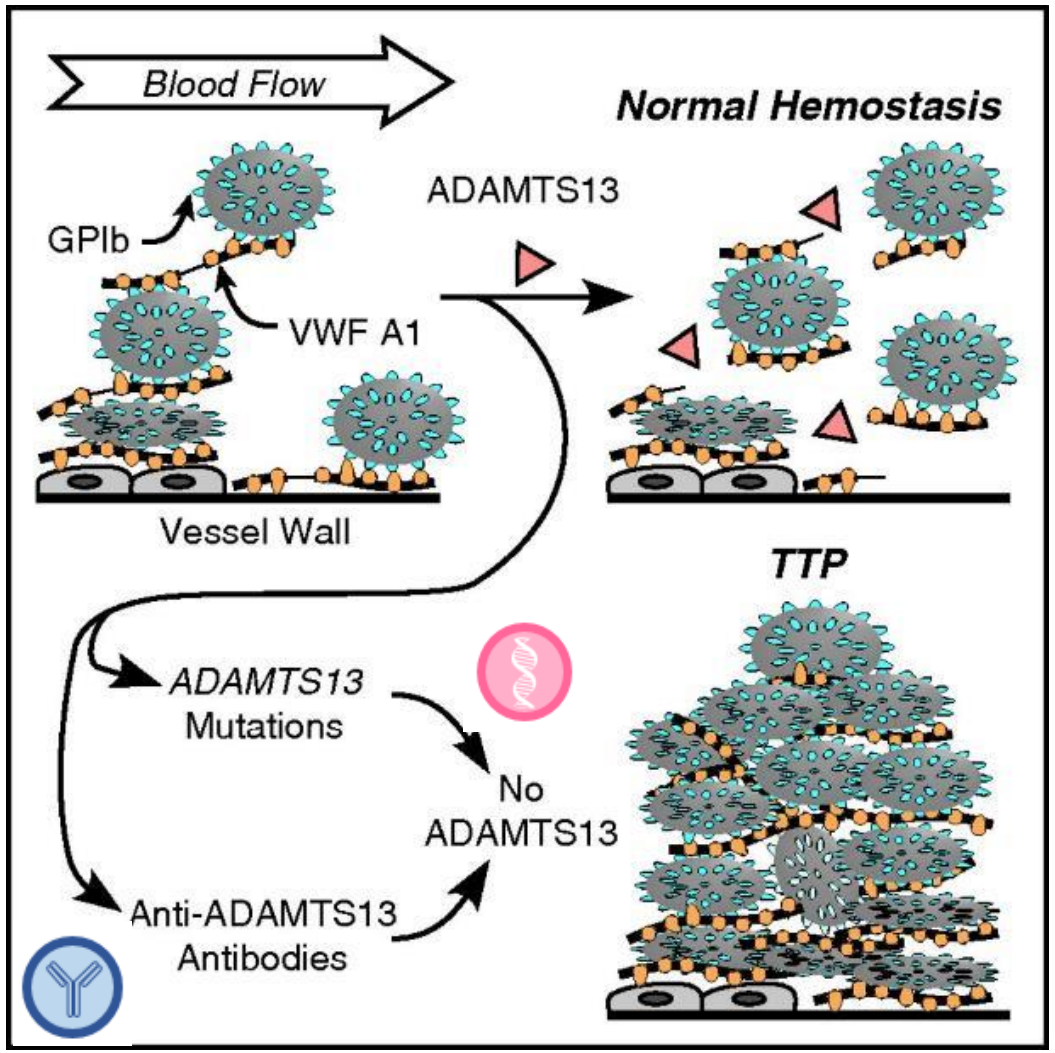
Pathophysiology TTP, HUS, aHUS

TTP = ADAMTS13 <10%

- Congenital TTP (cTTP)
- Immune-mediated TTP (iTTP)

HUS

- D+/STEC HUS (Shiga-toxin)
- **aHUS (cm-TMA):** no diagnostic assay; clinical diagnosis after exclusion of other TMAs; 50-60% of pat. harbor germline variants (GoF/ LoF) or acquired Abs against proteins of AP (C3; FH; FI; MCP/CD46; FB; THBM);



Sadler JE. Blood 2017;130:1811f

AKI:
Acute kidney injury
AP: alternative pathway of complement
cm-TMA:
complement-med. TMA

Why always at 2 a.m ?

- Circadian presentation ? No.
- Awareness ? Rare → low on DD list

Annual incidence:

All TMA	~11 /10^6
iTTP	~2 /10^6
aHUS	~0.5 /10^6

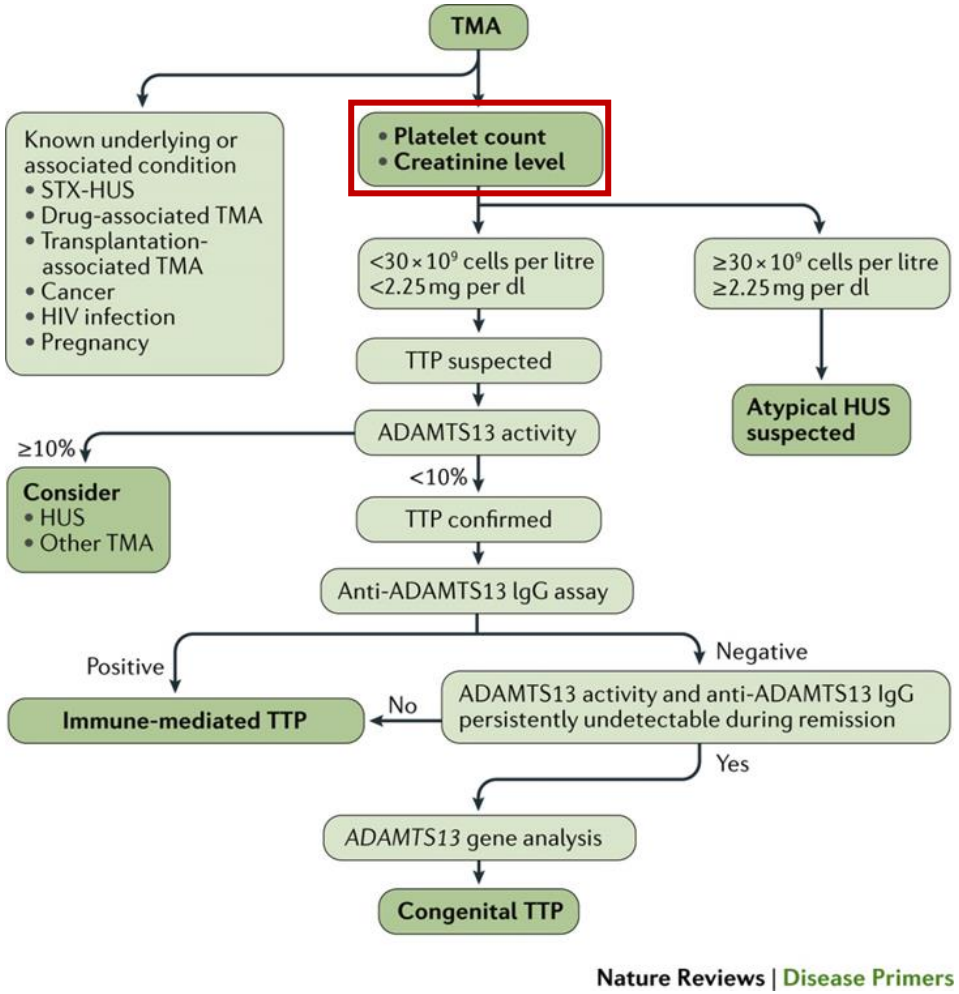
Spiegel Panorama 11.01.2024

Why always at 2 a.m ?

- Circadian presentation ? No.
- Awareness ? Rare → low on DD list
- "Fear/Stress" ? On duty = resident;
  reduced personnel;
  limited lab tests available; …

- What needs to be decided at 2 a.m ?
  - ✓ TTP vs. HUS > start treatment immediately or "wait"
  - ✓ ICU vs. normal ward

Diagnostic algorithm



Kremer Hovinga JA *et al*. Nat Rev Dis Primers. 2017 Apr 6;3:17020

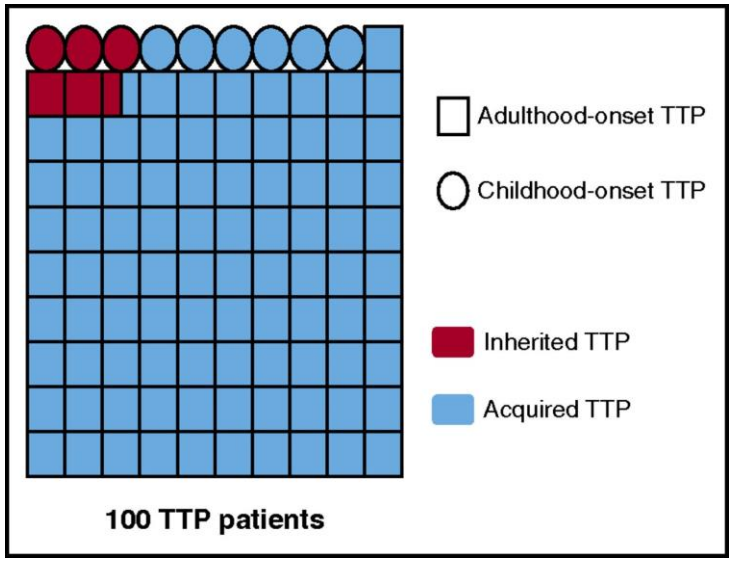
Creatinine
2.25mg/dl = 200 µmol/l
2.0 mg/dl = 176 µmol/l

Clinical context of ADAMTS13 <10%

Table 1. Main associated clinical contexts identified at the initial acute episode of TTP in reports involving more than 50 patients (both adults and children)

Series (year)	USS, %	Idiopathic, %	Infection* and HIV, %	Autoimmune disease, %	Cancer and/or organ/HSPC transplant, %	Pregnancy and postpartum, %	Other, %	Drugs, %
Scully et al (2008)[3] [N = 176]	5	77	<1 and 7	—	2	5†	4	<1
Kremer Hovinga et al (2010), Deford et al (2013)[6,8] [N = 60]	0	77	7	5	2 and 2	5	3	0
Lotta et al (2010)[4] [N = 136]	0	79	0	7	0	9	1	4
Fujimura et al (2010)[5] [N = 326]	12	60	0	14	2 and 0	1	4	7
Jang et al (2011)[7] [N = 66]	0	59	9	6	8 and 1	6	3	8
Blombery et al (2016)[9] [N = 57]	0	75	3 and 0	18	0	2	0	2
Coppo et al (2016)[10] [N = 772]	3	49	12 and 3	11	9 and 4	5	3	1

HIV, human immunodeficiency virus; HPSC, hematopoietic stem-cell; N, number of patients.
*Specific diagnosis made.
†Pregnancy and combined oral contraceptive pill.



Joly BS *et al*. Blood 2017;129:2836f

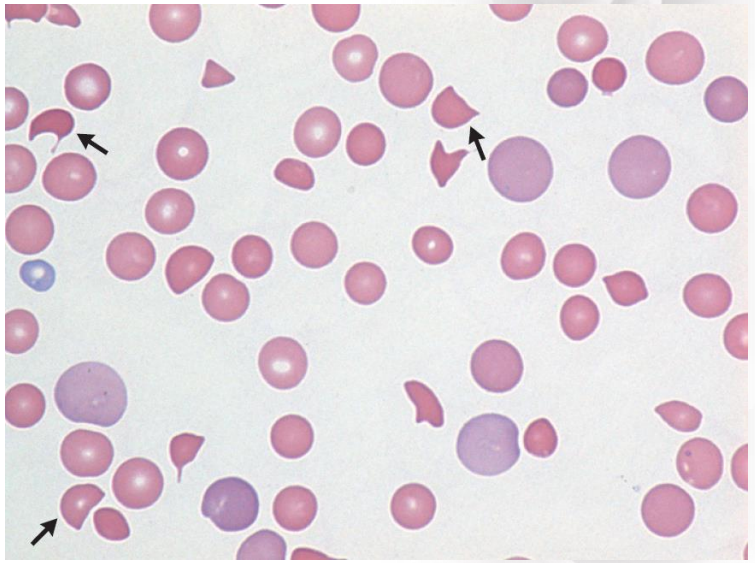
USS = cTTP
(Upshaw-Schulman syndrome)

Patient case

- 35j male, so far healthy
- Lab
  - Hb 86g/L; platelets 6x10e9/L; numerous schistocytes on smear
  - Bilirubin & LDH increased; haptoglobin < LLD
  - Creatinine 1mg/dl (88µmol)
  - HIV negative
  - ❖ no Information on INR or MCV

FRENCH Score: 2/2 points
PLASMIC Score: 5 (+1-2)/7 points

➢ **ADAMTS13 <1%**

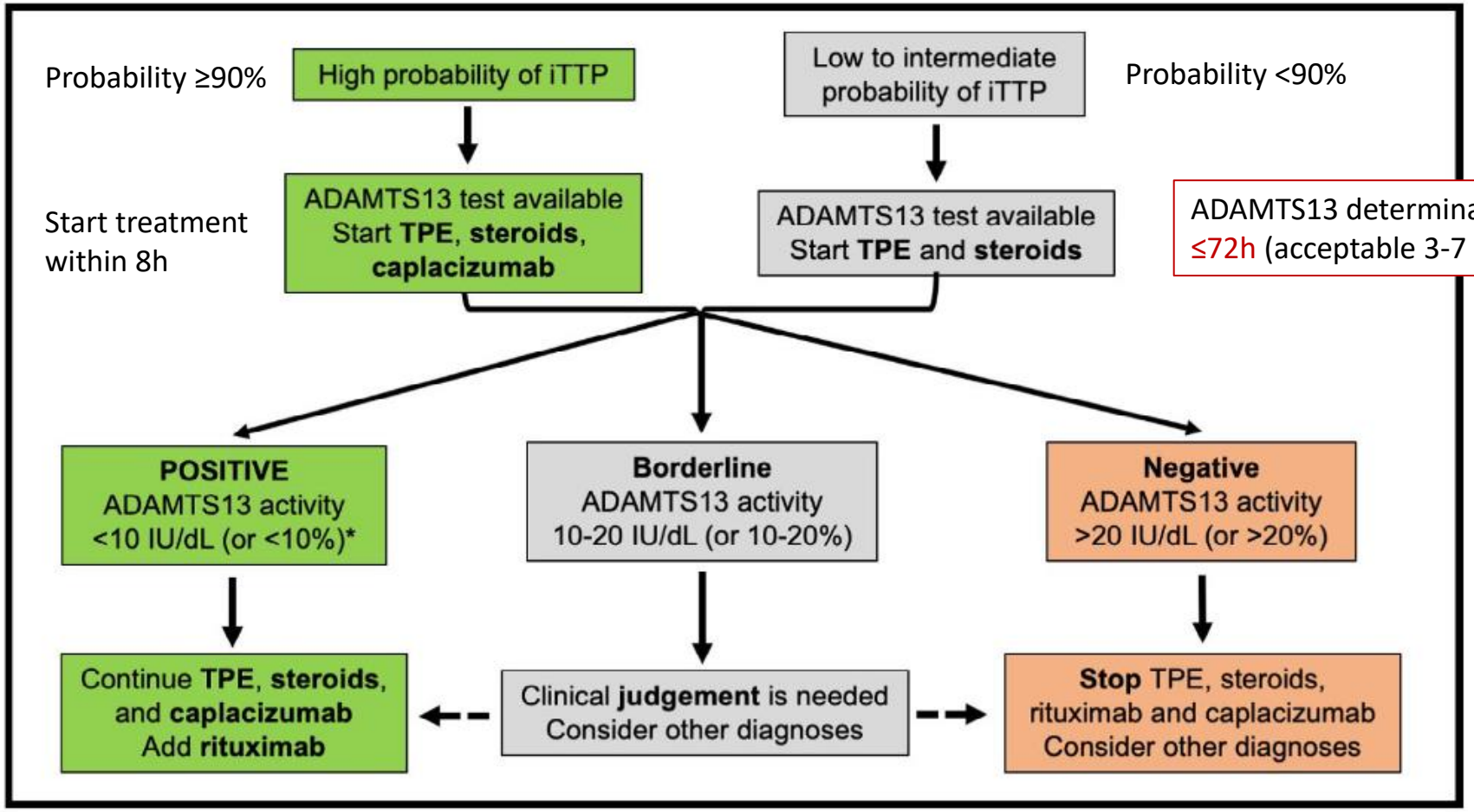


Additional biomarkers suggestive of TTP:

✓ ↑ troponin (non-STEMI) → indication for ICU/telemetry
✓ ↑ a-amylase, lipase (pancreatitis);
✓ etc.

Bhandari S & Kumar R. NEJM 2019;380;16:e23

Treatment iTTP – Guidelines ISTH 2020



ADAMTS13 determination ≤72h (acceptable 3-7 days)

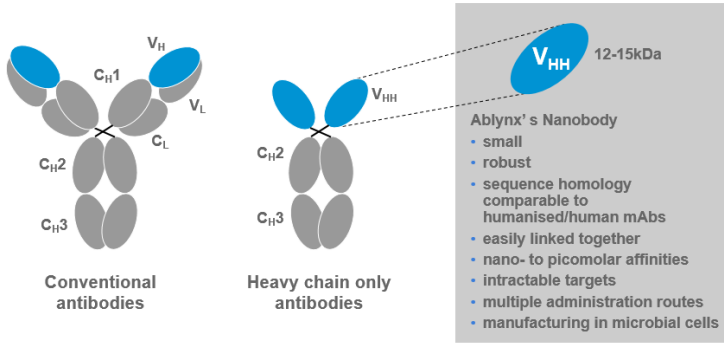
??

Zheng XL *et al*. JTH 2020;18:2486f – ISTH Diagnosis Guideline 2020
Zheng XL *et al*. JTH 2021;19:1864f – Review

*Caplacizumab
Only when ADAMTS13 test is available

Off-label use of Rituximab

Treatment iTTP – Caplacizumab



TITAN (phase 2) and HERCULES (phase 3) trials

- 108 SoC + Caplacizumab vs. 112 SoC + placebo
  - Death/major TE event/TTP exacerbation 14 (13%) vs. 53 (47.3%)

Peyvandi F *et al*. N Engl J Med 2016:374:511f
Scully M *et al*. N Engl J Med 2019:380:335f
Peyvandi F *et al*. Blood Adv 2021;5:2137f - Integrated data

TTP Registry
Hereditary Thrombotic Thrombocytopenic Purpura Upshaw Schulman Syndrome

Real World Data – confirm RCT experience

- Germany, 29 Sites; 60 pat. (06/2018 – 12/2019), 46/60 (76.7%) 1st iTTP episode
  - 8 (13.3%) as in HERCULES, 52 «free» protocol; 35 «front-line», 25 «rescue»
  - ADAMTS13 at time of stop of caplacizumab:
    - <10% : 11/34 pat. had relapse /exacerbation; 91% <28 days of capla stop
    - >10% : NO relapse / exacerbation

Völker LA *et al.* Blood Adv 2020;4:3085f
Völker LA *et al.* Blood Adv 2020;4:3093f

- UK, 115 pat (incl. 5 pediatr.; 05/18 – 01/20); 85 evaluable vs. 39 historic controls
  - **5 deaths** – Capla start "delayed" as «salvage therapy» days 2, 3, 8, 19 and 22

Dutt T *et al.* Blood 2021;137:1731f

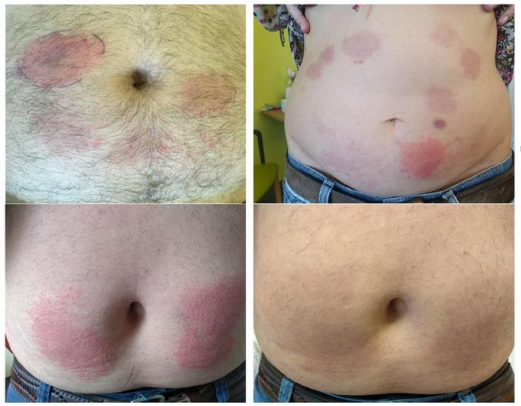
SoC Standard of Care

Treatment iTTP – Caplacizumab 2

- FRANCE, 90 pat. triplet regimen
  vs. 180 historic controls
  - Triplet regimen
    - **TPE** from dy 1
    - **Caplacizumab** from dy 1
    - **Rituximab within dy 1-3**
      (as soon as ATS13 is available)
  - **Prim. outcome** (refractoriness & death) 2.2 **vs. 12.2% (p = 0.01)**
    (one death due to central PE)
  - **Second. outcomes:**
    - exacerbation 3.4 vs. 44% (p = 0.01)
    - platelet recovery 1.8x faster
    - days in hospital 13 vs. 22 (p < 0.01)

Adverse event	Number of adverse events	Description
Major bleeding*	2	One with hemorrhagic shock with lower digestive bleeding One with abundant menorrhagia with a decrease in hemoglobin level of 2.5 g/dL
Clinically relevant nonmajor bleeding*	11	Three with macroscopic gastrointestinal hemorrhage Seven with epistaxis One with subcutaneous hematoma larger than 25 cm^2
Non–clinically relevant nonmajor bleeding *	17	Nine with ecchymosis or small hematoma Six with gingival bleedings Two with catheter site hemorrhage
Inflammatory reaction	6	Inflammatory swelling at the injection site, especially at the end of the treatment course
Thrombocytosis	19	Platelet count ($\times 10^3/mm^3$) >450-600: 11 cases >600-900: 7 cases >900: 1 case

Coppo P *et al.* Blood 2021;137:733f



Kaufeld J *et al.*
Ann Hematol 2021;100:3051f

* No patient received a
- VWF concentrate, or
- hemostatic treatment

Off-label use of Rituximab

iTTP – where to? TPE – free algorithm

Patient with (suspected) TTP (ADAMTS13 <10%; high PLASMIC / FRENCH Score)

- diagnostic samples and procedures, incl. preparing for TPE but w/o central line (yet), avoid Tc transfusion
- 1st injection of 10mg Caplacizumab i.v. & methylprednisolone 1-2mg kg/BW p.o. or 100mg i.v.
  - Consider to give plasma infusion (2-4 units of fresh frozen plasma/Octaplas)
  - Monitor vital signs and neurology
  - Re-test platelet count (Tc) and organ function markers after ~ 6 – 8 (ev. 12 ?) hours

IMPROVING:
platelet count increasing, stable organ function
= Response to treatment – no TPE needed

Daily 10mg Caplacizumab s.c. until ATS13 >20%
Start Rituximab
CBC and organ function markers daily
Discharge w. Tc >150 G/l on 2 consecutive days

NOT IMPROVING:
Start TPE, and continue until Tc >150 G/l & stable

Daily 10mg Caplacizumab s.c. until ATS13 >20%
Start Rituximab
CBC and organ function markers daily
Discharge w. Tc >150 G/l on 2 consecutive days

Kühne *et al*. Blood 2024;144:1486f – MAYARI study (caplacizumab until ADAMTS13 >50%) – SOP UKH-HZL Inselspital Bern

Off-label use of Rituximab and of Caplacizumab

iTTP – where to? TPE – free algorithm

- GERMANY (REACT-2020 TTP Registry) & AUSTRIA (ATMAR) – no uniform protocol
  - SOC (TPE, immunosuppression) with frontline caplacizumab
    - 59 iTTP pat., 59 episodes treated with TPE, immunosuppression & caplacizumab
  - TPE-free regimen (caplacizumab and immunosuppression only)
    - 41 iTTP pat., 42 episodes

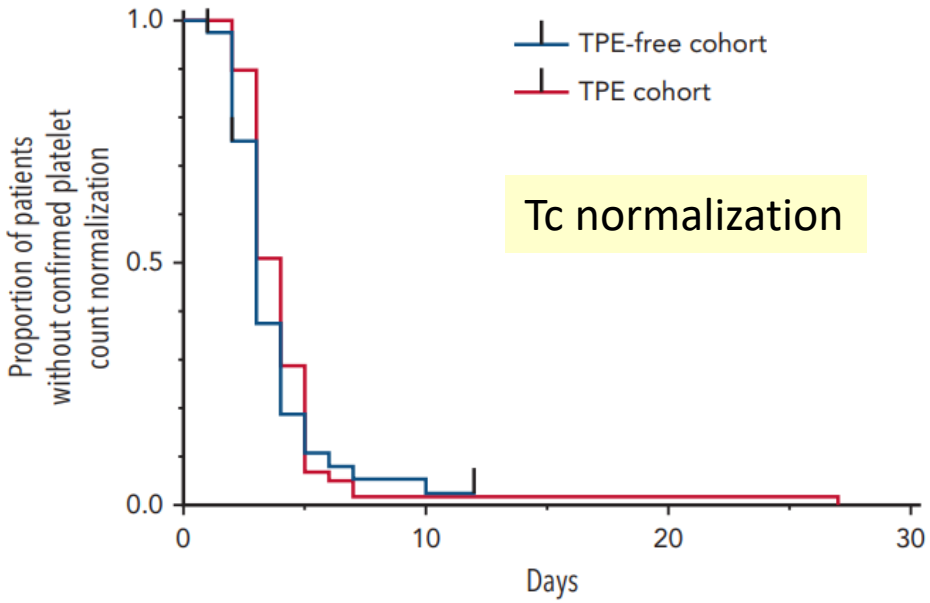
Parameter	TPE-free cohort (n = 42)	TPE cohort (n = 59)	*P* value
Median age (range), y	43 (20-83)	47 (20-80)	.43
Median LDH (range), U/L	703 (214-2500)	1052 (373-3467)	<.01
Initial troponin			.17
Elevated, n (%)	16 (38.1)	27 (45.8)	
Not elevated, n (%)	11 (26.2)	8 (13.6)	
Data missing, n (%)	15 (35.7)	24 (40.7)	
Median serum creatinine (range), mg/dL	0.95 (0.57-5.30)	1.07 (0.5-3.65)	.07
Neurological symptoms upon admission, n (%)			
Patients with at least 1 neurological symptom	24 (57.1)	26 (44.1)	.23

Kühne *et al*. Blood 2024;144:1486f

Off-label use of Rituximab and of Caplacizumab

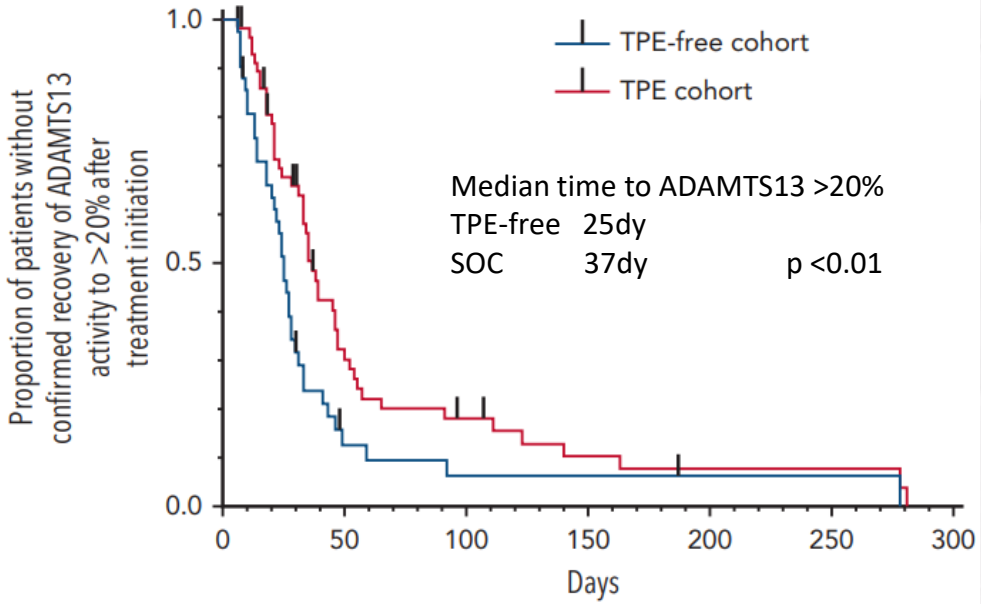
iTTP – where to? TPE – free algorithm

- GERMANY (REACT-2020 TTP Registry) & AUSTRIA (ATMAR)
  - SOC (TPE, immunosuppression) with frontline caplacizumab; 59 iTTP pat & episodes
  - TPE-free regimen (caplacizumab and immunosuppression)
    - 38/42 (90.5%) clinical response w/o TPE; 4/42 +TPE, initiated median +1.5dy (range 1-2)



Tc normalization

No.at risk							
TPE-free cohort	42	7	2	0	0	0	0
TPE cohort	59	17	1	1	1	1	0



No.at risk							
TPE-free cohort	42	4	2	2	1	1	0
TPE cohort	59	16	8	4	2	2	0

ADAMTS13 >20%

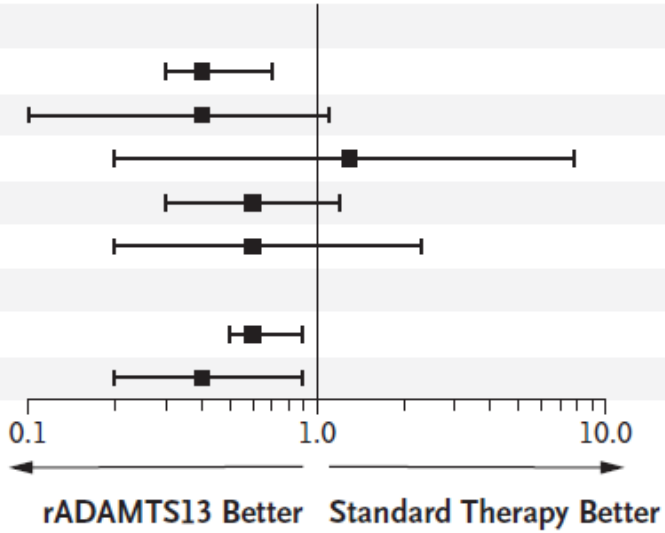
Kühne *et al*. Blood 2024;144:1486f

Off-label use of Rituximab and of Caplacizumab

cTTP – rADAMTS13 (TAK-755; Adzynma®)

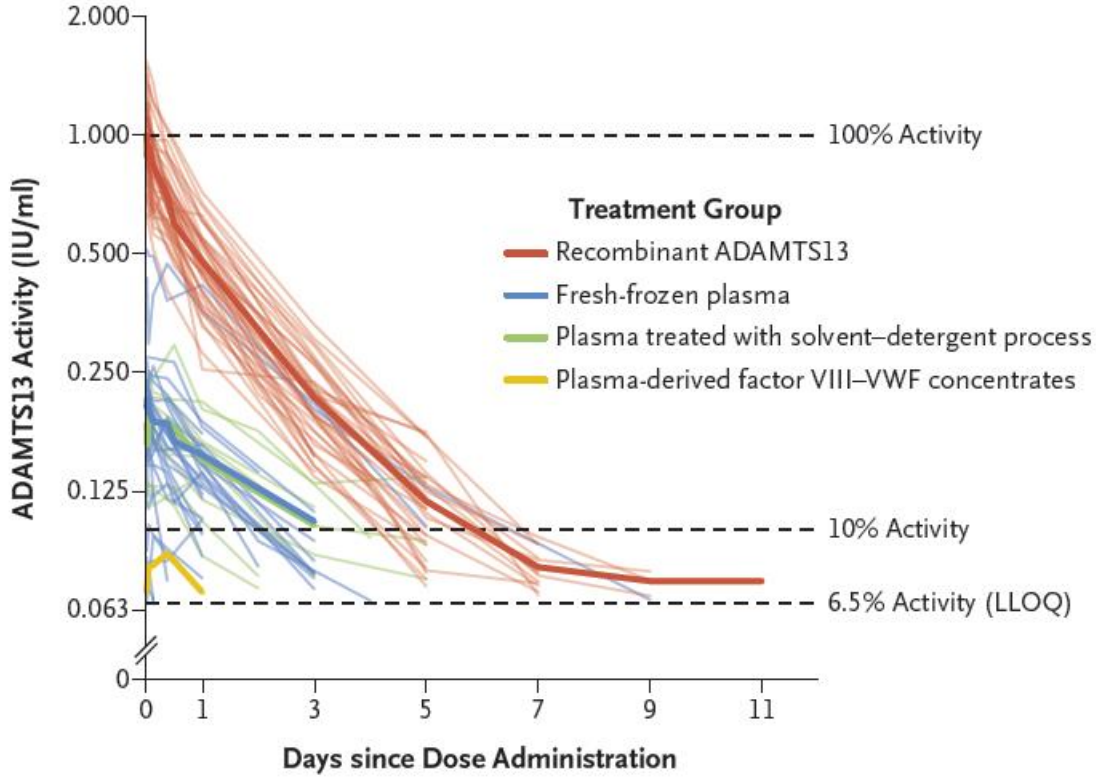
Approval status: FDA 11/23; EMA 08/24; SwissMedic expected 09/25

Outcome	rADAMTS13	Standard Therapy	Estimated Ratio (95% CI)
	least-squares mean annualized incidence rate (95% CI)		
Prespecified TTP manifestations			
Thrombocytopenia	0.74 (0.37–1.50)	1.73 (0.92–3.23)	0.4 (0.3–0.7)
Elevated LDH level	0.26 (0.10–0.72)	0.74 (0.38–1.44)	0.4 (0.1–1.1)
Increased creatinine level	0.10 (0.02–0.47)	0.08 (0.02–0.36)	1.3 (0.2–7.8)
Neurologic symptoms	0.18 (0.06–0.51)	0.29 (0.11–0.78)	0.6 (0.3–1.2)
Abdominal pain	0.11 (0.03–0.39)	0.17 (0.06–0.52)	0.6 (0.2–2.3)
Exploratory outcomes			
Composite TTP manifestations	2.28 (1.35–3.88)	3.68 (2.23–6.08)	0.6 (0.5–0.9)
Other TTP manifestations	0.32 (0.14–0.72)	0.81 (0.44–1.49)	0.4 (0.2–0.9)



Scully *et al*. NEJM 2024;390:1584f

cTTP – rADAMTS13 (TAK-755; Adzynma®)

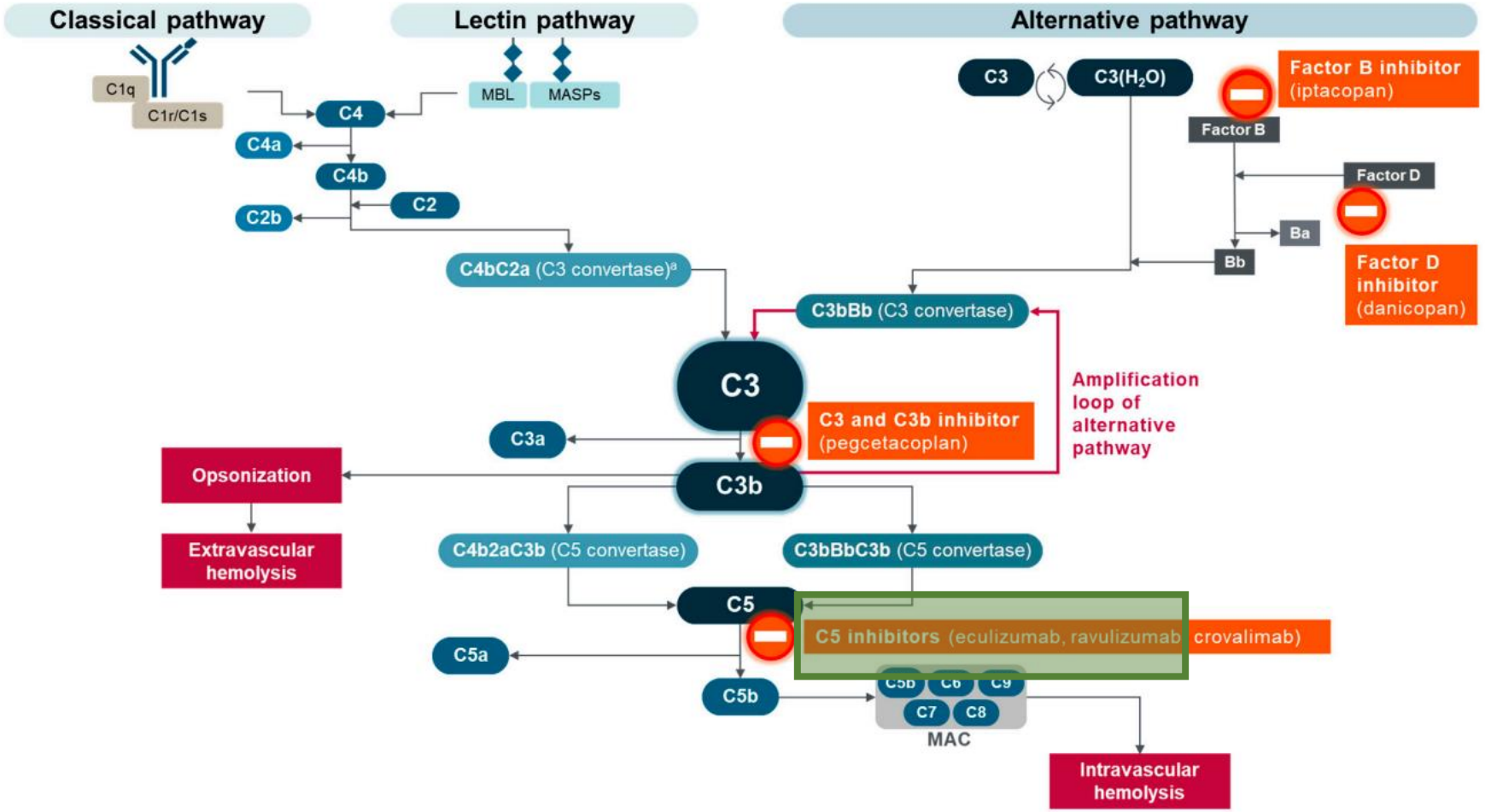


No. of Patients						
Recombinant ADAMTS13	36	39	34	31	13	3
Fresh-frozen plasma	23	27	11	2		1
Plasma treated with solvent–detergent process	7	9	5	3		
Plasma-derived factor VIII–VWF concentrates	2	1				

rADAMTS13 dose:
40 U/kg body weight

Scully *et al*. NEJM 2024;390:1584f

PNH / aHUS – complement inhibition



Approved for aHUS

Hillmen *et al*. Int J Mol Sci 2024;25:9477

Summary

- ADAMTS13 activity assays (widely) available in DACH countries
  - TTP = ADAMTS13 <10%
  - aHUS: clinical diagnosis; after exclusion of other TMAs
- Pathophysiology-based treatment of iTTP
  - Triplet-regimen vs. TPE-free

KoGu required: Rituximab (Art 71a) – unproblematic; Caplacizumab (Art 71b) – problematic !!

- Recomb. ADAMTS13 (ADZYMNA®) for cTTP
  - ➢ iTTP phase 3 trial – rADAMTS13 in addition to TPE underway
- Complement inhibition for aHUS –
  - anti-C5 inhibition highly effective (initiation within days - weeks)
  - Vaccination against encapsulated bacteria !

thank you