Webinars

Thrombotic Microangiopathies

Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

Caplacizumab and treatment of iTTP without plasma exchange

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12th May 2021

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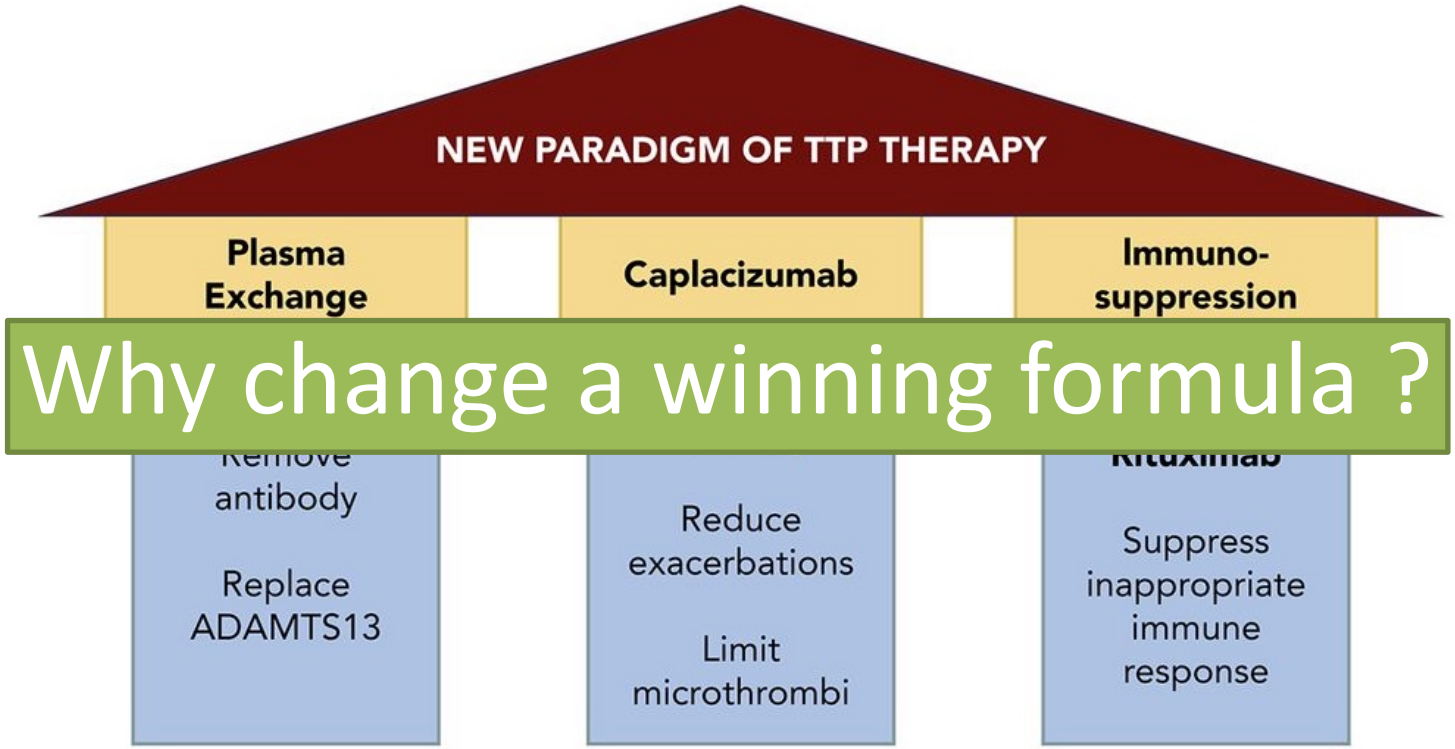
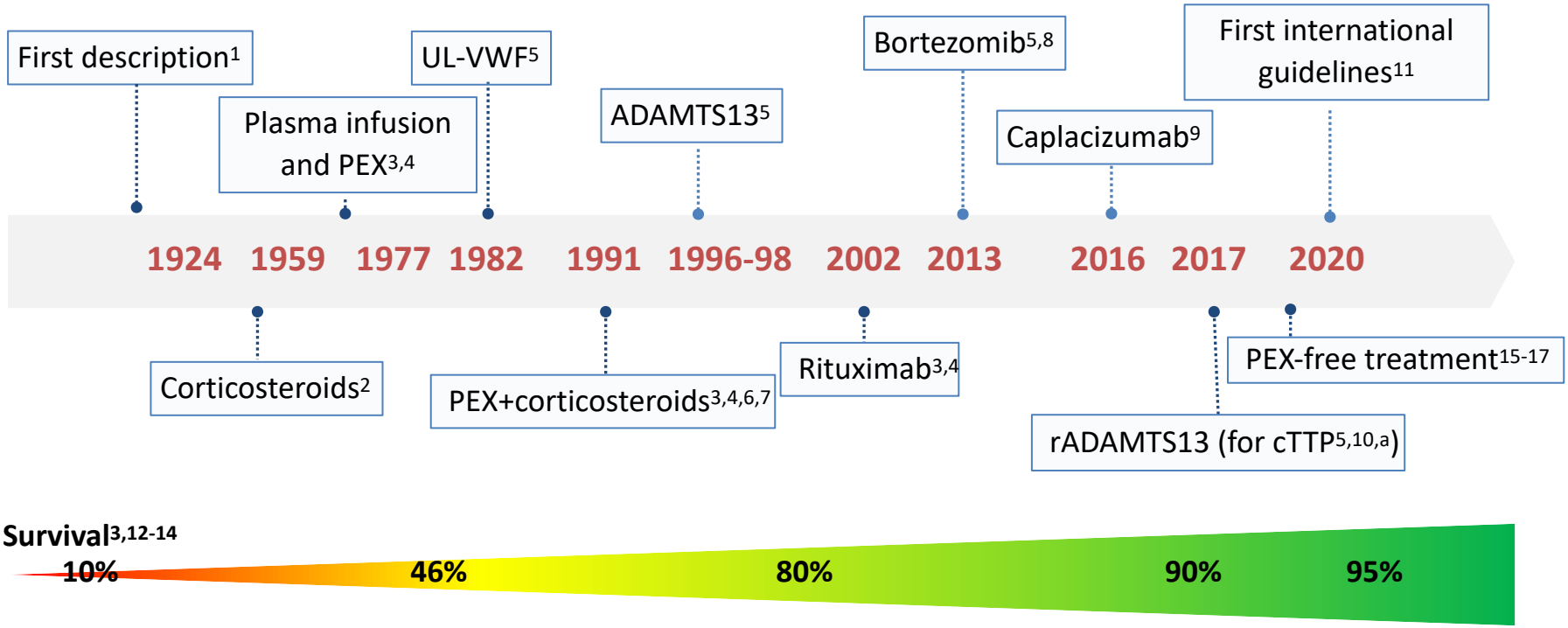


Mazepa MA et al. Blood 134, 415–420 (2019)

1. Evolution of iTTP therapy
2. Managment of iTTP without plasma Exchange
3. Caplacizumab and its impact on PEX free management of iTTP
4. Proposed algorithm for acute management of iTTP

Evolution of iTTP treatment

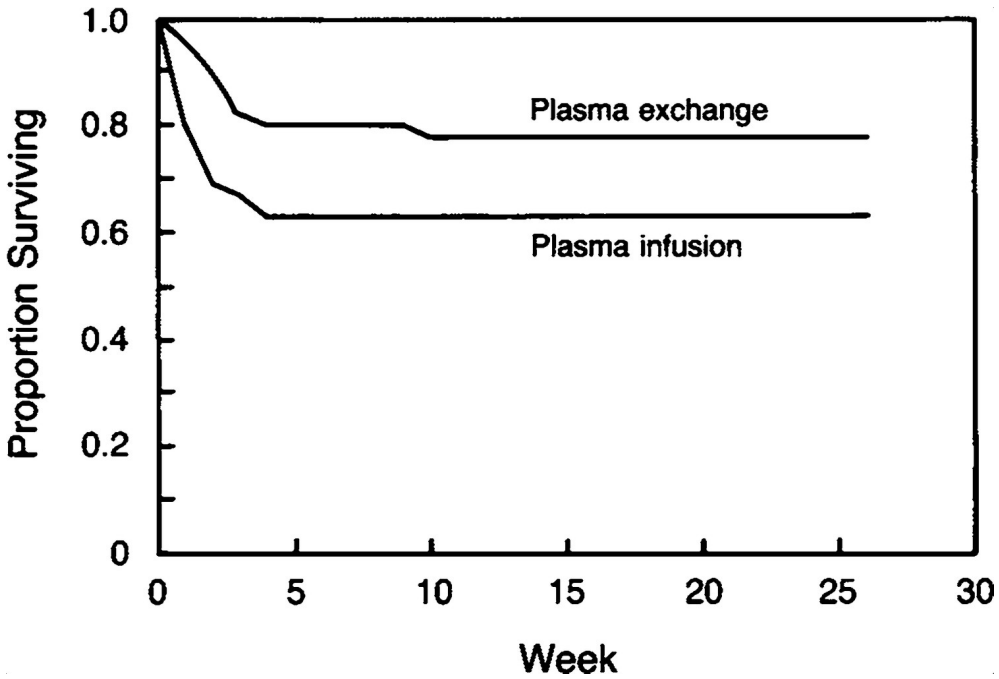


1. Moschcowitz, E. 1924; *Proc New York Path Soc* 24:21. 2. Burke HA and Hartmann RC. *AMA Arch Intern Med.* 1959;103(1):105-112. 3. George JN. *Am J Hematol.* 2012;87 Suppl 1:S88-91. 4. George JN. Blood 2021;137(6):719-720. 5. Coppo P, et al. *Res Pract Thromb Haemost.* 2018;3(1):26-37. 6. Rock GA, et al. *N Engl J Med.* 1991;325(6):393-397. 7. Bell WR, et al. *N Engl J Med.* 1991;325(6):398-403. 8. Shortt J, et al. *N Engl J Med.* 2013:368(1):90-92. 9. Peyvandi F, et al. *N Engl J Med.* 2016;374(6):511-522. 10. Scully M, et al. *Oncoscience.* 2017;4(11-12):160-161. 11. Zheng XL, et al. *J Thromb Haemost.* 2020;18(10):2496-2502. 12. Völker L, et al. *Blood Adv.* 2020;4(13):3085-3092. 13. Coppo P, et al. *Blood.* 2021;137(6):733-742. 14. Dutt T, et al. *Blood.* 137(13):1731-1740. 15. Chander DP et al.N Engl J Med. 2019 Jul 4;381(1):92-94, 16. Sukumar S et al..Am J Hematol. 2020 Apr;95(4):E76-E77, 17. Völker LA et al., J Thromb Haemost 2020 Nov; 18(11): 3061–3066

Vol. 325 No. 6 PLASMA EXCHANGE VS. PLASMA INFUSION FOR TTP — ROCK ET AL. 393

COMPARISON OF PLASMA EXCHANGE WITH PLASMA INFUSION IN THE TREATMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA

GAIL A. ROCK, PH.D., M.D., KENNETH H. SHUMAK, M.D., NOEL A. BUSKARD, M.D., VICTOR S. BLANCHETTE, M.D., JOHN G. KELTON, M.D., RAMA C. NAIR, PH.D., ROBERT A. SPASOFF, M.D., AND THE CANADIAN APHERESIS STUDY GROUP*



Rock GA et al. N Engl J Med 1991;325:393-397

Table 1. Size and distribution of some of the proteins removed by therapeutic plasma exchange

Protein	Concentration, mg/ml	M.W. × 10^3 D	Percentage Intravascular
IgG (except IgG3 subclass)	12	150	45
IgG3	0.7	150	64
IgMa	0.9	950	78
IgA	2.5	160	42
IgD	0.02	175	75
IgE	0.0001	190	45
Albumin	45	66	44
C3	1.4	240	67
C4	0.5	200	66
Fibrinogen	3–4	340	81
Factor VIII	0.1	100–340	71
Antithrombin III	0.2	56–58	45
Lipoprotein cholesterol	1.5–2.0	1300	>90

M.W., molecular weight. Modified from refs. 4 and 5, with permission.

Ahmed S and Kaplan A, Therapeutic Plasma Exchange Using Membrane Plasma Separation, CJASN 15: 1364–1370, 2020

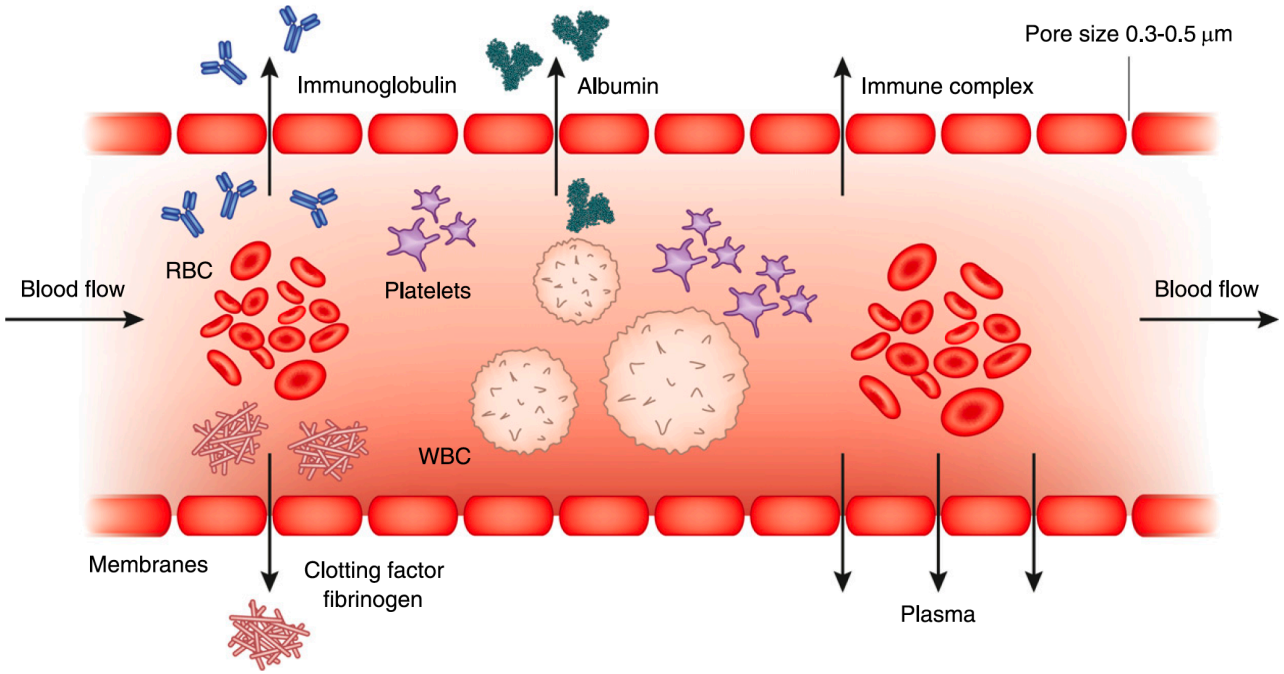


Figure 1. | **Schematic section of a hollow fiber for plasma exchange.** Whole blood flows lengthwise along the interior of the fiber, whereas its plasma components, such as Igs, clotting factors, fibrinogen, and albumin, pass through the pores in the fiber wall and collect outside the fiber. The wall of the hollow fiber functions as the separating membrane with a pore size that allows penetration by plasma but not by the blood's cellular components (red blood cells [RBCs], white blood cells [WBCs], and platelets).

Ahmed S and Kaplan A, Therapeutic Plasma Exchange Using Membrane Plasma Separation, CJASN 15: 1364–1370, 2020

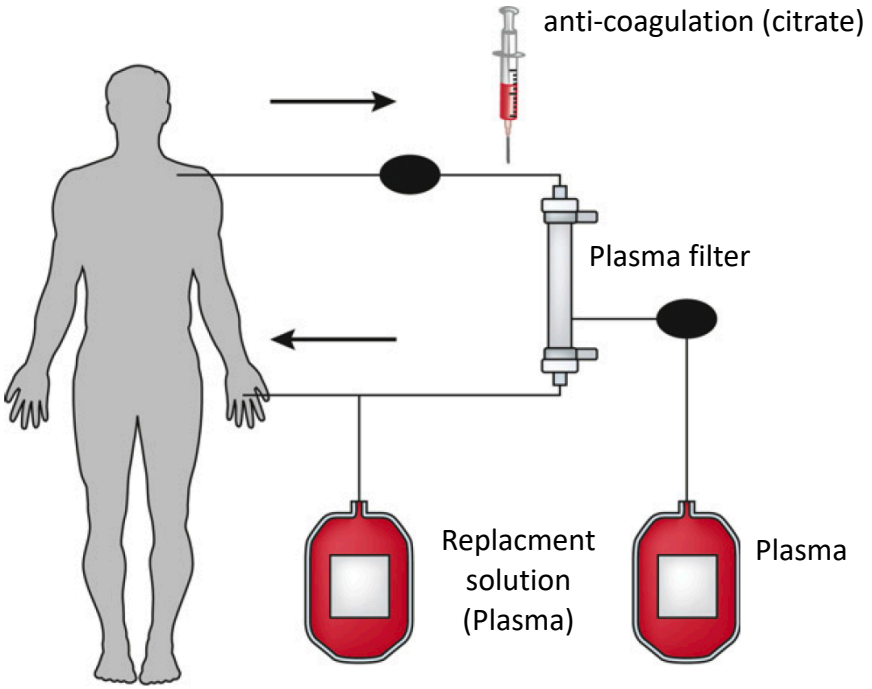


Figure 2. | Blood flowing through the plasma filter, plasma separation and infusion of replacement solution, and return to the patient.

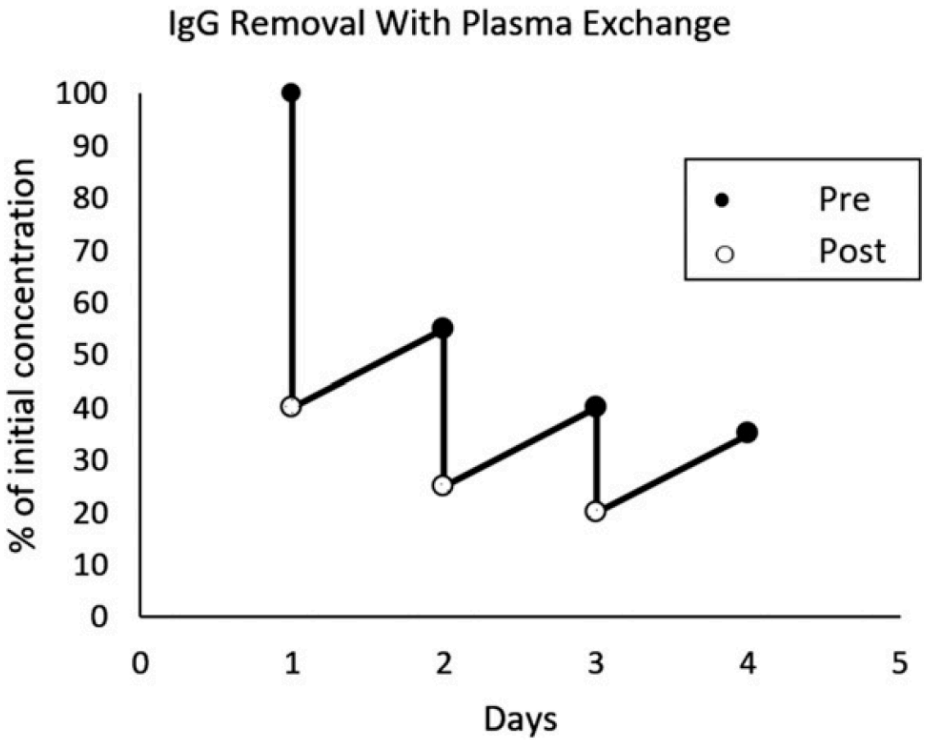
Ahmed S and Kaplan A, Therapeutic Plasma Exchange Using Membrane Plasma Separation, CJASN 15: 1364–1370, 2020

Table 2. Comparison of available membrane separation therapeutic plasma exchange filters in the United States with a dialyzer for hemodialysis

Specification	TPE 2000 Filter	Asahi Plasmaflo Filter	F200NR Dialyzer
Indication for use	Plasma exchange	Plasma exchange	Hemodialysis
Molecular mass cutoff, D	3 million	NA but estimated close to 3 million	Estimated 15,000
Pore size, μm	0.5	0.3	NA
Fiber material	Polypropylene	Polyethylene	Polysulfone
Hollow fibers	Yes	Yes	Yes
Surface area, m^2	0.35	0.5	2
Blood volume in filter, ml	55	41	113
TMP, mm Hg	120–193	100	600 (maximum)
Anticoagulation	Heparin (citrate rare)	Heparin (citrate rare)	Heparin
Blood flow rate, ml/min	100–250	Up to 200	Up to 600
Sieving coefficient			
Albumin	0.97	0.99	0
IgG	1	1	0
IgA	1	1	0
IgM	0.92	1	0
Sterilization	Ethylene oxide	γ-Ray	Ethylene oxide

NA, not available; TMP, transmembrane pressure.

Ahmed S and Kaplan A, Therapeutic Plasma Exchange Using Membrane Plasma Separation, CJASN 15: 1364–1370, 2020



Ahmed S and Kaplan A, Therapeutic Plasma Exchange Using Membrane Plasma Separation, CJASN 15: 1364–1370, 2020

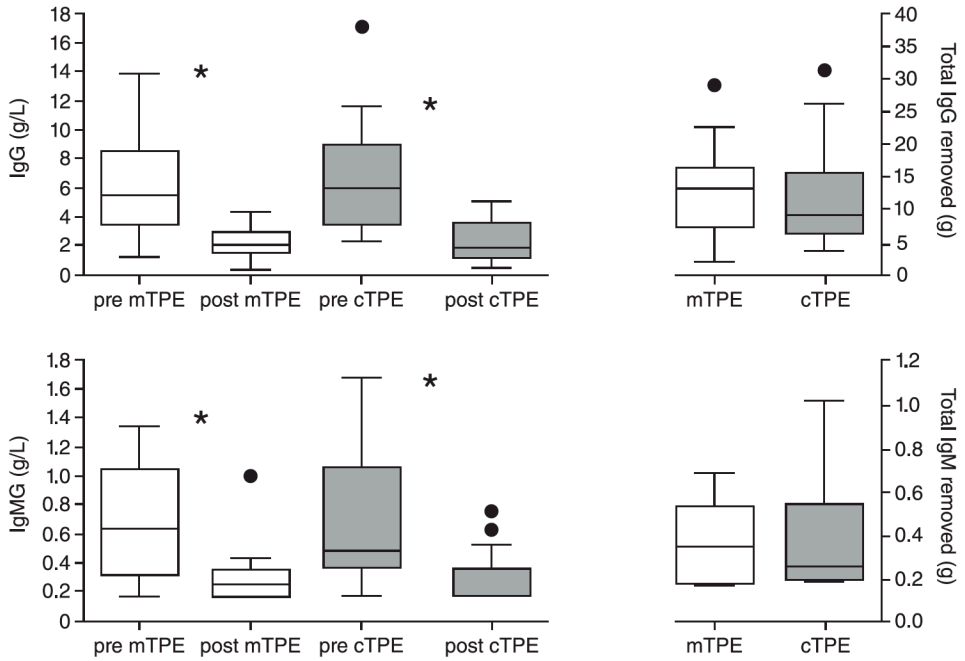


Figure 3. | Comparison between efficacy of membrane separation therapeutic plasma exchange (mTPE) and centrifugation therapeutic plasma exchange (cTPE). IgG and IgM levels before and after showing similar removal with the two techniques. Reprinted from ref. 11, with permission.

Ahmed S and Kaplan A, Therapeutic Plasma Exchange Using Membrane Plasma Separation, CJASN 15: 1364–1370, 2020

1. Evolution of iTTP therapy
2. **Managment of iTTP without plasma exchange**
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4. Proposed algorithm for acute management of iTTP

EXCEPTIONAL CASE REPORT

blood advances

Management of thrombotic thrombocytopenic purpura without plasma exchange: the Jehovah's Witness experience

James N. George,[1,2] Steven A. Sandler,[3] and Joanna Stankiewicz[3]

[1]Department of Medicine, College of Medicine, and [2]Department of Biostatistics and Epidemiology, College of Public Health, The University of Oklahoma Health Sciences Center, Oklahoma City, OK; and [3]Presence Resurrection Medical Center, Chicago, IL

George J et al., Blood Adv. 2017 Oct 30;1(24):2161-2165

Table 1. Clinical course and treatment of our Jehovah's Witness patient

Day	Hgb, g/dL	Plt, $\times 10^9$/L	Clinical course	Treatments*
1	8.4	12	Transient aphasia, bilateral arm and face numbness and weakness, hand clumsiness.	MP 375, folic acid
2	7.8	16	Neurologic symptoms resolved.	
3	7.8	24		Rituximab
4	7.5	10		Apheresis, Epo
5	6.9	9	Acute transient episode of feeling faint, aphasia, left arm weakness.	Apheresis, IVIg
6	6.0	10	Neurologic symptoms resolved; no further neurologic abnormalities.	
7	5.7	15		MP 1000, IVIg
8	—	—		MP 1000, IV iron, rituximab
9	6.6	28		MP 1000
10	—	—	Gradual improvement. Hallucinations and proximal muscle weakness attributed to corticosteroids.	Koate, prednisone 80
11	7.2	45		
12	7.7	74		Rituximab
14	9.1	96		Prednisone 40
16	9.3	109	Discharged to rehabilitation for steroid-induced proximal muscle weakness. Regained strength with physical therapy.	
19	10.0	115		Rituximab
21	11.8	90		
23	12.7	125		
28	13.0	231	Discharged to home. ADAMTS13, 99%.	
60	—	—	Return to work.	

Days begin with hospital admission on day 1.
Epo, recombinant human erythropoietin; Hgb, hemoglobin concentration; MP, methylprednisolone (and prednisone); Plt, platelet count.
*Doses, regimens: apheresis, plasmapheresis with albumin replacement; Epo, 10 000 U then 20 000 U, 3 times per week; folic acid, 1 mg per day; IVIg, 70 g (1 g/kg); IV iron, ferrous gluconate, 125 mg IV daily; Koate, 2000 U (30 U/kg), given once; MP, milligrams per day; rituximab, 375 mg/m^2.

George J et al., Blood Adv. 2017 Oct 30;1(24):2161-2165

Table 2. Clinical course of the 4 previously published Jehovah's Witness patients with TTP

Patient*/year/reference	Age/sex	Past medical history, presenting symptoms, laboratory data	Treatment	Outcome
1/2007/5	19/F	Previous mixed connective tissue disease treated with hydroxychloroquine and prednisone. Chest pain, headache, syncope. Hgb, 4.9; Plt <10; Cr, 1.0; LDH, 1131; ADAMTS13, <5%; Inh, <0.4 BU	MP, 1000 mg on days 1-3. Vincristine, day 3, 2 mg; days 6 and 9, 1 mg.	Plt, <10 on days 1-3; 125 on day 4; 280 on day 5
2/2015/6	41/F	Previous SLE, treated with hydroxychloroquine. Bruising, dyspnea, abdominal pain. Hgb, 6.1; Plt, 29; Cr, "normal"; LDH, 477; ADAMTS13, <5%; Inh, 1.4 BU	Dex, 40 mg days 1-4, IVIg, 1 g/kg days 1, 2, 5. Vincristine, 2 mg days 3, 8. Rituximab, 375 mg/m^2 days 3, 8, 15. Apheresis with albumin replacement days 2, 3, 6, 7. Epo, 30 000 U days 6-11.	Plt, 9-29 until 50 on day 8; 200 on day 12. Nadir Hgb, 3.2 on day 8, 6.3 on day 16. At 6 mo: Hgb, 12.6; Plt, 225; ADAMTS13, 90%
3/2015/8	58/F	First episode: Hgb, 5.4; Plt, 16; Cr, 1.2; LDH, 1605; Hpt, <10; ADAMTS13, NR Second episode: Transient aphasia, blurred vision. Hgb, 9.1; Plt, 30; Cr, 1.1; LDH, 756; ADAMTS13, NR	First episode: rituximab, cyclophosphamide Second episode: rituximab, IVIg	Both episodes: "Significant improvement within few days" (remission is assumed)
4/2017/7	22/F	Purpura. Hgb, 10.1; Plt, 12; LDH, increased; Hpt, decreased; ADAMTS13, <5%; Inh, >8 BU	"High-dose steroid," Epo, folic acid beginning day 1. Apheresis, albumin replacement: days 2, 5; cryoprecipitate replacement, days 7, 9, 10, 12, 13. Rituximab, days 3, 10, 17. Vincristine, days 6, 16. Sanguinate, days 10-13.	Discharge on day 19: Hgb, 8.8; Plt, 221

Doses, regimens: Cr, mg/dL; Hgb, g/dL; Hpt, mg/dL; LDH, U/L; Plt, $\times 10^9$/L.
BU, Bethesda unit; Cr, serum creatinine; Dex, dexamethasone; Hpt, haptoglobin; Inh, functional ADAMTS13 inhibitor; LDH, lactate dehydrogenase; MP, methylprednisolone; NR, not reported; SLE, systemic lupus erythematosus.
*Patients 1, 2, and 4: platelet count values were extrapolated from the published figures. Patient 3 was described in an abstract with minimal detail. No presenting symptoms were described for her first episode; ADAMTS13 activity was not reported. No regimens or days of administration were reported for the treatments; no outcomes were described for either episode. Patient 4: Sanguinate (pegylated bovine carboxyhemoglobin) is a product in development for patients with severe anemia (NCT02754999). For patients 3 and 4, drug doses were not reported.

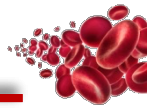
George J et al., Blood Adv. 2017 Oct 30;1(24):2161-2165

Recommendations by George J et al. (2017):

- Rituximab 375mg/m2 twice weekly for 2 weeks
- Methylprednisolone 1000mg per day for 3 days, followed by 1mg/kg
- Erythropietin / folic acid to support erythropoiesis

- FVIII/VWF replacement therapy (Koate) to provide ADAMTS13 if thrombocytopenia persits
- Additional immunosuppressive agents / apheresis with albumin

George J et al., Blood Adv. 2017 Oct 30;1(24):2161-2165



EXCEPTIONAL CASE REPORT

blood advances

Management of thrombotic thrombocytopenic purpura without plasma exchange: the Jehovah's Witness experience

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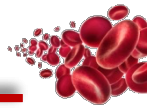
"... **This proposed regimen will change with the anticipated approval of new treatments for TTP.** Caplacizumab, a nanobody that blocks von Willebrand factor interaction with platelets, can promptly prevent micro-vascular thrombosis. Recombinant ADAMTS13 will provide ADAMTS13 activity to decrease the concentration of ultra-large von Willebrand factor multimers. These new treatments may provide a major benefit for Jehovah's Witness patients."

George J et al., Blood Adv. 2017 Oct 30;1(24):2161-2165



EXCEPTIONAL CASE REPORT

blood advances

Management of thrombotic thrombocytopenic purpura without plasma exchange: the Jehovah's Witness experience

James N. C
[1]Department
Center, Oklah
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"... These observations on Jehovah's Witness patients suggest the **possibility that PEX may not be an essential treatment of TTP**. If PEX could be avoided, management of patients with TTP could be simpler and safer."

George J et al., Blood Adv. 2017 Oct 30;1(24):2161-2165

Why change a winning formula ?

Adverse reactions to PEX among Oklahoma TTP Registry patient (1995-2015):

- 3/78 TTP patients (4%) have died of complications of PEX (2 sepsis, 1 hemorrhage caused by central venous catheter insertion)
- 12/78 (18%) have had sepsis with documented bacteremia, related to their central venous catheter.
- 3/78 have had venous thrombosis at the central venous catheter site requiring systemic anticoagulation.
- 1/78 had an anaphylactic reaction to plasma with cardiac arrest; she had a complete recovery.

Rizvi MA et al. Transfusion. 2000;40(8):896-901., Page EE et al. Blood Adv. 2017;1(10):590-600., Kremer Hovinga JA et al. Blood. 2010;115(8):1500-1511

Why change a winning formula ?

Additional complications:

- Electrolyte disturbances (hypocalcaemia) / metabolic alcalosis (citrate)

> Citrate is used as regional anticoagulation in patients with high risk of bleeding.

> Citrate is metabolized in the liver and produces HCO_3- and citric acid. Accumulation of citrate may occur if liver metabolism is impaired and may result in metabolic alkalosis („citrate toxicity“).

Rizvi MA et al. Transfusion. 2000;40(8):896-901., Page EE et al. Blood Adv. 2017;1(10):590-600., Kremer Hovinga JA et al. Blood. 2010;115(8):1500-1511

Why change a winning formula ?

- PEX requires specialized personnel and instruments that may not be available in many hospitals or at all times.

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Transfusion and Apheresis Science xxx (xxxx) xxx

Contents lists available at ScienceDirect

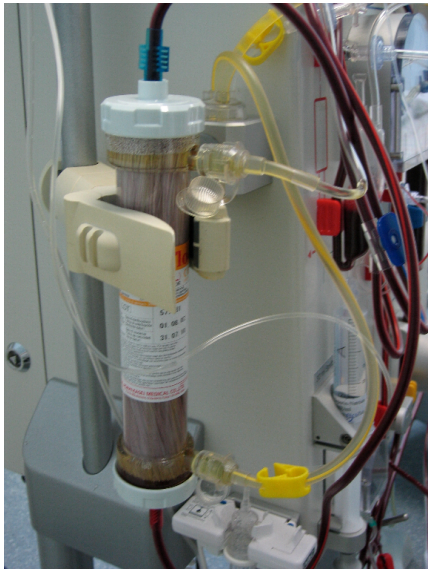
Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Treating thrombotic thrombocytopenic purpura without plasma exchange during the COVID-19 pandemic. A case report and a brief literature review

César David Galindo-Calvillo [1], Carlos Saúl Rodríguez-Roque [1], Andrés Gómez-De León, Luz Tarín-Arzaga, David Gómez-Almaguer *

Facultad de Medicina y Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico



Galindo-Calvillo CD et al., Transfus Apher Sci. 2021 Feb 27;103107

1. Evolution of iTTP therapy
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The NEW ENGLAND JOURNAL of MEDICINE

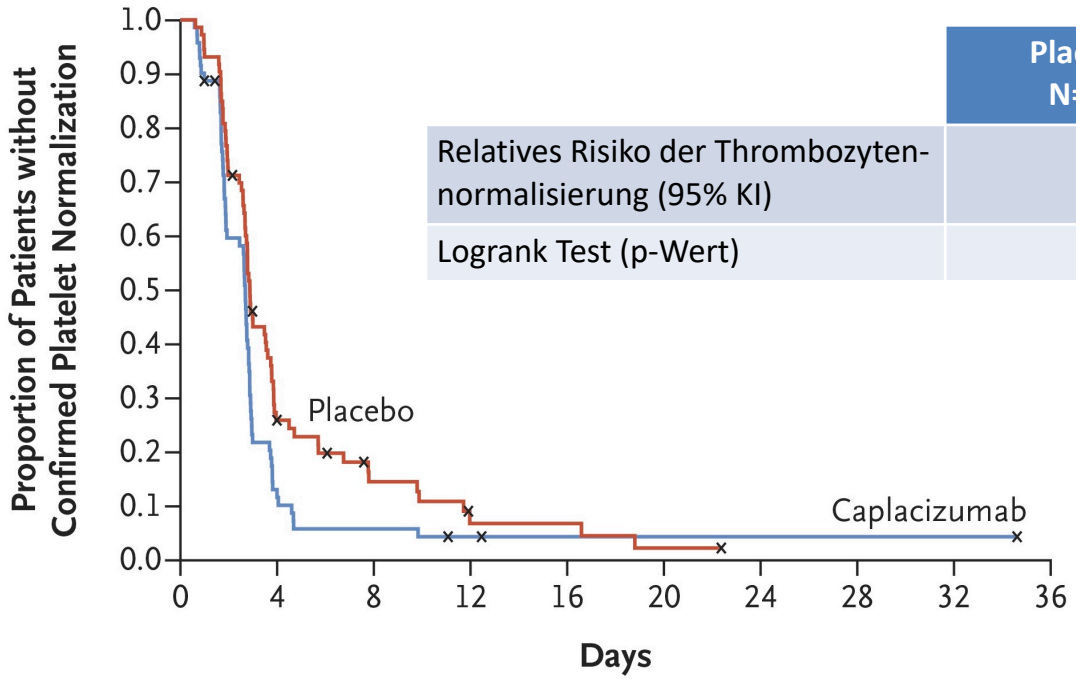
ORIGINAL ARTICLE

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

M. Scully, S.R. Cataland, F. Peyvandi, P. Coppo, P. Knöbl, J.A. Kremer Hovinga, A. Metjian, J. de la Rubia, K. Pavenski, F. Callewaert, D. Biswas, H. De Winter, and R.K. Zeldin, for the HERCULES Investigators*

N ENGL J MED 380;4 NEJM.ORG JANUARY 24, 2019

Scully M et al. N Engl J Med 2019;380:335-346



	Placebo N=73	Caplacizumab N=72
Relatives Risiko der Thrombozyten-normalisierung (95% KI)	1.55 (1.10 -2.20)	
Logrank Test (p-Wert)	P <0.01	

Scully M et al. N Engl J Med 2019;380:335-346

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Caplacizumab Therapy without Plasma Exchange for Acquired Thrombotic Thrombocytopenic Purpura

Chander DP, Loch MM, Cataland SR, George JN.N Engl J Med. 2019 Jul 4;381(1):92-94.

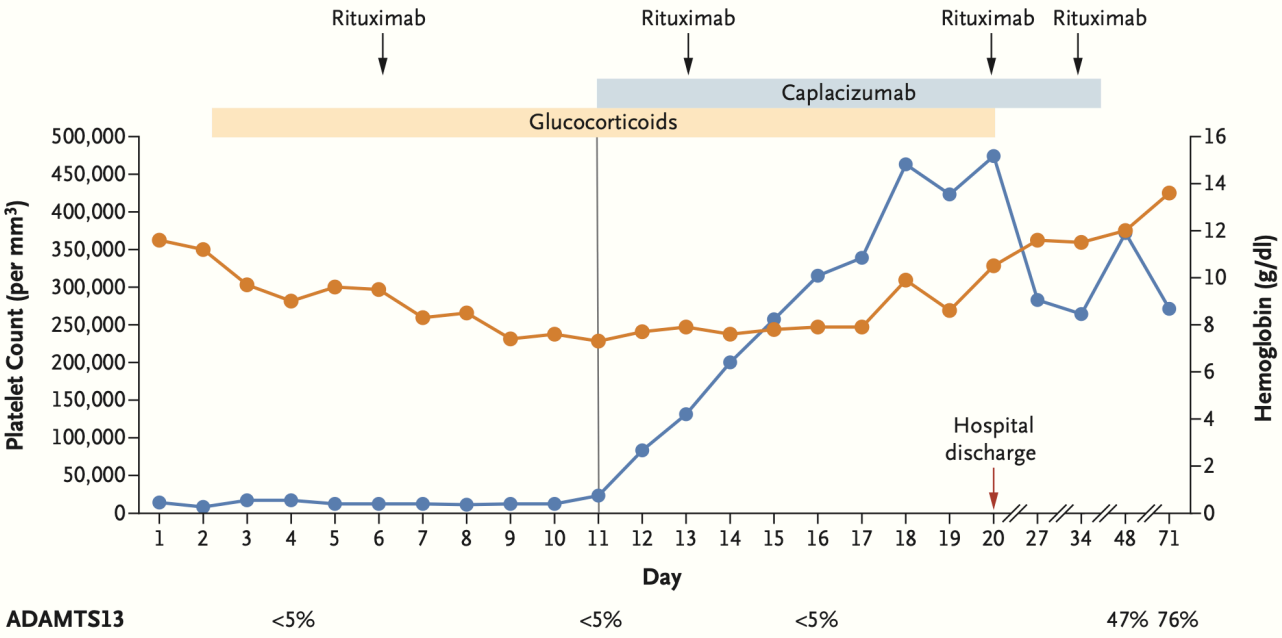


Figure 1. Acquired Thrombotic Thrombocytopenic Purpura (TTP) in a Jehovah's Witness Patient Treated with Caplacizumab.

Shown is the clinical course of an initial episode of TTP in a 63-year-old woman who presented with spontaneous purpura and who declined to undergo plasma exchange because of religious prohibition. Data are presented from hospital admission (day 1) until the most recent follow-up at 51 days after hospital discharge and 31 days after caplacizumab was discontinued on day 40.

Chander DP, Loch MM, Cataland SR, George JN.N Engl J Med. 2019 Jul 4;381(1):92-94.

Received: 27 December 2019 | Accepted: 30 December 2019

DOI: 10.1002/ajh.25715

CORRESPONDENCE

Shared decision making, thrombotic thrombocytopenic purpura, and caplacizumab

We described the recent availability of caplacizumab, a humanized immunoglobulin which targets the A1 domain of von Willebrand Factor (vWF) and inhibits platelet binding. We described the recent clinical trials that had documented prompt platelet count recovery in patients with TTP who received caplacizumab, plasma exchange, and immunosuppression.[4] We described how caplacizumab prevents the formation of microvascular thrombi and resultant tissue ischemia. We described how caplacizumab had been effective for treatment of a Jehovah's Witness

Sukumar S, George JN, Cataland SR.Am J Hematol. 2020 Apr;95(4):E76-E77.

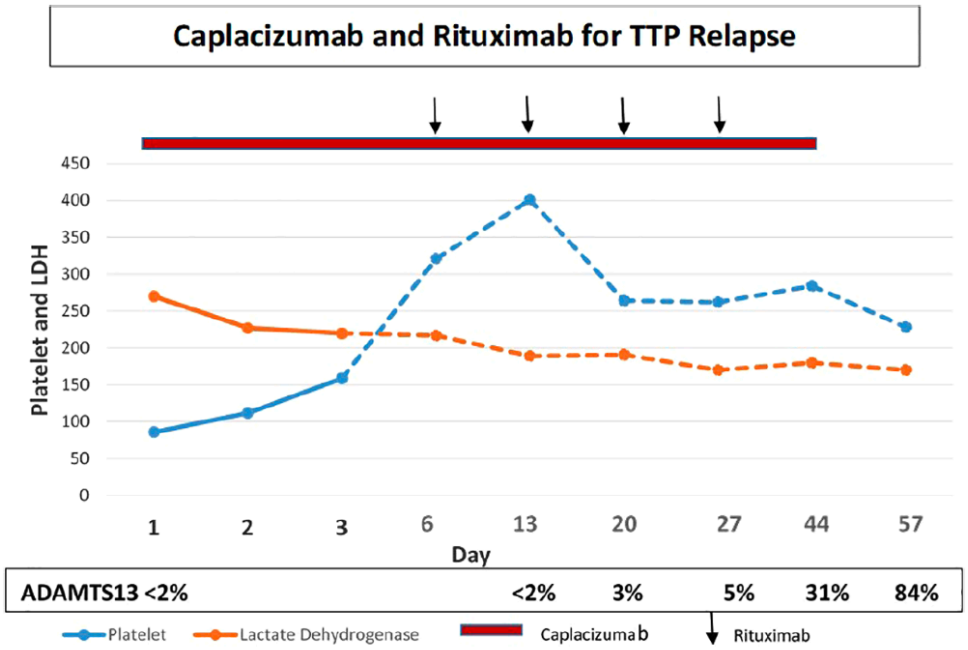


FIGURE 1 Caplacizumab and Rituximab for TTP Relapse. The patient's clinical course and treatments are illustrated. Caplacizumab was begun on day 1 and continued daily until ADAMTS13 activity recovered on day 44. She remains well with normal ADAMTS13 activity of 84% now 2 months following her relapse

Sukumar S, George JN, Cataland SR.Am J Hematol. 2020 Apr;95(4):E76-E77.

Received: 27 April 2020 | Accepted: 29 July 2020

DOI: 10.1111/jth.15045

BRIEF REPORT

Treatment of acquired thrombotic thrombocytopenic purpura without plasma exchange in selected patients under caplacizumab

Linus A. Völker[1,2] | Paul T. Brinkkoetter[1,2] | Paul N. Knöbl[3] | Miroslav Krstic[4] | Jessica Kaufeld[5] | Jan Menne[5] | Veronika Buxhofer-Ausch[6] | Wolfgang Miesbach[7]

Völker LA et al., J Thromb Haemost 2020 Nov; 18(11): 3061–3066

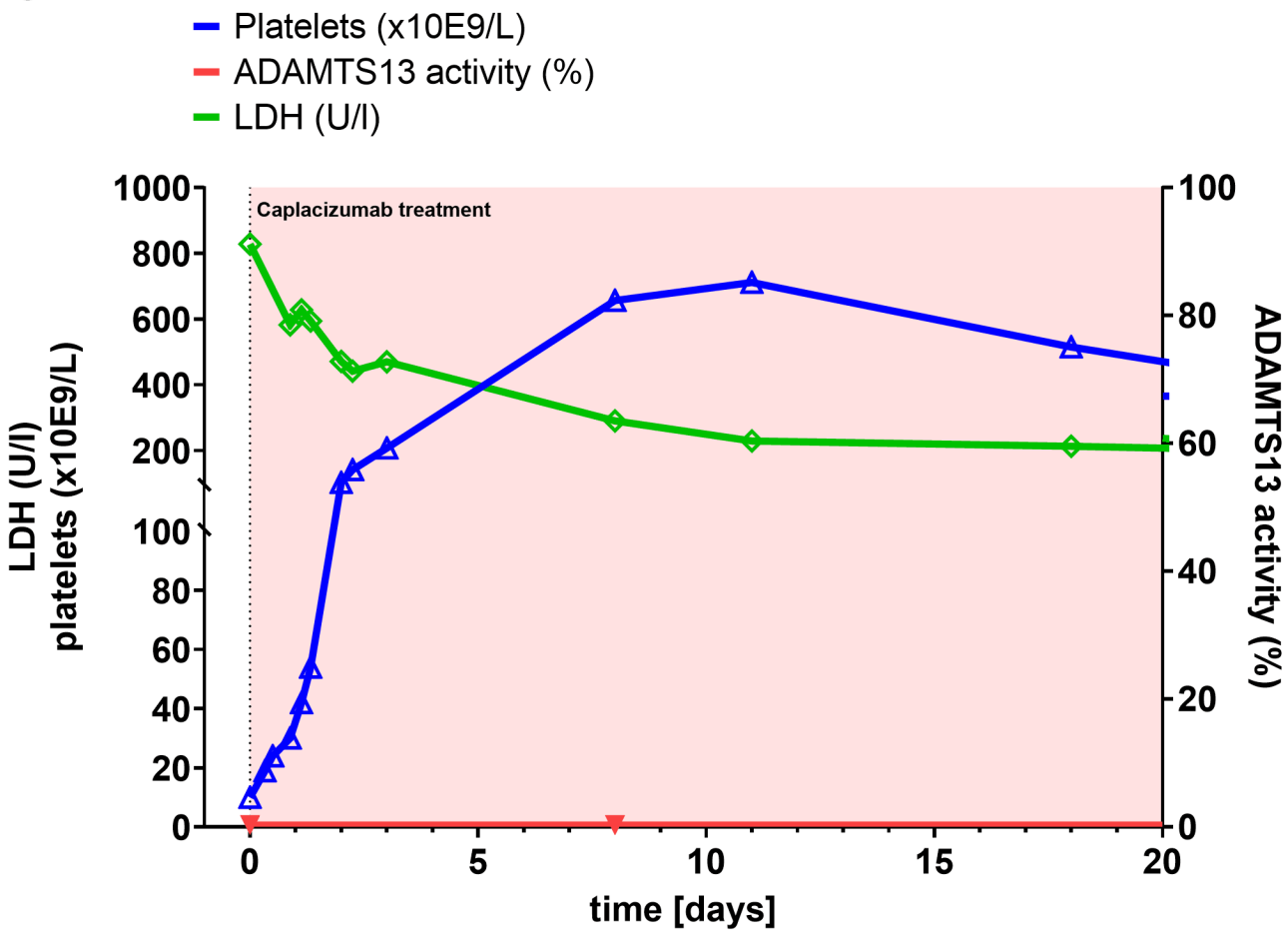
Case Presentation: 46-Year-Old White Female

Clinical symptoms:
known history of iTTP (2002)
Fatigue
Petechiae / hematomas
Gingival bleeding

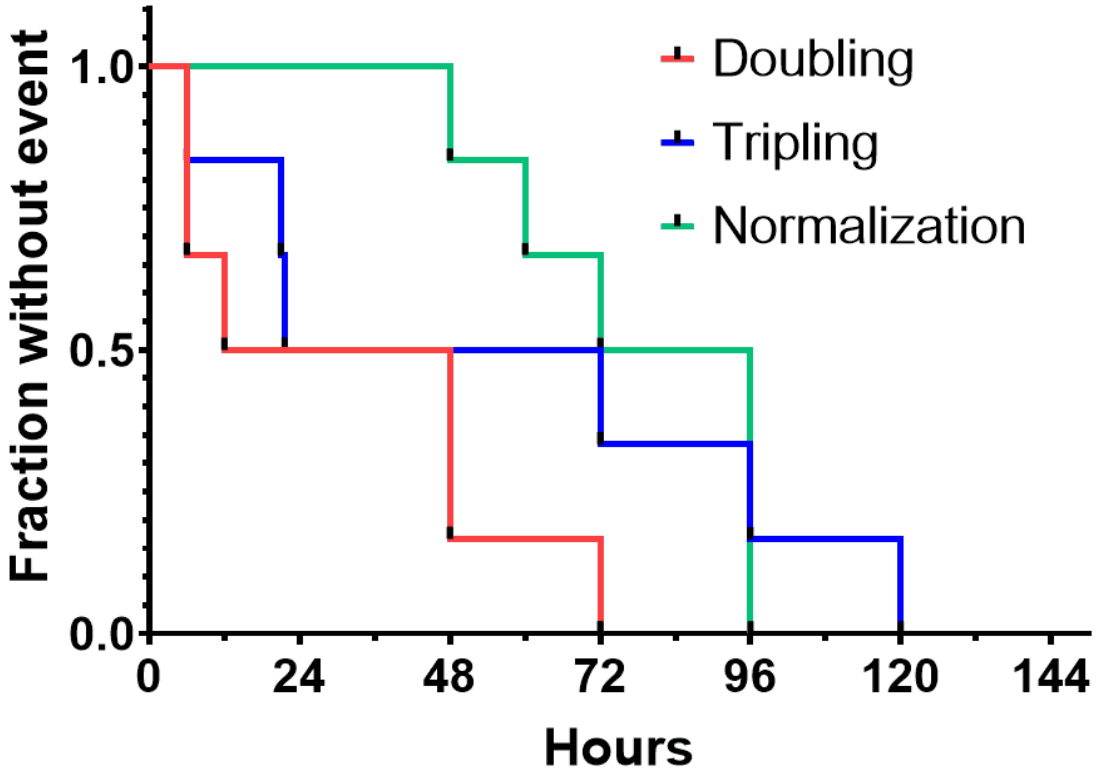
Laboratory findings:	
Creatinine	0.82 mg/dL
Albuminuria	>3.5g/dl creatinine
LDH	828 U/L
Haptoglobin	<0.2 g/L
Hemoglobin	11.3 g/dL
Schistocytes	27/1000 Ery
Platelet count	10×10^9/L

ADAMTS13 activity <0.3%
inhibitory autoantibodies (99 U/ml)

Völker LA et al., J Thromb Haemost 2020 Nov; 18(11): 3061–3066



Völker LA et al., J Thromb Haemost 2020 Nov; 18(11): 3061–3066



Völker LA et al., J Thromb Haemost 2020 Nov; 18(11): 3061–3066

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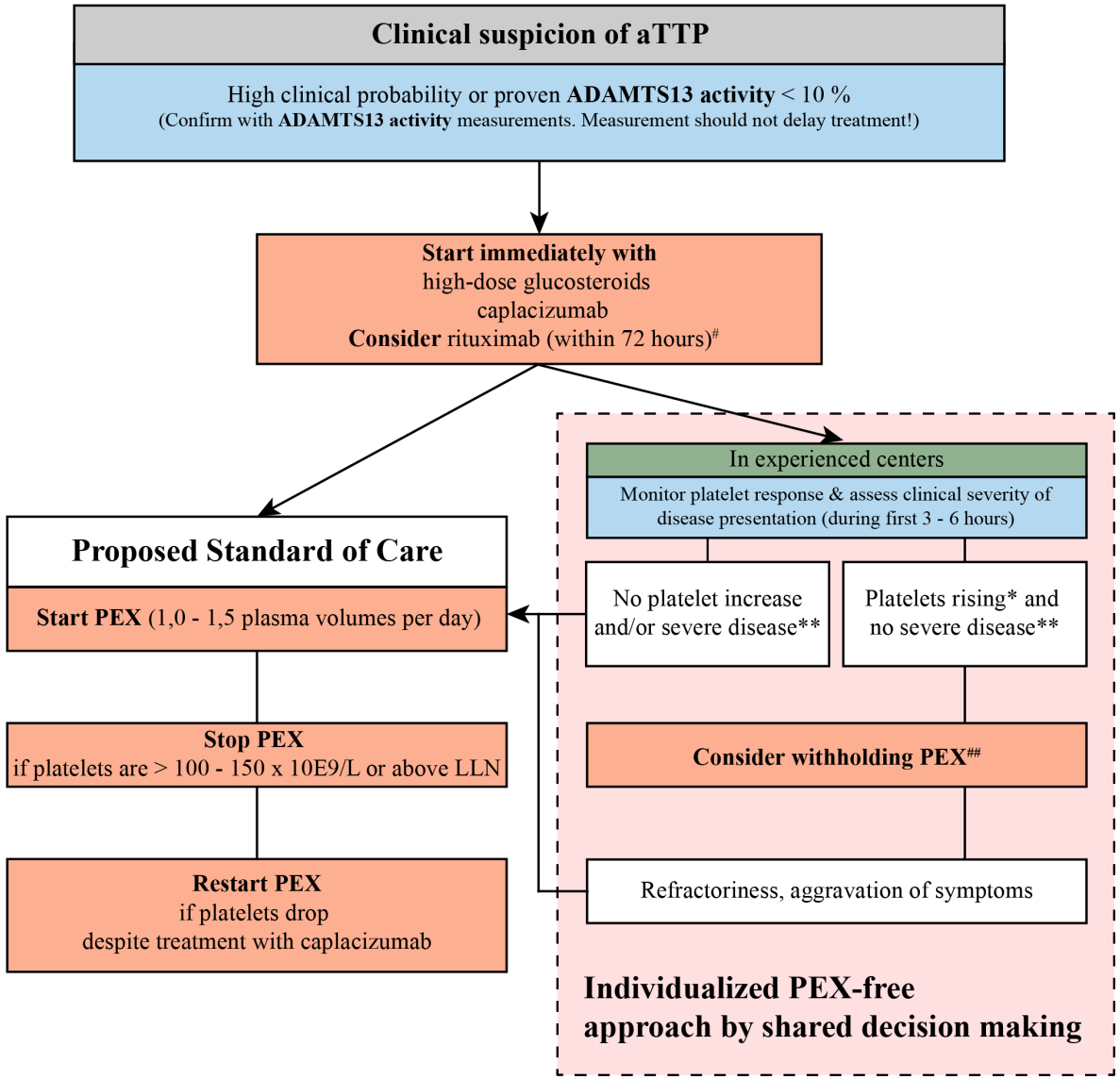
Clinical suspicion of aTTP
High clinical probability or proven ADAMTS13 activity < 10 %
(Confirm with ADAMTS13 activity measurements. Measurement should not delay treatment!)
Start immediately with
high-dose glucosteroids
caplacizumab
Consider rituximab (within 72 hours)#
Proposed Standard of Care
Start PEX (1,0 - 1,5 plasma volumes per day)
Stop PEX
if platelets are > 100 - 150 x 10E9/L or above LLN
Restart PEX
if platelets drop
despite treatment with caplacizumab
In experienced centers
Monitor platelet response & assess clinical severity of disease presentation (during first 3 - 6 hours)
No platelet increase and/or severe disease**
Platelets rising* and no severe disease**
Consider withholding PEX##
Refractoriness, aggravation of symptoms
Individualized PEX-free approach by shared decision making

Discussion