APPENDIX A: Guideline Teams

Panel members

X. Long Zheng, MD, PhD, The University of Kansas Medical Center, USA, *clinical co-chair*
Sara Vesely, PhD, University of Oklahoma Health Sciences Center, USA, *methods co-chair*
Brian Geldziler, PhD, USA, *patient representative*
Julie Valdes, MBS, PharmD, USA, *patient representative*
Spero Cataland, MD, Ohio State University, USA
Paul Coppo, MD, PhD, Saint-Antoine - Hôpital Saint-Antoine, Centre de Référence des Microangiopathies Thrombotiques, Service d'Hématologie, France
Masanori Matsumoto, MD, PhD, Nara Medical University, Japan
Reem Mustafa, MBBS, PhD, MPH, University of Kansas Medical Center, USA
Flora Peyvandi, MD, PhD, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale, Italy
Gail Rock, MD, PhD, Canadian Apheresis Group, Canada
Lene Russell, MD, PhD, Copenhagen University Hospital, Denmark
Rawan Tarawneh, MD, Ohio State University Wexner Medical Center, USA

McMaster Methods Team

Alfonso Iorio, MD, PhD, FRCPC, McMaster University, Canada
Menaka Pai, MD, MSc, FRCPC, McMaster University, Departments of Medicine and Pathology and Molecular Medicine and Hamilton Regional Laboratory Medicine Program, Canada
Samantha Craigie, MSc, McMaster University, Department of Health Research Methods, Evidence, and Impact, Canada
Federico Germini, MD, MSc, McMaster University, Department of Health Research Methods, Evidence, and Impact, Canada
Elisabetta Trinari, MD, McMaster University, Department Health Research Methods, Evidence, and Impact, Canada
Cindy HT Yeung, MSc, University of Waterloo, School of Pharmacy, Canada

Scoping Panel Members

Flora Peyvandi, MD, PhD, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale, Italy, *scoping panel chair*
Spero Cataland, MD, Ohio State University, USA
Paul Coppo, MD, PhD, Saint-Antoine - Hôpital Saint-Antoine, Centre de Référence des Microangiopathies Thrombotiques, Service d'Hématologie, France
Paul Knoebl, MD, Medical University of Vienna, Austria
Johanna Kremer Hovinga, MD, Bern University Hospital & University of Bern, Switzerland
Bernhard Lämmle, MD, Universitätsmedizinder Johannes Gutenberg-Universität Mainz, Germany
Masanori Matsumoto, MD, PhD, Nara Medical University, Japan
Gail Rock, MD, PhD, Canadian Apheresis Group, Canada
J Evan Sadler, MD, PhD, Washington University Medical School, USA
Marie Scully, MD, University College London Hospitals, UK
Karen Vanhoorelbeke, PhD, Laboratory for Thrombosis Research, KU Leuven Campus Kortrijk, Belgium
X. Long Zheng, MD, PhD, The University of Kansas Medical Center, USA

APPENDIX B: Conflict of Interest Framework

1) Financial Interests
    a. Does the proposed panel member receive funding from commercial entities that may influence their judgements about guideline recommendations?
        i. Consider downgrading COI if funding is indirect (e.g., research funding, especially that directed to the individual's institution)
        ii. Consider upgrading COI if there is ownership interest
        iii. Consider downgrading COI if funding is <$5000 USD
        iv. Consider spousal interests as equal to potential panel member interests.
2) Non-financial Interests
    a. Is the proposed panel member involved in research on TTP or other thrombotic microangiopathies?
        i. Consider upgrading COI if entirety of individual's research has been on TTP/TMA
        ii. Consider upgrading COI if the potential panel member has been the primary investigator on studies or trials that may be the subject of guideline recommendations (e.g., high impact clinical studies)
    b. Does the proposed panel member depend on specific practices around TTP/TMA for their income/vocation?
        i. Consider upgrading COI if the proposed member is a director or involved in the management of such a TTP/TMA treatment centre.
        ii. Consider upgrading or downgrading COI based on amount of financial dependence regarding the above.
    c. Consider upgrading if the proposed panel member expresses personal beliefs, previous opinions, advocacy, or employment interests that call into question the individual's ability to participate impartially

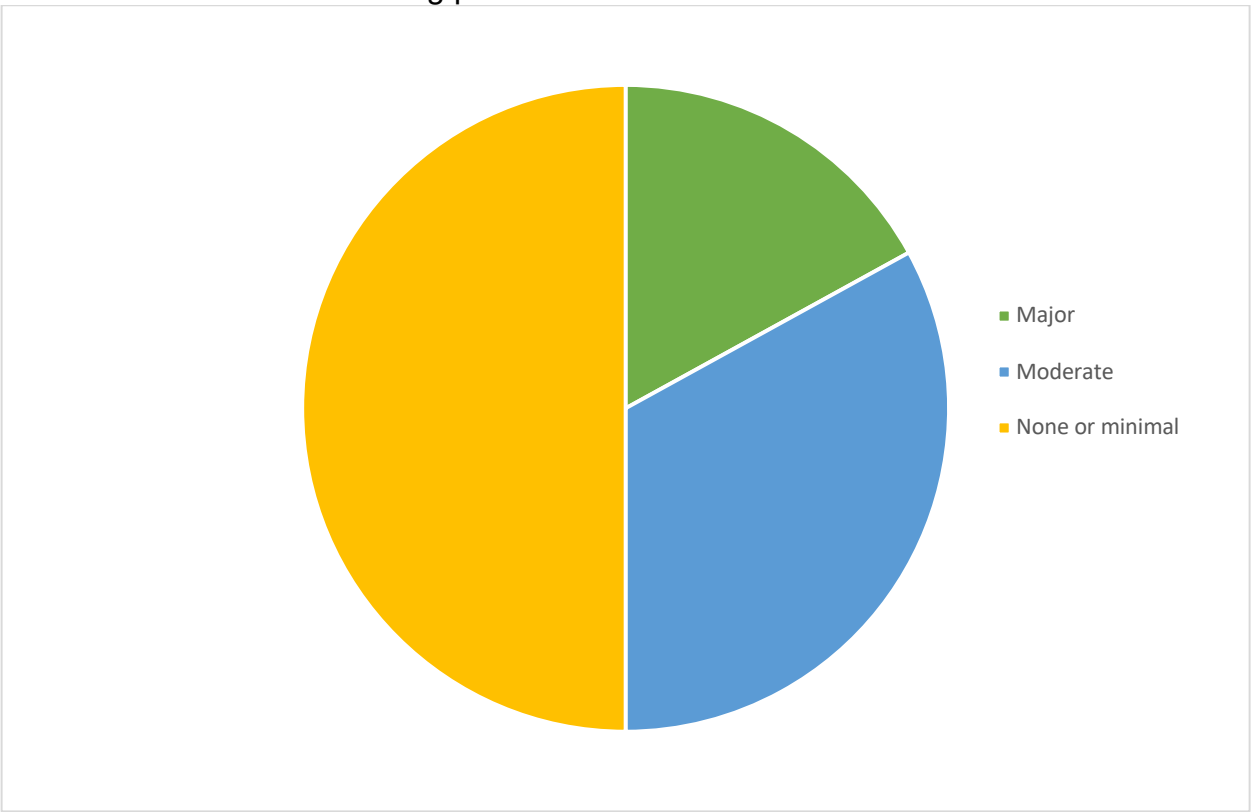
Potential COIs were deemed to be absent / low / moderate / high in each category. (Weighted at 1, 2, 3, and 4 points, respectively.) A summative "score" for overall potential COI was generated for each panel candidate. Scores of 2 or less were marked "none," scores of 3 to 4 were marked "minor," scores of 5 to 6 to 8 were marked "moderate," and scores above 7 were marked "major."

If necessary, panel members were given the opportunity to divest themselves of relevant interest before the first panel meeting.

	Examples	Score
Financial		
None	No conflicts reported	1
Minor	Small amt of fees, industry-funded research	2
Moderate	Multiple speakers' fees and/or honoraria, >$5000	3
Major	Equity or ownership	4
Non-Financial		
None	No conflicts reported	1
Minor	Some research, reviews	2
Moderate	PI on TTP studies; most research conducted in field of TMA, strong published opinions on TMA/TTP	3
Major	PI on relevant high-impact clinical study; director of treatment centre	4

Summative score: financial + non-financial	
1-2	None
3-4	Minor
5-6	Moderate
7-8	Major

Final breakdown of COI among panel members



APPENDIX C: PICO Questions

iTTP, the first event

- Should TPE plus corticosteroids vs. TPE alone be used for patients with iTTP experiencing the first acute event?
- Should rituximab be added or not to TPE and corticosteroids for patients with iTTP experiencing the first acute event?
- Should caplacizumab be used or not for patients with iTTP experiencing the first acute event?

iTTP, the relapse episode

- Should TPE plus steroids vs TPE alone be used for patients with iTTP experiencing a relapse?
- Should rituximab be added to TPE and steroids or not for patients with iTTP experiencing a relapse?
- Should caplacizumab vs. no caplacizumab be used for patients with iTTP experiencing a relapse?

iTTP and cTTP, during remission

- Should rituximab as prophylaxis vs no prophylaxis be used for patients with iTTP in remission?
- Should plasma infusion vs. a watch and wait strategy be used for patients with cTTP in remission?
- Should a factor VIII concentrate infusion vs a watch and wait strategy be used for patients with a cTTP in remission?
- Should plasma infusion vs. a factor VIII concentrate infusion be used for patients with cTTP in remission?

iTTP and cTTP during pregnancy but in remission

- Should prophylactic immunosuppression vs a watch and wait strategy be used for patients with iTTP who are pregnant, having a decreased level of plasma ADAMTS13 but without other signs/symptoms of TMA?
- Should plasma infusion vs a factor VIII concentrate infusion be used for patients with cTTP who are pregnant but in remission?

APPENDIX D: TTP REGISTRIES

Figure D-1: List of TTP Registries contacted

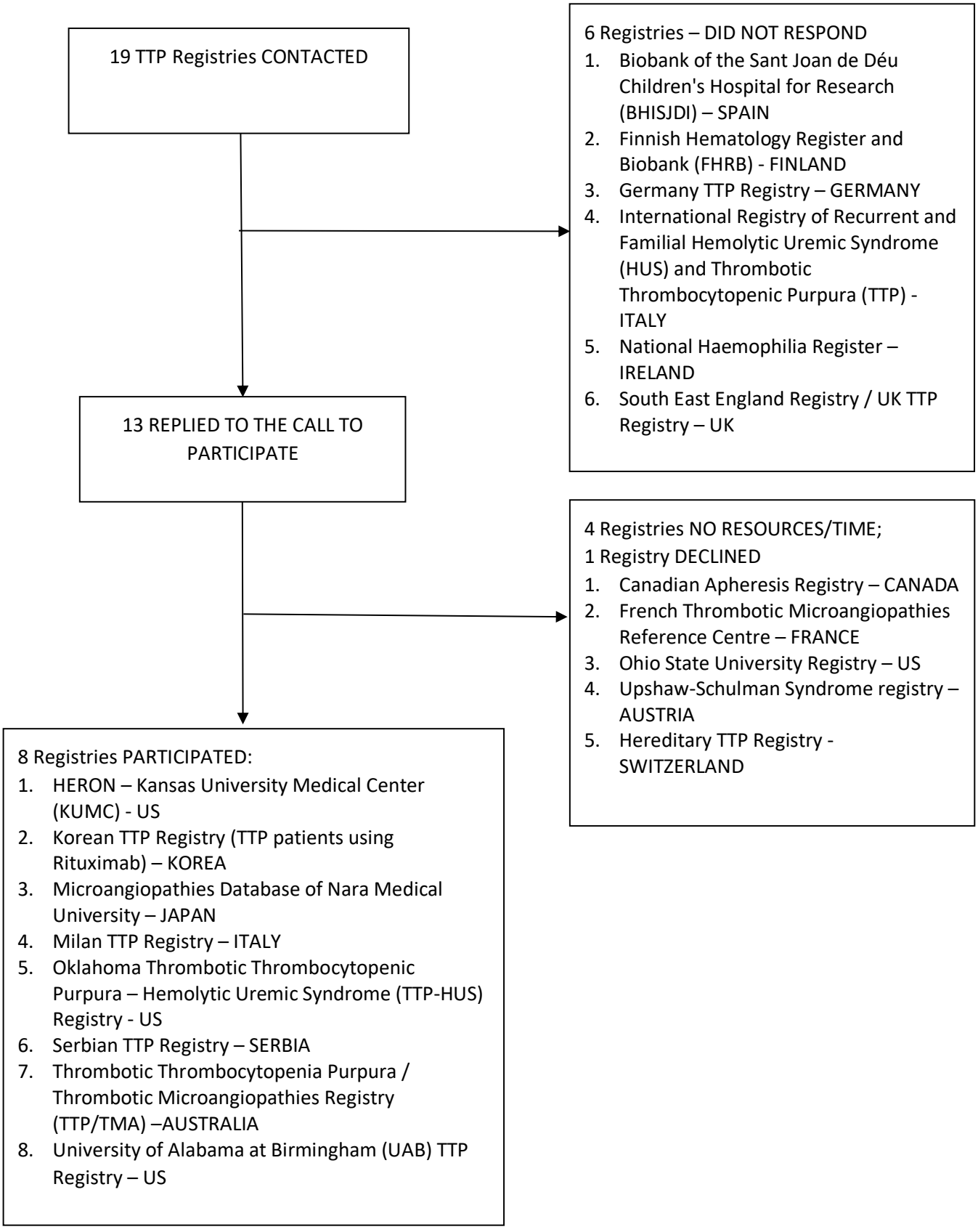


Figure D-2: List of participating registries

Country	Registry	Owner/principal contact	Website
AUSTRALIA	Thrombotic Thrombocytopenia Purpura / Thrombotic Microangiopathies Registry (TTP/TMA)	Erica Wood	https://www.monash.edu/medicine/sphpm/registries/ttp
SERBIA	Serbian TTP Registry (Serbian registry of hemophilia and von Willebrand disease patients)	Danijela Mikovic	http://www.nbti.org.rs/cms/view.phphttps://www.orpha.net/consor/cgi-bin/ResearchTrials_RegistriesMaterials.php?lng=EN&data_id=72221&RegistryMaterialName=Registar-osoba-sa-hemofilijom-i-von-Willebrandovim-
JAPAN	Microangiopathies Database of Nara Medical University	Masanori Matsumoto	http://www.naramed-u.ac.jp/university/english/subjects_and_departments/university_hospital/central_clinical_facilities/department_of_blood_transfusion_medicine.html
KOREA	Korean TTP Registry (TTP patients using rituximab)	Oh Doyeun	
OKLAHOMA (US)	Oklahoma Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome (TTP-HUS) Registry	Sara K. Vesely	https://www.ouhsc.edu/platelets/TMA.htm
ITALY	Milan TTP Registry	Flora Peyvandi	http://rbdd.org/ttp/
ALABAMA (US)	University of Kansas Medical Center – TTP Registry	X. Long Zheng	http://www.kumc.edu/school-of-medicine/pathology/faculty-and-staff/clinical-faculty/x-long-zheng-md-phd.html
KANSAS (US)	HERON – Kansas University Medical Centre	Reem Mustafa	http://www.kumc.edu/miea/medical-informatics/heron.html

APPENDIX E: SEARCH STRATEGIES

E-1: TTP Diagnosis Search Strategy

Database: Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present; Ovid Embase 1974 to 201 Feb 5
Date Searched: February 5, 2019
Records Retrieved: 2024

1. thrombotic thrombocytopenic purpura/
2. thrombotic thrombocytopenic purpura.ti,ab.
3. upshaw-schulman syndrome.mp.
4. moschcowitz disease.mp.
5. Thrombotic Microangiopathies/
6. thrombotic microangiopath*.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. ADAMTS13 Protein/ or (ADAMTS13 or ADAMTS-13).mp.
9. (sensitiv: or predictive value:).mp. or accurac:.tw.
10. thrombotic thrombocytopenic purpura/
11. thrombotic thrombocytopenic purpura.ti,ab.
12. upshaw-schulman syndrome.mp.
13. moschcowitz disease.mp.
14. Thrombotic Microangiopathies/
15. thrombotic microangiopath*.mp.
16. 10 or 11 or 12 or 13 or 14 or 15
17. von Willebrand factor cleaving proteinase/ or von Willebrand factor cleaving proteinase.ti,ab.

18. (adamts-13 or adamts13).ti,ab.
19. sensitiv:.tw. or diagnostic accuracy.sh. or diagnostic.tw.
20. FRETS-VWF73.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
21. (ELISA adj5 assay).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]

22. enzyme-linked immunosorbent assay.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
23. (seldi adj5 assay).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, an, ui, sy]
24. 20 or 21 or 22 or 23
25. 7 and 8 and 9
26. 25 use ppez
27. 17 or 18
28. 16 and 19 and 27
29. 28 use oemezd
30. 26 or 29
31. 8 or 24
32. 7 and 9 and 31
33. 32 use ppez
34. 24 or 27
35. 16 and 19 and 34
36. 35 use oemezd
37. 33 or 36
38. 37 not 30
39. limit 38 to english language

40. limit 39 to humans

E-2: TTP Economics Search Strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date searched: December 21, 2018
Records retrieved: 22

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1 Purpura, Thrombotic Thrombocytopenic/
2 thrombotic thrombocytopenic purpura.ti,ab.
3 upshaw-schulman syndrome.mp.
4 moschcowitz disease.mp.
5 1 or 2 or 3 or 4
6 exp "costs and cost analysis"/
7 costs.tw.
8 cost effective:.tw.
9 6 or 7 or 8
10 5 and 9

E-3: TTP Values and Preferences Search Strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date searched: January 2, 2019
Records retrieved: 129

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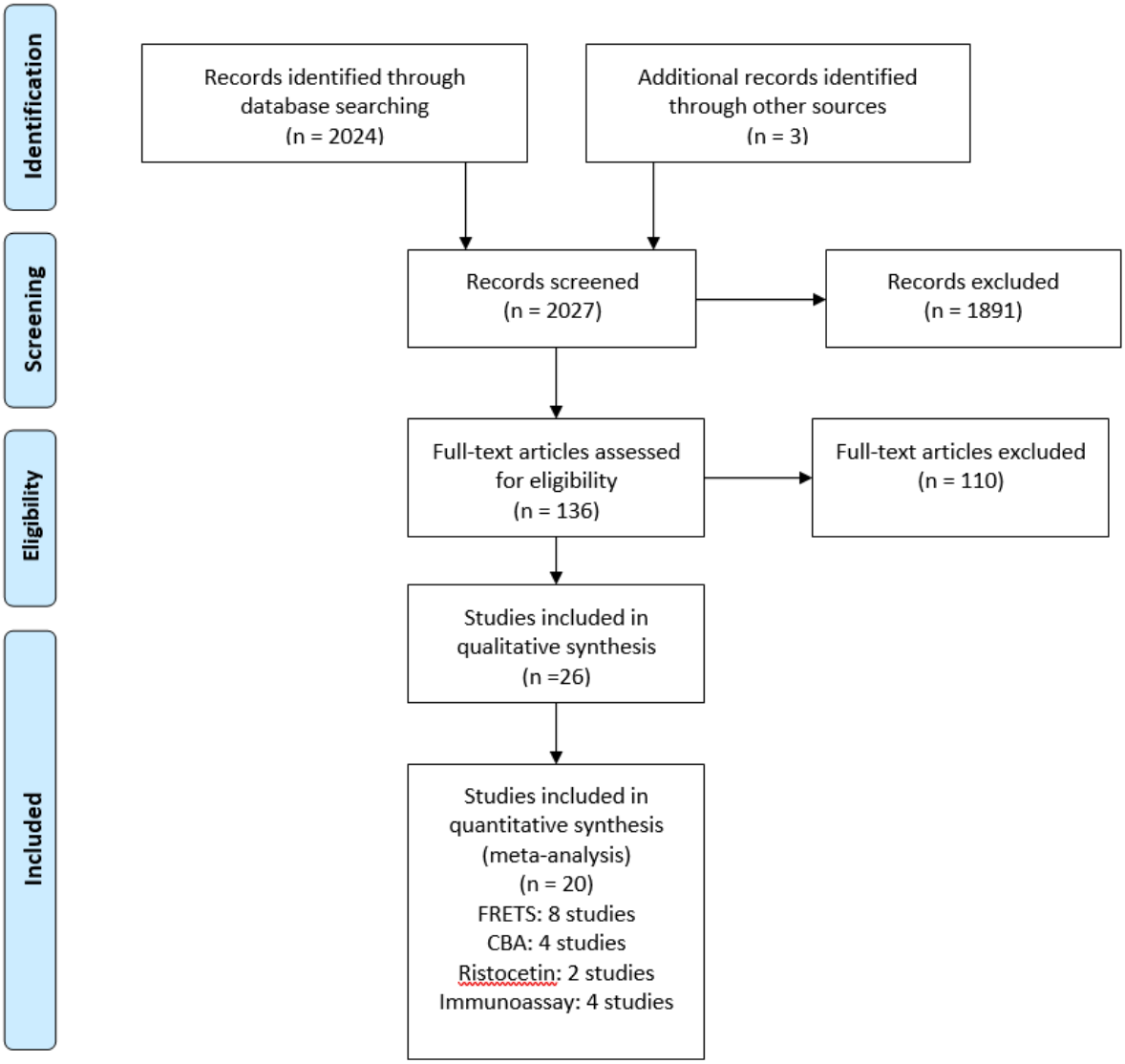
1 exp patient participation/ or exp patient satisfaction/ or exp attitude to health/ or exp "patient acceptance of health care"/ or exp quality-adjusted life years/ or exp decision making/ or exp Health Status Indicators/ or exp decision support techniques/ or exp decision support system/ or exp "Severity of Illness Index"/ or exp decision tree$/
2 (patient$ participation or patient$ satisfaction or attitude to health or patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ acceptance or patient$ perspective$ or patient$ value$ or patient$ utilit$ or health utilit$ or quality of life or quality adjust$ life year$ or qaly$ or health related quality of life or health stat$ utilit$ or health stat$ indicator$ or decision support$ technique$ or decision support$ system$ or decision analys?s or decision mak$ or decision aid$ or decision tree$ or risk$ perception$ or risk$ manag$ or risk$ control$ or risk$ communicat$ or euroqol or EQ5D or EQ-5D or SF-6D or SF6D or SF36 or SF-36 or short$ form$ or QWB or Quality of Well-Being or health utilit$ index or daly$ or disab$ adjust$ life year$ or HYE or healthy-year equivalen$ or standard gambl$ or time trade off or willingness to pay or visual analog scale or VAS or "visual analog$ adj 2 scal$" or probability trade-off or best-worst scaling).mp.
3 (health stat$ adj2 valu$).mp.
4 1 or 2 or 3
5 Purpura, Thrombotic Thrombocytopenic/
6 thrombotic thrombocytopenic purpura.ti,ab.
7 upshaw-schulman syndrome.mp.
8 moschcowitz disease.mp.

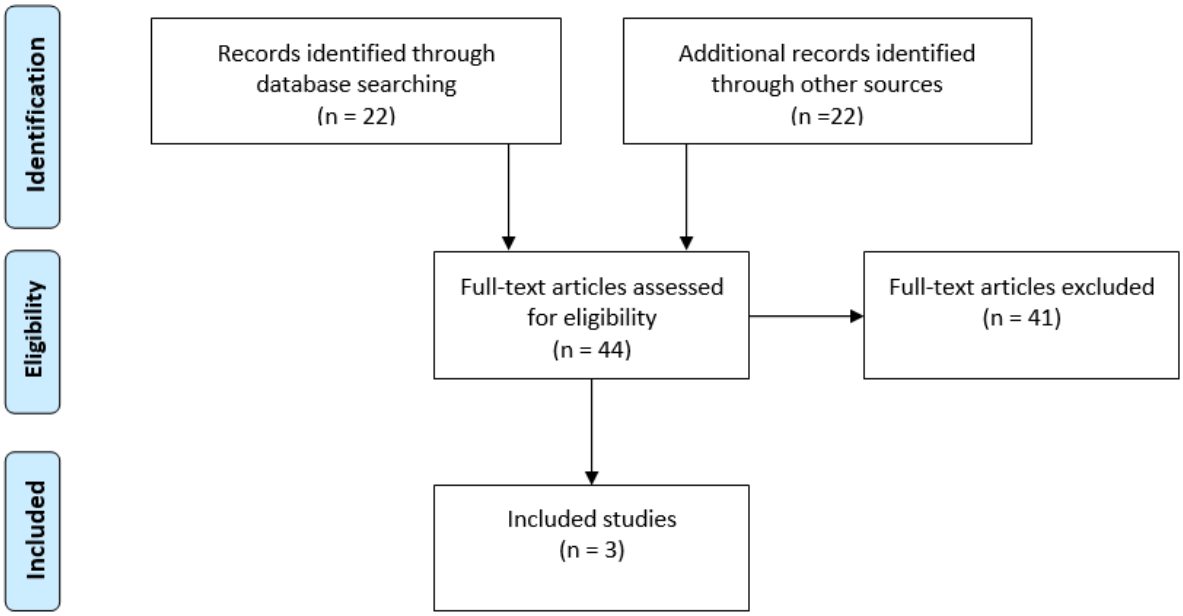
9 5 or 6 or 7 or 8
10 4 and 9

APPENDIX F: PRISMA FLOW DIAGRAMS

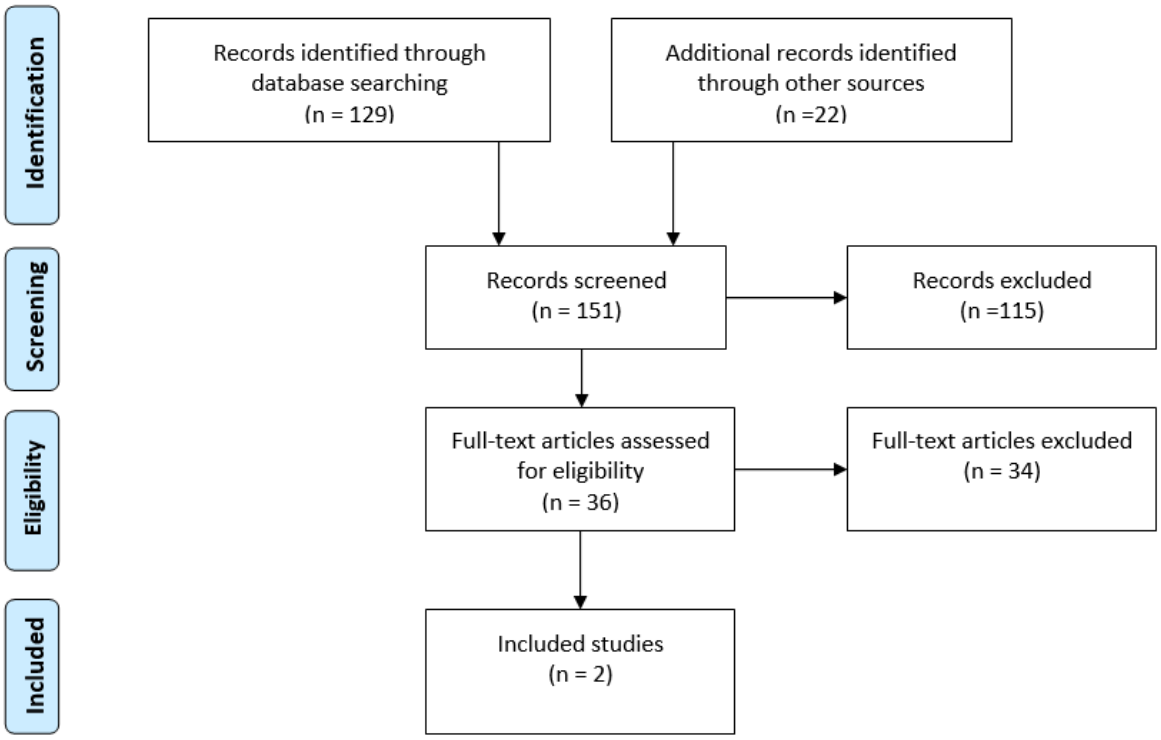
D-1: Diagnosis systematic review



F-2: Economics review



F-3: Values and preferences review



APPENDIX G: Evidence to Decision Tables and Evidence Profiles

G-1. Should TPE + steroids vs. TPE alone be used for patients with immune TTP experiencing a first acute event?

G-1.1 Evidence to Decision Table

Should TPE + steroids vs. TPE alone be used for patients with immune TTP experiencing a first acute event?	
POPULATION:	patients with immune TTP experiencing a first acute event
INTERVENTION:	TPE + steroids
COMPARISON:	TPE alone
MAIN OUTCOMES:	All-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events
SETTING:	Hospital
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Therapeutic plasma exchange (TPE) is the standard of care treatment for patients with immune TTP, reducing mortality from 80-90% to 20% or less. Corticosteroids are routinely used as an adjunct to TPE, based on the autoimmune characteristics of the disease. However, data are lacking for the efficacy of steroids in the treatment of TTP.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of steroids.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See EPs.	Panel suggested patients who received steroids may have had more severe disease. Effect on mortality and platelet count appear large, but given that studies are small, pooled effects appear less large.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See EPs.	Panel suggested patients who received steroids may have had more severe disease. Challenging to determine if outcomes are due to disease or ADEs of therapies.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Very low quality evidence, including registry data.	Heterogeneous evidence in terms of populations studied and interventions used (e.g.. dose, drug). Small studies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No published data on how individuals value the main outcomes of interest. **Panel members ranked the outcomes, from most to least important, as follows:** 1. All-cause mortality 2. All CV events 3. Stroke/TIA/clinically obvious neurologic deficit 4. Platelet count recovery 5. Relapse 6. Time to relapse 7. Acute kidney injury/dialysis 8. Days in hospital or days of TPE 9. Exacerbation 10. Normal ADAMTS13 level **Add ranges in ETD **Suggested considerations from panel members - interviews** Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission.	Panel considered overall ranking as well as range of ranking. The patient point of view was felt to be most important. There was variability around perception of importance for the highest ranked outcomes.n of outcome.

	Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	See EPs.	We do have some data, albeit sparse and very low certainty. Panel commented that expert treaters and non-expert treaters may have different level of comfort with steroids and their adverse effects, and its use in particular patients thought to be more susceptible to adverse effects (e.g., older adults).

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates for costs of TPE** · $1,500 USD per day · 1,750€ per day (Denmark) · 3,000€ per day (France) Panelists noted that in the U.S., costs for TPE (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Some U.S. panelists stated that the average cost per session was slightly lower in their jurisdiction. Panelists noted that in the E.U., costs could be variable. Panelists stated that this treatment was available in large and medium sized hospitals, or available in only a few large, specialized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **TPE complications** · $1800 - $13,500 USD · *EU figures TBD* Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists noted that in the E.U., costs of complications	There is a possibility that we will appreciate savings (less antibody formation, shorter hospitalization, fewer TPE). However this is uncertain, and the savings may be small.

	could range from tens of euros for mild allergic reactions to thousands of euros for severe allergic reactions requiring ICU admission. **Estimates for costs of steroids** · $16.35 CAD daily · $12 USD daily · 26€ to 60€ daily (Denmark) · 11€ daily (France) Panelists noted that in the U.S., costs for steroids (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists noted that in the E.U., costs could be variable. Outpatient treatment would generally cost less. Panelists stated that this treatment was available widely in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Other costs** Patient panelists stated that hematologist and emergency department visits can involve a copay in the U.S. Patient panelists stated that laboratory tests are often fully covered by insurance, regardless of frequency or type of assay, if they go to a preferred laboratory in the U.S.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		We know cost is low. There is a possibility that we will appreciate savings (less antibody formation, shorter hospitalization, fewer TPE). However this is uncertain, and the savings may be small.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical "Pentad") may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often "luck" that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment, Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient's ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between "haves" and "have nots."	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients' and	Physicians may not find steroids acceptable in older patients - but there is scant data on this. The panel suggested that steroids be used with caution in vulnerable populations (e.g., psychiatric comorbidities, hypertension, diabetes mellitus, elderly).

	providers' realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to steroids' acceptability included concerns around long term side effects, however patients acknowledged that the tapering schedule used in TTP minimized exposure to side effects. Threats to TPE's acceptability included concerns around transfusion associated adverse effects, and special considerations for individuals who do not accept blood products (e.g., Jehovah's Witnesses)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A "back to basics" strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

For patients with immune TTP experiencing a first acute event the panel **recommends for** adding steroids to plasmapheresis versus plasmapheresis alone. (Strong recommendation in the context of very low quality evidence.)

Justification

The panel commented that this may fit the first paradigm of making a strong recommendation in the setting of weak evidence – an intervention in a life threatening condition. The panel commented that exceptional patients may be more affected by adverse effects of steroids. DISSENTING COMMENTS: consideration of duration of treatment, and panelists would be more likely to vote for a strong recommendation if shorter duration.

Subgroup considerations

The panel suggested that steroids be used with caution in vulnerable populations (e.g., psychiatric comorbidities, hypertension, diabetes mellitus, elderly).

Implementation considerations

Monitoring and evaluation

Research priorities

The panel felt there is a specific, medium term (5 year) research priority to generate stronger evidence for this PICO question. Consider different methodologies. Consider how to improve existing research programs.

G-1.2. Evidence Profile: TPE plus steroids compared to TPE alone

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with immune TTP experiencing a first* acute event, what is the effect of **TPE plus steroids** compared to **TPE alone** on all-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events?
Setting: Hospital
Bibliography: See reference list below

Summary: Twenty-nine studies included patients with a first acute TTP event. Four studies (Jayabose 2013, Moatti-Cohen 2012, Zheng 2004, Zhou 2016) were comparative studies (case series) including patients in both treatment arms. Six studies included patients who received TPE alone, and 19 studies included patients on TPE plus steroids. One study (Moatti-Cohen) included pregnant patients.
Two of the four comparative studies were not estimable for mortality (Jayabose, Moatti-Cohen) due to zero mortality events in both groups. Pooled results from Zheng and Zhou indicated a lower mortality rate (although the pooled analysis demonstrated inconsistency) in patients using TPE plus steroids compared with TPE alone.
Twenty single-arm observational studies indicated similar rates of mortality between groups.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	TPE plus steroids	TPE alone	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 1 months to 108 months)												
4 [11,15,28,29] (103 patients)	observational studies (comparative)	not serious	serious [b]	not serious	not serious	none	5/63	8/40	OR 0.10 (0.02-0.39)	176 fewer per 1,000 (from 195 fewer to 111 fewer)	⊕◯◯◯ VERY LOW	
15 [1,2,4,5,8,10,12,14,16,17,21,22,24,26,27] (268 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	not serious	not serious	-	none	24/268 Pooled estimate 6% (95% CI 2%-10%)	-	-	-	⊕◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	TPE plus steroids	TPE alone	Relative (95% CI)	Absolute (95% CI)		
5 [13,19,20,23,25] (150 patients)	Observational studies (single arm, TPE alone)	serious [a]	not serious	not serious	-	none	-	13/150 Pooled estimate 7% (95% CI 2%-13%)	-	-	⊕◯◯◯ VERY LOW	
Platelet count recovery (follow up: range 1 months to 12 years) [d]												
3 [11,28,29] (74 patients)	observational studies (comparative)	not serious	serious [b]	not serious	not serious	none	43/48	18/26	OR 10.43 (2.57-42.31)	267 more per 1,000 (from 160 more to 297 more)	⊕◯◯◯ VERY LOW	
11 [1-3,8,10,12,14,16,18,26,27] (158 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	serious [b]	not serious	-	none	128/158 Pooled estimate 85% (95% CI 67%-97%)	-	-	-	⊕◯◯◯ VERY LOW	
3 [19,23,25] (84 patients)	observational studies (single arm, TPE alone)	serious [a]	not serious	not serious	-	none	-	66/84 Pooled estimate 80% (95% CI 70%-88%)	-	-	⊕◯◯◯ VERY LOW	
Normal ADAMTS13 activity levels (follow up: 30 days)												
2 [2,3] (18 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	not serious	not serious	-	none	6/18 Pooled estimate 28% (95% CI 8%-53%)	-	-	-	⊕◯◯◯ VERY LOW	
Exacerbation (follow up: range 1 months to 72 months)												
4 [3,4,22,27] (49 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	not serious	not serious	-	none	11/49 Pooled estimate 22% (95% CI 9%-37%)	-	not estimable	-	⊕◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**TPE plus steroids**	**TPE alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [25] (25 patients)	observational studies (single arm, TPE alone)	serious [a]	-	not serious	-	none	-	13/25 Pooled estimate 52% (95% CI 33%-70%)	-	-	⊕◯◯◯ VERY LOW	
Days in hospital/days of TPE (up to 3.5 years)												
2 [21,24] (76 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	not serious	not serious	-	none	76 patients Mean 18-20 days Range 5-62 days	-	-	-	⊕◯◯◯ VERY LOW	
Relapse (follow up: range 1 months to 12 years)												
2 [11,28] (25 patients)	observational studies (comparative)	not serious	not serious	not serious	not serious	none	2/11	0/14	OR 42.52 (1.72 to 1051.26)	-	⊕⊕◯◯ LOW	
14 [1,4,6,8,12,14,16-18,21,22,24,26,27] (224 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	serious [b]	not serious	-	none	57/224 Pooled estimate 20% (95% CI 9%-32%)	-	-	-	⊕◯◯◯ VERY LOW	
3 [20,23,25] (85 patients)	observational studies (single arm, TPE alone)	serious [a]	serious [b]	not serious	-	none	-	9/85 Pooled estimate 12% (95% CI 0%-53%)	-	-	⊕◯◯◯ VERY LOW	
Time to relapse (follow up: range 1 years to 11 years)												
2 [17,21] (30 patients)†	observational studies (single arm, TPE plus steroids)	serious [a]	not serious	not serious	-	none	30 patients** Median TTR 18 mo to 3.1 y, range 3 mo to 5.9 y.	-	-	-	⊕◯◯◯ VERY LOW	
All CV events – not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**TPE plus steroids**	**TPE alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [12] (5 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	-	not serious	-	-	1/5 Pooled estimate 20% (95% CI 4%-62%)	-	-	-	⨁◯◯◯ VERY LOW	
1 [25] (25 patients)	observational studies (single arm, TPE alone)	serious [a]	-	not serious	-	-	-	1/25 Pooled estimate 4% (95% CI 1%-20%)	-	-	⨁◯◯◯ VERY LOW	
REGISTRY DATA (7 registries)[50,51,52,53,54,55,56]	(single arm, TPE plus steroids)						24/173¥ Range 2.4% - 56.3%					
REGISTRY DATA (3 registries)[50,55,56]	(single arm, TPE alone)							1/11 Range 0%-33.3%				
Stroke/TIA/clinically obvious neurological deficit (follow up: up to 1 month)												
1 [15] (29 patients)	observational studies (comparative)	not serious	-	not serious	not serious	none	1/15§	1/14§	OR 0.93 (0.06 to 15.69)	5 fewer per 1,000 (from 67 fewer to 475 more)	⨁⨁◯◯ LOW	
1 [9] (13 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	-	not serious	-		4/13*** Pooled estimate 31% (95% CI 13%-58%)	-	-	-		
1 [7] (5 patients)	observational studies (single arm, TPE alone)	serious [a]	-	not serious	-		-	2/5 Pooled estimate 40% (95% CI 12%-77%)	-	-		
Acute kidney injury/dialysis (follow-up: unclear)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**TPE plus steroids**	**TPE alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [15] (29 patients)	observational studies (comparative)	serious [e]	-	not serious	not serious	none	1/15‡	0/14‡	OR 6.91 (0.14 to 349.18)	-	⨁◯◯◯ VERY LOW	
1 [25] (18 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	-	not serious	-		5/18 Pooled estimate 28% (95% CI 12%-51%)	-	-	-		
Adverse events (mild to moderate) (follow up: range 1 months to 72 months)												
5 [4,14,22,24,27] (89 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	serious [b]	not serious	-	none	21/89 Pooled estimate 27% (95% CI 0%-79%)	-	-	-	⨁◯◯◯ VERY LOW	
Serious adverse events (follow up: 6 months)												
1 [20] (61 patients)	observational studies (single arm, TPE alone)	serious [a]	-	not serious	-	none	-	0/61 Pooled estimate 0% (95% CI 0%-6%)	-	-	⨁◯◯◯ VERY LOW	
Adverse events (in other non-TTP populations)												
20 [30-49]	Systematic reviews and observational studies	not serious	not serious	serious [e]	not serious	none	TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6% Steroids per patient: 335/867 Range 31%-51%	TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6%	-	-	⨁⨁⨁◯ MODERATE	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	TPE plus steroids	TPE alone	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (in other non-TTP populations)												
20 [30-49]	Systematic reviews and observational studies	not serious	not serious	serious [e]	not serious	none	TPE: 93/373 Range 23.8%-29.6% Steroids: 257/2183 Range 1.8%-37.0%	TPE: 93/373 Range 23.8%-29.6%	-	-	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **OR:** Odds ratio; **TPE**: Plasma exchange; **SD:** Standard deviation; **TIA:** Transient ischemic attack

* Note that majority of study patients experienced a first TTP event, but some studies include up to 20% relapsed patients. Elected not to rate down for indirectness for this alone; studies with over 20% relapsed patients as well as patients with a first event were included in acute event analysis.

** Page reported 9 relapses of 21 patients receiving TPE and steroids with median time to relapse 3.1 y (range 0.4-5.9 y). Scully reported 21 relapses in 38 patients receiving TPE plus steroids with median time to relapse 18 months (range 3 to 60 months).

† 30 patients out of 59 total patients relapsed. The remaining 29 patients were censored.

§ Moatti-Cohen et al 2012 report a series of 29 patients with a first TTP event during pregnancy. 1/15 patients receiving TPE plus steroids and 1/14 patients receiving TPE alone developed "neurologic sequellae".

*** Gasparovic 2001 reports a series of 13 patients with a first TTP event. The nature of neurological events were not specified: “CNS manifestations were confirmed in 11 patients at admission… and two weeks later neurologic lesions were present in four patients.”

‡ Moatti-Cohen et al 2012 report a series of 29 patients with a first TTP event during pregnancy. 1/15 patients receiving TPE plus steroids and 0/14 patients receiving TPE alone developed "renal sequellae".

¥ Data reported in the registry may also have been reported, in whole or in part, in published literature.

Explanations

a. Risk of bias assessed as serious for non-comparative studies, Including case series and single arm studies.
b. Inconsistency considered serious if all three of following criteria are met: confidence intervals minimally overlapping; statistical test for heterogeneity shows a low P value (<0.05); and I^2 is >60%
c. Note that a pooled estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as very

low, due to serious concerns about risk of bias. Therefore, certainty in the body of evidence was not further downgraded for imprecision.
d. The outcome of “platelet count recovery” was, in some cases, taken from a composite outcome of “response/remission” which, along with platelet count recovery, included normal LDH, resolution of neurologic symptoms, and/or normal laboratory values
e. Adverse events and serious adverse events for TPE and for steroids were gathered from larger population studies including Cochrane reviews of uses of these treatments in other (non-TTP) populations. It is expected that adverse events of these treatments will be the same regardless of the indication for treatment.

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G-2. Rituximab + TPE + steroids vs. TPE + steroids for patients with immune TTP experiencing a first acute event?

G-2.1 EVIDENCE TO DECISION TABLE

Should rituximab added to TPE + steroids vs. TPE + steroids be used for patients with immune TTP experiencing a first acute event?	
POPULATION:	patients with immune TTP experiencing a first acute event
INTERVENTION:	rituximab added to TPE + steroids
COMPARISON:	TPE + steroids
MAIN OUTCOMES:	All-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events
SETTING:	Hospital
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Rituximab is an anti-CD20 monoclonal antibody that has had demonstrated effectiveness in other antibody-mediated autoimmune disorders. Rituximab was first introduced in patients with refractory or exacerbated disease, with the aim of suppressing the production of anti-ADAMTS13 antibodies. Recently it has become more common to use rituximab as a first-line therapy, on the basis that it could prevent patients from relapsing.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of rituximab.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See EPs.	Panel comments that intention of rituximab is to prevent relapse (but emphasizes that in this case, we are using it up front, in a first acute event). Many patients with first episode do not go on to relapse. Data on relapse is non-randomized. Some used historical controls. Possible selection bias – is rituximab used in more severe patients?

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See EPs.	Difficult to differentiate disease effects from drug effects. Panel reviewed direct and indirect data.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No published data on how individuals value the main outcomes of interest. **Panel members ranked the outcomes, from most to least important, as follows:** 1. All-cause mortality 2. All CV events 3. Stroke/TIA/clinically obvious neurologic deficit 4. Platelet count recovery 5. Relapse 6. Time to relapse 7. Acute kidney injury/dialysis 8. Days in hospital or days of TPE 9. Exacerbation 10. Normal ADAMTS13 level **Suggested considerations from panel members - interviews** Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Are there data that mortality is lower in recurrent disease? Is there a benefit in waiting to start rituximab, to catch patients with more severe disease and minimize use of rituximab?

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates of rituximab costs** · $2500 - $3000 CAD per dose · $2000 AUD per dose · 5616€ per 2400 mg dose (Denmark) · 4235€ per 2550 mg dose (France) o Truxima (biosimilar) is 47% less expensive (Italian information: 500 Euros for biosimilar) · $2200 - $7000 USD per dose Panelists noted that in the U.S., costs for rituximab (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that rituximab was either available widely, or available in large and medium sized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Estimates for costs of TPE** · $1500 USD per day - machine, nurse · 1750€ per day (Denmark) - machine, nurse	A course of rituximab is 4 doses. Cost is context dependent - costs vary (higher in Asia, lower in Western countries), coverage varies, and that affects access. May save resources through relapse reduction ultimately.

	· 3000€ per day (France) - all in cost Italy 570 Euros Panelists noted that in the U.S., costs for TPE (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Some U.S. panelists stated that the average cost per session was slightly lower in their jurisdiction. Panelists stated that this treatment was available in large and medium sized hospitals, or available in only a few large, specialized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **TPE complications** · $1800 - $13,500 USD · *EU figures TBD* Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. **Estimates for costs of steroids** · $16.35 CAD daily · $12 USD daily · 26€ to 60€ daily (Denmark) · 11€ daily (France) Panelists noted that in the U.S., costs for steroids (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that this treatment was available widely in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		TPE cost - Not well defined, heterogenous in terms of what was included. Variable. Rituximab cost - are we sure about the cost and regional variability? (And variability within countries, such as the U.S.?)Are we sure about the cost of side effect management?

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment, Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient’s ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma	Treatment may be given out of hospital. There are barriers to coming to hospital, creates challenges for patients. May enhance equity through relapse reduction,

	exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between “haves” and “have nots.”	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients’ and providers’ realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to rituximab’s acceptability included concerns about cost and access (which is often limited to individuals with insurance, and individuals under the care of expert healthcare providers with experience giving the drug). Threats to steroids’ acceptability included concerns around long term side effects, however patients acknowledged that the tapering schedule used in TTP minimized exposure to side effects. Threats to TPE’s acceptability included concerns around transfusion associated adverse effects, and special considerations for individuals who do not accept blood products (e.g., Jehovah’s Witnesses)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.**	Insurance varies geographically. Access can be a concern if patients have to come back for infusion.

	A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A “back to basics” strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. · Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For patients with immune TTP experiencing a first acute event the panel **suggests for** adding rituximab to steroids and plasmapheresis versus steroids and plasmapheresis.

Justification

System change is necessary to improve equity.

Subgroup considerations

Data on patients with severe autoimmune disorder are not available. In the absence of evidence, clinicians may consider more strongly the use of rituximab in these patients. Similarly, patients with severe disease may benefit more from rituximab.

Implementation considerations

Non-expert treaters need guidance on cardiovascular involvement and rituximab use. The panel felt that cardiac involvement is not a concern / contraindication (and notes that 50% of patients with TTP have cardiac involvement). They also acknowledge it is difficult to know if cardiac toxicity is from disease or drug.

Monitoring and evaluation

Research priorities

G-2.2 Evidence profile: rituximab plus TPE plus steroids compared to TPE plus steroids

Author(s): McMaster Methodology Team

Date: May 10, 2019
Question: For patients with immune TTP experiencing a first* acute event, what is the effect of **rituximab plus TPE plus steroids** compared to **TPE plus steroids** on all-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events?
Setting: Hospital
Bibliography: See reference List

Summary: Thirty studies included patients receiving rituximab for a first acute event.
Six studies compared patients who had received rituximab to patients receiving TPE plus steroids. One study (Scully) compared patients using rituximab to historic controls not receiving rituximab. One study (McDonald) included pediatric patients. In several studies, rituximab was administered to patients who did not respond to initial therapy with TPE and steroids.

Comparative studies showed no difference in mortality, platelet count recovery, or days in hospital. Fewer relapses were reported in the patients receiving rituximab. Three studies reported time to relapse. 55 out of a total of 147 in these three studies relapsed. All non-relapsing patients were censored. Page 2016 reported 2 relapses in 16 patients receiving rituximab with patients relapsed at 2.5 and 9.9 years, and 9 relapses of 21 patients receiving no rituximab with median time to relapse 3.1 y (range 0.4-5.9 y). Scully 2011 reported 4 relapses in 27 patients receiving rituximab with median time to relapse 27 months (range 17-31 months), and 21 relapses in 38 patients not receiving rituximab with median time to relapse 18 months (range 3 to 60 months). Falter 2018 reported 5 relapses in 17 patients with rituximab who did not reach median TTR at 4000 days (11 y) and 14 of 28 patients relapsing without rituximab with median time to relapse 1337 days (3.7 y).

Fourteen studies included a single group of patients receiving rituximab. Rates of mortality and platelet count recovery were similar to those reported for rituximab in the comparative studies. A lower rate of relapse was noted in the single-arm studies.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	Rituximab plus TPE plus steroids	TPE plus steroids	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 2 weeks to 11 years)												
4 [11,13, 16,17] (167 patients)	observational studies (comparative)	not serious	not serious	not serious	serious [a]	none	5/82 (6%)	5/85 (6%)	OR 1.10 (0.30 to 3.94)	6 more per 1,000 (from 40 fewer to 139 more)	⊕◯◯◯ VERY LOW -	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**Rituximab plus TPE plus steroids**	**TPE plus steroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
10 [1-5, 8-10,12, 20] (113 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	not serious	not serious	-	none	10/113 Pooled estimate 4% (95% CI 0%-11%)	-	-	-	⨁◯◯◯ VERY LOW	
Platelet count recovery – (follow up: up to 142 months)												
1 [11] (7 patients)	observational studies (comparative)	not serious	-	not serious [e]	-	none	6/6 (100%)	1/1 (100%)	Not estimable	-	⨁◯◯◯ VERY LOW	
13 [1,3-6,8-10,12-13,15,18] (129 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	serious [d]	not serious [e]	-	none	115/129 Pooled estimate 86% (95% CI 67%-99%)		-	-	⨁◯◯◯ VERY LOW	
1 [14] (31 patients)	observational studies (single arm, TPE plus steroids)	serious [b]	-	not serious [e]	-	none		31/31 (100%)			⨁◯◯◯ VERY LOW	
Normal ADAMTS13 level (follow up: up to 142 months)												
10 [1,3,6,8-12,15,18] (91 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	not serious	not serious	-	none	81/91 Pooled estimate 94% (95% CI 84%-100%)	-	-	-	⨁◯◯◯ VERY LOW	
Exacerbation (follow up: 30 days)												
2 [1,8] (46 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	not serious	not serious	-	none	3/46 Pooled estimate 6% (95% CI 1%-16%)	-	-	-	⨁◯◯◯ VERY LOW	
Days in hospital/days of TPE (follow up: 3.5 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**Rituximab plus TPE plus steroids**	**TPE plus steroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [16,17] (134 patients)	observational studies (comparative)	not serious	serious [d]	not serious	not serious	none	58 patients Mean 16.5-22.9 days	76 patients Mean 18-20 days	-	MD 0.39 days more (7.82 fewer to 8.60 more)	⨁⨁◯◯ LOW	
Relapse (follow up: range 6 months to 142 months)												
6 [7,11,13,14,16,17] (231 patients)	observational studies (comparative)	not serious	not serious	not serious	not serious	none	16/95 (17%)	53/136 (39%)	OR 0.27 (0.15 to 0.48)	253 fewer per 1,000 (from 317 fewer to 160 fewer)	⨁◯◯◯ VERY LOW	
11 [1-3,5,6,8-10,12,15,16,18,19] (111 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	not serious	not serious	-	none	7/111 Pooled estimate 2% (95% CI 0%-8%)	-	-	--	⨁◯◯◯ VERY LOW	
Time to relapse in months (follow up: up to 11 years)												
3 [7,13,16] (55 patients)†	observational studies (comparative)	not serious	serious [d]	not serious	not serious	none	11 patients Range 17 months to >11 years	44 patients Median 18 months to 3.7 years (range 3 months to 5.9 years)	-	-	⨁⨁◯◯ LOW	
REGISTRY DATA (5 registries) [43,44,46,47,49]	(single arm, rituximab plus TPE and steroids)						(15/127 relapsed patients [43,44,45,46,47,49])¥ Median 6.6-120 months Total range across registries 6.6-120 months					
REGISTRY DATA (6 registries) [43,44,45,46,47,49]	(single arm, TPE and steroids)							(69/283 relapsed patients) Median 1-24 months Total range across registries 1-170 months				

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	Rituximab plus TPE plus steroids	TPE plus steroids	Relative (95% CI)	Absolute (95% CI)		
All CV events (follow up: 2 weeks)												
1 [9] (11 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	-	not serious	-	none	1/11 ** Pooled estimate 9% (95% CI 2%-38%)	-	-	-	⨁◯◯◯ VERY LOW	
REGISTRY DATA (5 registries)[43,44,45,48,49]	(single arm, rituximab plus TPE and steroids)						12/76 Range 0.0% - 63.6%					
REGISTRY DATA (6 registries)[43,44,45,47,48,49]	(single arm, TPE and steroids)							19/117 Range 0.0%-56.3%				
Stroke/TIA/clinically obvious neurological deficit (follow up: 1 years)												
2 [1,16] (64 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	not serious	not serious	-	none	3/64 Pooled estimate 5% (95% CI 0%-12%)	-	-	-	⨁◯◯◯ VERY LOW	
Acute kidney injury / dialysis (follow up: up to 1 year)												
2 [9,16] (55 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	serious [b]	not serious	not serious	-	none	1/55 (1.8%)‡ Pooled estimate 0% (95% CI 0%-5%)	-	-	-	⨁◯◯◯ VERY LOW	
Adverse events (follow up: up to 84 months)												
9 [2,3,5,6,8-10,12,18] (86 patients)	observational studies (single arm, rituximab plus TPE plus steroids)	not serious	serious [d]	not serious	-	none	17/86 Pooled estimate 17% (95% CI 2%-39%)	-	-	-	⨁◯◯◯ VERY LOW	
Adverse events (in other non-TTP populations)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	Rituximab plus TPE plus steroids	TPE plus steroids	Relative (95% CI)	Absolute (95% CI)		
22 [21-42]	Systematic reviews and observational studies	not serious	not serious	serious [f]	not serious	none	Rituximab per patient: 68/69 (98.6%) TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6% Steroids per patient: 335/867 Range 31%-51%	TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6%	-	-	⊕⊕⊕◯ MODERATE	
Serious adverse events (in other non-TTP populations)												
22 [21-42]	Systematic reviews and observational studies	not serious	not serious	serious [f]	not serious	none	Rituximab: 367/1261 Range 13.0%-30.4% TPE: 93/373 Range 23.8%-29.6% Steroids: 257/2183 Range 1.8%-37.0%	TPE: 93/373 Range 23.8%-29.6%	-	-	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **TPE:** Plasma exchange; **TIA:** Transient ischemic attack

* Note that majority of study patients experienced a first TTP event, but some studies include up to 20% relapsed patients. Elected not to rate down for indirectness for this alone; studies with over 20% relapsed patients as well as patients with a first event were included in acute event analysis.

** Jasti et al 2008 reported one myocardial infarction leading to death in a series of 11 patients. This patient is also counted in the outcome “all-cause mortality”.

† 36 out of a total of 114 in these three studies relapsed. All non-relapsing patients were censored. Page reported 2 relapses in 16 patients receiving rituximab with patients relapsed at 2.5 and 9.9 years, and 9 relapses of 21 patients receiving no rituximab with median time to relapse 3.1 y (range 0.4-5.9 y). Scully reported 4 relapses in 27 patients receiving rituximab with median time to relapse 27 months (range 17-31 months), and 21 relapses in 38 patients not receiving rituximab with median time to relapse 18

months (range 3 to 60 months). Falter reported 5 relapses in 17 patients with rituximab who did not reach median TTR at 4000 days (11 y) and 14 of 28 patients relapsing without rituximab with median time to relapse 1337 days (3.7 y).

‡Scully et al 2011 reported no cases of acute anuric/oliguric renal failure in a series of 40 patients. Jasti et al 2008 reported one case of severe renal failure in a series of 11 patients.

¥ Data reported in the registry may also have been reported, in whole or in part, in published literature.

Explanations

a. Rated down for imprecision as confidence interval (CI) crosses clinical decision threshold between recommending and not recommending treatment
b. Risk of bias assessed as serious for non comparative studies, Including case series and single-arm studies
c. Note that a pooled estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as very low, due to serious concerns about risk of bias. Therefore, certainty in the body of evidence was not further downgraded for imprecision
d. Inconsistency considered serious if all three of following criteria are met: confidence intervals minimally overlapping; statistical test for heterogeneity shows a low P value (<0.05); and I^2 is >60%
e. The outcome of “platelet count recovery” was, in some cases, taken from a composite outcome of “response/remission” which, along with platelet count recovery, included normal LDH, resolution of neurologic symptoms, and/or normal laboratory values
f. Adverse events and serious adverse events for TPE and for steroids were gathered from larger population studies including Cochrane reviews of uses of these treatments in other (non-TTP) populations. It is expected that adverse events of these treatments will be the same regardless of the indication for treatment

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G-3. TPE plus steroids vs TPE alone for patients with immune TTP experiencing a relapse

G-3.1. Evidence to Decision Table

Should TPE plus steroids vs. TPE alone be used for patients with immune TTP experiencing a relapse?	
POPULATION:	patients with immune TTP experiencing a relapse
INTERVENTION:	TPE plus steroids
COMPARISON:	TPE alone
MAIN OUTCOMES:	All-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events
SETTING:	Hospital
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Therapeutic plasma exchange (TPE) is the standard of care treatment for patients with immune TTP, reducing mortality from 80-90% to 20% or less. Corticosteroids are routinely used as an adjunct to TPE, based on the autoimmune characteristics of the disease. However, data are lacking for the efficacy of steroids in the treatment of TTP.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of steroids.	Important to clarify use of steroids in this setting - different than acute TTP first event. **Clinicians may have concerns about using steroids again if the patient relapsed after using steroids for first event

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See EPs. Indirect evidence (from first event) informed this decision.	Scant evidence, often single arm. Registry data. Evidence less than in acute first event. Challenging to anticipate prognosis and severity of a relapsed episode.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See EPs. Indirect evidence (from first event) informed this decision.	Patient now being exposed to longer duration of steroids in total. (Versus use just in first event.) Raises increased concerns for ADEs - steroid ADEs more pronounced with multiple courses of high dose, especially with subsequent events. Patients may be less willing to tolerate ADEs with subsequent relapses. With subsequent relapses, can consider ancillary therapies instead of steroids.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No published data on how individuals value the main outcomes of interest. **Panel members ranked the outcomes, from most to least important, as follows:** 1. All-cause mortality 2. All CV events 3. Stroke/TIA/clinically obvious neurologic deficit 4. Platelet count recovery 5. Relapse 6. Time to relapse 7. Acute kidney injury/dialysis 8. Days in hospital or days of TPE 9. Exacerbation 10. Normal ADAMTS13 level **Suggested considerations from panel members - interviews** Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	Text

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates for costs of TPE** · $1500 USD per day · 1750€ per day (Denmark) · 3000€ per day (France) Panelists noted that in the U.S., costs for TPE (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Some U.S. panelists stated that the average cost per session was slightly lower in their jurisdiction. Panelists stated that this treatment was available in large and medium sized hospitals, or available in only a few large, specialized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **TPE complications** · $1800 - $13,500 USD · *EU figures TBD* Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the	

	insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. **Estimates for costs of steroids** · $16.35 CAD daily · $12 USD daily · 26€ to 60€ daily (Denmark) · 11€ daily (France) Panelists noted that in the U.S., costs for steroids (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that this treatment was available widely in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment,	

	Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient's ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between "haves" and "have nots."	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients' and providers' realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to steroids' acceptability included concerns around long term side effects, however patients acknowledged that the tapering schedule used in TTP minimized exposure to side effects.	

	Threats to TPE's acceptability included concerns around transfusion associated adverse effects, and special considerations for individuals who do not accept blood products (e.g., Jehovah's Witnesses)	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A "back to basics" strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**

○	○	○	○	●

CONCLUSIONS

Recommendation

For patients with immune TTP experiencing a relapse the panel **recommends for** adding steroids to plasmapheresis versus plasmapheresis alone. (Text)

Justification

Panel emphasized risk profile / harms of steroids differs with repeated high dose long duration steroids. Pulse steroids used repeatedly (even in short duration) can carry serious ADEs. Panel commented that rituximab can prevent relapses, avoiding this situation. Not all patients in all jurisdictions have access to high level of care, with access to ancillary therapies that prevent relapse / repeated use of steroids. DISSENTING OPINIONS: Repeated steroid use is problematic, and is informing dissent. Concern regarding total lack of direct evidence informing a strong recommendation. However, panel agreed that as there appears to be no difference in mortality between first and relapsed events, the indirect evidence supporting steroid use is perhaps more direct.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

G-3.2. Evidence profile: TPE plus steroids compared to TPE alone in iTTP relapse

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with immune TTP experiencing a relapse, what is the effect of **TPE plus steroids** compared to **TPE alone** on all-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events?
Setting: Hospital
Bibliography: see reference list below

Summary: Four studies with a total of 35 patients included patients experiencing a relapse, all of which also included a separate cohort of patients with first events. One study was a comparative case series (Zheng 2003) and three were single-arm studies including patients receiving TPE plus steroids. No studies were found for patients using TPE alone. No mortality events were observed in any studies. The comparative study included 7 patients receiving TPE and steroids and one patient receiving TPE alone. No patients in this study died. All recovered platelet counts and all but one patient (receiving steroids) relapsed.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision[b]	Other considerations	steroids plus plasma exchange	plasma exchange alone	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 8 months to 33 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision[b]	Other considerations	steroids plus plasma exchange	plasma exchange alone	Relative (95% CI)	Absolute (95% CI)		
1 [3] (8 patients)	Observational studies (comparative)	not serious	-	not serious	-	none	0/7 (0%)	0/1 (0%)	Not estimable	-	⨁⨁◯◯ LOW	
2 (21 patients)	observational studies (single arm, TPE plus steroids	serious [a]	not serious	not serious	not serious	none	0/21 Pooled estimate 0% (95% CI 0%-9%)	-	-	-	⨁◯◯◯ VERY LOW	
Platelet count recovery (follow up: range 30 days to 33 months)												
1 [3] (8 patients)	Observational studies (comparative)	not serious	-	not serious [c]	not serious	none	7/7 (100%)	1/1 (100%)	not estimable	-	⨁⨁◯◯ LOW	
3 [1,2,4] (21 patients)	observational studies (single arm, TPE plus steroids	serious [a]	not serious	not serious [c]	not serious	none	6/13 Pooled estimate 46% (95% CI 18%-75%)	-	-	-	⨁◯◯◯ VERY LOW	
Normal ADAMTS13 activity levels (follow up: 30 days)												
2 [1,2] (13 patients)	observational studies (single arm, TPE plus steroids)	serious [a]	not serious	not serious	not serious	none	2/13 Pooled estimate 15% (95% CI 0%-43%)	-	-	-	⨁◯◯◯ VERY LOW	
Exacerbation (follow up: 30 days)												
1 [1] (6 patients)	observational studies (single arm, TPE plus steroids	serious [a]	-	not serious	-	none	3/6 Pooled estimate 50% (95% CI 19%-81%)	-	-	-	⨁◯◯◯ VERY LOW	
Days in hospital (follow up: 37 days)												
1 [4] (14 patients)	observational studies (single arm, TPE plus steroids	serious [a]	-	not serious	-	none	Median 8 days (range 2-37 days).	-	-	-	⨁◯◯◯ VERY LOW	
Relapse (follow up: range 8 months to 33 months)												
1 [3] (8 patients)	Observational studies (comparative)	not serious	-	not serious	-	none	6/7 (86%)	1/1 (100%)	OR 0.32 (0.00 to 119.52)	Not estimable	⨁⨁◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision[b]**	**Other considerations**	**steroids plus plasma exchange**	**plasma exchange alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [4] (14 patients)	observational studies (single arm, TPE plus steroids	serious [a]	-	not serious	-	none	4/14 Pooled estimate 29% (95% CI 12%-55%)	-	-	-	⨁◯◯◯ VERY LOW	
Time to relapse – not reported in the literature												
REGISTRY DATA (3 registries)[26,27,28]	(single arm, TPE plus steroids)						(33/81 relapsed patients [25,26,27,28]) Median 9-19 months Total range across registries 2-128 months					
REGISTRY DATA (1 registry)[30]	(single arm, TPE alone)							(3/4 relapsed patients) Median 18 months Total range 12-24 months				
All CV events – not reported in the literature												
REGISTRY DATA (5 registries)[25,26,27,28,29]	(single arm, TPE plus steroids)						3/32 Range 0% - 33.3%				-	-
REGISTRY DATA (2 registries)[29,30]	(single arm, TPE alone)							1/6 0%-50.0%				
Stroke/TIA/clinically obvious neurological deficit – not reported in the literature												
REGISTRY DATA (3 registries)[27,28,29]	(single arm, TPE plus steroids)						0/15 0%				-	-
REGISTRY DATA (2 registries)[29,30]	(single arm, TPE alone)							1/6 0%-50.0%				
Acute kidney injury/dialysis – not reported in the literature												
REGISTRY DATA (3 registries)[27,28,29]	(single arm, TPE plus steroids)						0/15 0%				-	-

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision[b]**	**Other considerations**	**steroids plus plasma exchange**	**plasma exchange alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
REGISTRY DATA (2 registries)[29,30]	(single arm, TPE alone)							1/6 0%-50.0%				
Adverse events (follow up not reported)												
1 [4] (14 patients)	observational studies (single arm, TPE plus steroids	serious [a]	-	not serious	-	none	0/14 Pooled estimate 0% (95% CI 0%-22%)	-	-	-	⨁◯◯◯ VERY LOW	
Adverse events (in other non-TTP populations)												
20 [5-24]	Systematic reviews and observational studies	not serious	not serious	serious [d]	not serious	none	TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6% Steroids per patient: 335/867 Range 31%-51%	TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6%	-	-	⨁⨁⨁◯ MODERATE	
Serious adverse events (in other non-TTP populations)												
20 [5-24]	Systematic reviews and observational studies	not serious	not serious	serious [d]	not serious	none	TPE: 93/373 Range 23.8%-29.6% Steroids: 257/2183 Range 1.8%-37.0%	TPE: 93/373 Range 23.8%-29.6%	-	-	⨁⨁⨁◯ MODERATE	

CI: Confidence interval

Explanations

a. Risk of bias assessed as serious for non-comparative studies, Including case series and single arm studies.
b. Note that a pooled estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as very low, due to serious concerns about risk of bias. Therefore, certainty in the body of evidence was not further downgraded for imprecision.
c. The outcome of “platelet count recovery” was, in some cases, taken from a composite outcome of “response/remission” which, along with platelet count recovery, included normal LDH, resolution of neurologic symptoms, and/or normal laboratory values
d. Adverse events and serious adverse events for TPE and for steroids were gathered from larger population studies including Cochrane reviews of uses of these treatments in other (non-TTP) populations. It is expected that adverse events of these treatments will be the same regardless of the indication for treatment.

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G-4. Rituximab added to TPE + steroids vs TPE + steroids for patients with immune TTP experiencing a relapse

G-4.1. EVIDENCE TO DECISION TABLE

Should rituximab added to TPE + steroids vs. TPE + steroids be used for patients with immune TTP experiencing a relapse?	
POPULATION:	patients with immune TTP experiencing a relapse
INTERVENTION:	rituximab added to TPE + steroids
COMPARISON:	TPE + steroids
MAIN OUTCOMES:	All-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events
SETTING:	Hospital
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Rituximab is an anti-CD20 monoclonal antibody that has had demonstrated effectiveness in other antibody-mediated autoimmune disorders. Rituximab was first introduced in patients with refractory or exacerbated disease, with the aim of suppressing the production of anti-ADAMTS13 antibodies.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of rituximab.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		Scant data. Treatment effect mostly on relapse. It seems that if patients relapse once, they tend to relapse again. Indirect data from first event population suggests benefit in preventing relapse.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No published data on how individuals value the main outcomes of interest. **Panel members ranked the outcomes, from most to least important, as follows** 1. All-cause mortality 2. All CV events 3. Stroke/TIA/clinically obvious neurologic deficit 4. Platelet count recovery 5. Relapse 6. Time to relapse 7. Acute kidney injury/dialysis 8. Days in hospital or days of TPE 9. Exacerbation 10. Normal ADAMTS13 level **Suggested considerations from panel members - interviews**	

	Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		In this settingwe are using rituximab in patients who have already relapsed once (eliminates theindividuals who would never relapse, and who perhaps have a different phenotype).

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates of rituximab costs** · $2500 - $3000 CAD per dose · $2000 AUD per dose · 5616€ per 2400 mg dose (Denmark) · 4235€ per 2550 mg dose (France) o Truxima (biosimilar) is 47% less expensive · $2200 - $7000 USD per dose Panelists noted that in the U.S., costs for rituximab (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that rituximab was either available widely, or available in large and medium sized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Estimates for costs of TPE** · $1500 USD per day · 1750€ per day (Denmark) · 3000€ per day (France) Panelists noted that in the U.S., costs for TPE (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Some U.S. panelists stated that the average cost per session was slightly lower in their jurisdiction. Panelists stated that this treatment was available in large and medium sized hospitals, or available in only a few large, specialized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **TPE complications** · $1800 - $13,500 USD · *EU figures TBD* Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. **Estimates for costs of steroids** · $16.35 CAD daily · $12 USD daily	

	· 26€ to 60€ daily (Denmark) · 11€ daily (France) Panelists noted that in the U.S., costs for steroids (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment,	

	Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient's ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between "haves" and "have nots."	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients' and providers' realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to rituximab's acceptability included concerns about cost and access (which is often limited to individuals with insurance, and individuals under the care of expert healthcare providers with experience giving the drug).	

	Threats to steroids' acceptability included concerns around long term side effects, however patients acknowledged that the tapering schedule used in TTP minimized exposure to side effects. Threats to TPE's acceptability included concerns around transfusion associated adverse effects, and special considerations for individuals who do not accept blood products (e.g., Jehovah's Witnesses)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A "back to basics" strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. · Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For patients with immune TTP experiencing a relapse the panel **suggests for** adding rituximab to steroids and plasmapheresis versus steroids and plasmapheresis alone.

Justification

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

G-4.2. Evidence profile

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with immune TTP experiencing a relapse*, what is the effect of **rituximab plus TPE plus steroids** exchange compared to **TPE + steroids** on all-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events
Setting: Hospital
Bibliography: See reference list below

Summary: Twelve studies included patients receiving rituximab for a relapse. Nine of these studies also included a separate cohort of patients having a first event. One study (Uhl) with 29 patients compared relapsing patients receiving rituximab to those not receiving rituximab. This study found no difference in mortality, days in hospital, or relapse rate between patients receiving and not receiving rituximab.
Eleven single-armed studies examined the use of rituximab in patients experiencing relapse. A majority of patients recovered their platelet counts and ADAMTS13 levels. 13% of patients experienced a relapse.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [a]	Other considerations	Rituximab plus TPE plus steroids	TPE plus steroids	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: up to 3.5 years)												
1 [10] (29 patients)	observational studies (comparative)	not serious	not serious	not serious	not serious	none	0/15 (0%)	0/14 (0%)	not estimable	-	⊕⊕◯◯ LOW	
6 [1,2,4,6,7,12] (32 patients)	observational studies (single arm, rituximab plus TPE and steroids)	serious [b]	not serious	not serious	-	none	1/32 Pooled estimate 0% (95% CI 0%-8%)	-	-	-	⊕◯◯◯ VERY LOW	
Platelet count recovery (follow up: up to 21 months) [†]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [a]	**Other considerations**	**Rituximab plus TPE plus steroids**	**TPE plus steroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
7 [2-7,9] (43 patients)	observational studies (single arm, rituximab plus TPE and steroids)	serious [b]	not serious [c]	not serious	-	none	42/43 Pooled estimate 100% (95% CI 95%-100%)	-	-	-	⨁◯◯◯ VERY LOW	
Normal ADAMTS13 – (follow up: range 1 month to 142 months)												
4 [3,6,8,9] (25 patients)	observational studies (single arm, rituximab plus TPE and steroids)	serious [b]	not serious	not serious	-	none	21/25 Pooled estimate 88% (95% CI 69%-99%)	-	-	-	⨁◯◯◯ VERY LOW	
Exacerbation – not reported in the literature												
REGISTRY DATA (4 registries)[36,37,39,40]	(single arm, rituximab plus TPE and steroids)						9/43 Range 0%-36.4%					
REGISTRY DATA (3 registries)[36,38,39]	(single arm, TPE and steroids)							3/12 Range 0%-33.3%				
Days in hospital/days of TPE (follow up: 2 months)												
1 [10] (27 patients)	observational studies (comparative)	not serious	not serious	not serious	not serious	none	14 patients Mean 17.59 (SD 10.19)	13 patients Mean 14.19 (SD 10.64)	-	MD 3.4 days more (4.47 fewer to 11.27 more)	⨁⨁◯◯ LOW	
Relapse (follow up: range 6 months to 13 years)												
1 [10] (21 patients)	observational studies (comparative)	not serious	not serious	not serious	serious [c]	none	3/13	3/8	OR 0.51 (95% CI 0.08-3.42)	141 fewer per 1,000 (from 329 fewer to 297 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [a]	**Other considerations**	**Rituximab plus TPE plus steroids**	**TPE plus steroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
8 [1,3,4,5,6,8,9,11] (74 patients)	observational studies (single arm, rituximab plus TPE and steroids)	serious [b]	not serious	not serious	-	none	8/45 Pooled estimate 13% (95% CI 0%-39%)	-	-	-	⊕◯◯◯ VERY LOW	
Time to relapse - not reported in the literature												
REGISTRY DATA (3 registries)[36,38,40]	(single arm, rituximab plus TPE and steroids)						(16/37 relapsed patients [35,36,37,38,40]) Median 11.2-24 months Total range across registries 3.9-45 months					
REGISTRY DATA (2 registries)[36,38]	(single arm, TPE and steroids)							(26/65 relapsed patients[35,36,38]) Median 14-19 months Total range across registries 2.1-128 months				
All CV events – not reported in the literature												
REGISTRY DATA (5 registries) [35,36,37,39,40]	(single arm, rituximab plus TPE and steroids)						10/44 Range 0% - 40.9%					
REGISTRY DATA (4 registries)[35,36,38,39]	(single arm, TPE and steroids)							2/17 Range 0.0%-33.3%				
Stroke /TIA/clinically obvious neurological deficit - not reported in the literature												
REGISTRY DATA (4 registries)[36,37,39,40]	(single arm, rituximab plus TPE and steroids)						6/43 Range 0% - 22.7%					

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [a]	**Other considerations**	**Rituximab plus TPE plus steroids**	**TPE plus steroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
REGISTRY DATA (3 registries)[36,38,39]	(single arm, TPE and steroids)							0/15 0.0%				
Acute kidney injury/dialysis - not reported in the literature												
REGISTRY DATA (4 registries)[36,37,39,40]	(single arm, rituximab plus TPE and steroids)						8/43 Range 0%-27.3%					
REGISTRY DATA (3 registries)[36,38,39]	(single arm, TPE and steroids)							0/15 0.0%				
Adverse events (follow up: range 6 months to 84 months)												
1 [10] (27 patients)	observational studies (comparative)	not serious	not serious	not serious	serious [d]	none	2/13	0/14	OR 8.67 (0.51 to 146.74)	Not estimable	⨁◯◯◯ VERY LOW	
2 [3,6] (11 patients)	observational studies (single arm, rituximab plus TPE and steroids)	serious [b]	not serious	not serious	-	none	0/11 Pooled estimate 0% (95% CI 0%-17%)	-	-	-	⨁◯◯◯ VERY LOW	
Adverse events (in other non-TTP populations)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [a]	Other considerations	Rituximab plus TPE plus steroids	TPE plus steroids	Relative (95% CI)	Absolute (95% CI)		
22 [13-34]	Systematic reviews and observational studies	not serious	not serious	serious [e]	not serious	none	Rituximab per patient: 68/69 (98.6%) TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6% Steroids per patient: 335/867 Range 31%-51%	TPE per procedure: 18321 procedures (3646 patients treated) Range 3.9%-17% TPE per patient: 55/124 Range 19.5%-60.6%	-	-	⨁⨁⨁◯ MODERATE	
Serious adverse events (in other non-TTP populations)												
22 [13-34]	Systematic reviews and observational studies	not serious	not serious	serious [e]	not serious	none	Rituximab: 367/1261 Range 13.0%-30.4% TPE: 93/373 Range 23.8%-29.6% Steroids: 257/2183 Range 1.8%-37.0%	TPE: 93/373 Range 23.8%-29.6%	-	-	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **TPE:** Plasma exchange; **SD:** Standard deviation;**TIA:** Transient ischemic attack

* Note that majority of study patients experienced a relapse event, but some studies may include up to 20% patients experiencing a first TTP event. Elected not to rate down for indirectness for this alone; studies with over 20% first event patients as well as patients with a relapse were included in acute event analysis.

† The outcome of “platelet count recovery” was, in some cases, taken from a composite outcome of “response/remission” which, along with platelet count recovery, included normal LDH, resolution of neurologic symptoms, and/or normal laboratory values

Explanations

a. Note that a pooled estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as very low, due to serious concerns about risk of bias. Therefore, certainty in the body of evidence was not further downgraded for imprecision
b. Risk of bias assessed as serious for non-comparative studies, including case series and single-arm studies
c. The outcome of “platelet count recovery” was, in some cases, taken from a composite outcome of “response/remission” which, along with platelet count recovery, included normal LDH, resolution of neurologic symptoms, and/or normal laboratory values
d. Rated down for imprecision as confidence interval (CI) crosses clinical decision threshold between recommending and not recommending treatment.
e. Adverse events and serious adverse events for TPE and for steroids were gathered from larger population studies including Cochrane reviews of uses of these treatments in other (non-TTP) populations. It is expected that adverse events of these treatments will be the same regardless of the indication for treatment

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G-5. Caplacizumab vs no caplacizumab for patients with immune TTP experiencing an acute event

G-5.1. Evidence to Decision Table

Should caplacizumab vs. no caplacizumab be used for patients with immune TTP experiencing an acute event?	
POPULATION:	patients with immune TTP experiencing an acute event
INTERVENTION:	caplacizumab
COMPARISON:	no caplacizumab
MAIN OUTCOMES:	All-cause mortality; Platelet count recovery; Exacerbation; Relapse; Days of plasma exchange; All CV events; Stroke/TIA/other neurological outcome; Days in hospital; Relapse at 12 months; Days of TPE; Adverse events; Serious adverse events;
SETTING:	Hospital
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Caplacizumab is a nanobody that targets the A1 domain of VWF, preventing the formation of microthrombotic disease by blocking the interaction of VWF and platelets. The theory behind this approach is that by inhibiting the interaction of VWF and platelets, a more rapid clinical remission could be attained with plasma-based therapy and prevent or minimize acute and chronic complications of TTP.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of the need for synthesized data on the value of caplacizumab.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See EPs. Create additional row for bleeding as an ADE.	Selection bias in study - mortality low in both arms of RCTs, which is not what is seen in TTP overall. Significant effect on exacerbation. Relapse at 12 months is increased. Caplacizumab's mechanism of action is NOT to prevent relapse in the long term - it keeps patients out of an acute event, and if stopped, a large proportion of patients relapse. Caplacizumab does not cure disease – it addresses symptoms. Platelet count goes up while on the drug because consumption goes down, but it doesn't extinguish disease process (immune stimulus).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See EPs. Create additional row for bleeding as an ADE.	Comment on bleeding side effects – the panel felt they are meaningful.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		Outcome certainty ratings are between moderate and high (due to imprecision).

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No published data on how individuals value the main outcomes of interest. **Panel members ranked the outcomes, from most to least important, as follows:** 1. All-cause mortality 2. All CV events 3. Stroke/TIA/clinically obvious neurologic deficit 4. Platelet count recovery 5. Relapse 6. Time to relapse 7. Acute kidney injury/dialysis 8. Days in hospital or days of TPE 9. Exacerbation 10. Normal ADAMTS13 level **Suggested considerations from panel members - interviews**	Noted that exacerbation is rated lower than relapse. Discussion around who finds what outcomes meaningful. Patient panelists focussed on data we currently have.

	Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There are no published data on required resources. Not available in China. Not available in Japan - though trial is planned.	Not widely available. May reduce use of TPE (though not sure that is the correct strategy when using this drug). Likely will not dramatically reduce cost.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment,	No biosimilar exists. At time of panel meeting, 8 countries have approved drug. As a subcutaneous drug, needs no special infrastructure to administer.

	Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient's ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between "haves" and "have nots."	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients' and providers' realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. *** Add threats to caplacizumab's acceptability Threats to steroids' acceptability included concerns around long term side effects, however patients acknowledged that the tapering schedule used in TTP minimized exposure to side effects.	Administered at home - self injection. Study was done with a home nurse and then with self injection. Panel mentioned some patients didn't want to self inject.

	Threats to TPE's acceptability included concerns around transfusion associated adverse effects, and special considerations for individuals who do not accept blood products (e.g., Jehovah's Witnesses)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A "back to basics" strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	Administered at home - self injection. No noted problems with feasibility. Easy to implement - but requires teaching to patient. Drug is still not available in many countries.

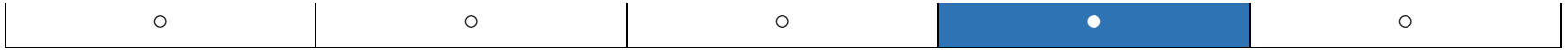
SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention



CONCLUSIONS

Recommendation

For patients with immune TTP experiencing an acute event (first event or relapsed) the panel **suggests for** using caplacizumab versus no caplacizumab.

Justification

Subgroup considerations

Implementation considerations

Patients must be managed differently when on this drug. We are seeing more relapses with caplacizumab, which requires us to ask how to protect against those relapses. While you're on caplacizumab, you must give ancillary therapies, as the drug normalizes the platelet count without TPE until rituximab kicks in. This is a major change in treatment paradigm; previously we used TPE + steroids, and endpoints were platelet count and LD. In this study, we see a new treatment paradigm, where the drug prevents exacerbation until ADAMTS13 level recovers. Caplacizumab should be used by experienced treaters who know how to start the drug, when to stop it, and when to stop other therapies.

Monitoring and evaluation

The use of this drug in the absence of immunosuppressive treatment is not believed to be appropriate. The optimal use of this drug with ADAMTS13 monitoring and ancillary therapies needs to be further investigated.

Research priorities

The clinical and research community needs to come together to create a management pathway, and a consensus statement on the detailed use of this drug with other treatments.

G-5.2. Evidence Profile: caplacizumab compared to no caplacizumab

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with immune TTP experiencing an acute event, what is the effect of **caplacizumab** compared to **no caplacizumab** on all-cause mortality, platelet count recovery, normal ADAMTS13 level, exacerbation, days in hospital/days of TPE, relapse, time to relapse, all CV events, stroke/TIA/clinically obvious neurological deficit, acute kidney injury/dialysis, adverse events?[c]
Setting: Hospital
Bibliography: see reference list below

Summary: Data from two randomized trials informed this question. In both trials, patients were treated with caplacizumab or placebo from beginning of TTP treatment to 28-30 days after finishing TPE treatment, then followed for an additional 30 days after ending caplacizumab/placebo treatment. One study additionally followed patients for 12 months post treatment (Peyvandi 2016). Pooled results showed no difference between caplacizumab and placebo groups for all-cause mortality and platelet count recovery at 28-30 days post treatment. Patients treated with placebo were more likely to experience an exacerbation (defined as a TTP recurrence up to 30 days after cessation of TPE), but patients treated with caplacizumab were more likely to relapse within 28-30 days after stopping caplacizumab. Patients treated with caplacizumab were also more likely to experience a relapse at 12 months.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Caplacizumab	No caplacizumab	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: 28-30 days post treatment)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Caplacizumab	No caplacizumab	Relative (95% CI)	Absolute (95% CI)		
2 [1,3]	randomized trials	not serious	not serious	not serious	not serious [b]	none	1/108 (0.9%)	5/112 (4.5%)	OR 0.27 (0.05 to 1.34)	**32 fewer per 1,000 (from 42 fewer to 14 more)**	⨁⨁⨁⨁ HIGH	
Platelet count recovery (follow up: 28-30 days post treatment)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [a]	none	96/108 (88.9%)	92/112 (82.1%)	OR 1.71 (0.80 to 3.63)	**66 more per 1,000** (from 35 fewer to 122 more)	⨁⨁⨁◯ MODERATE	
Normal ADAMTS13 level after plasmapheresis complete – not reported in the literature												
REGISTRY DATA (1 registry)[c]	(single arm, adding caplacizumab) 1st event [5]						3/6 50.0%					
REGISTRY DATA (3 registries)[c]	(single arm, any other therapy) 1st event [4,5,6]							44/57 Range 62.5%-100.0%				
	(single arm, any other therapy) Relapse [4,5,6]							24/28 Range 81.8%-100.0%				
Exacerbation[d] (follow up: 28-30 days post treatment)												
2 [1,3]	randomized trials	not serious	not serious	not serious	not serious [b]	none	6/108 (5.6%)	39/112 (34.8%)	OR 0.17 (0.09 to 0.32)	**265 fewer per 1,000** (from 302 fewer to 202 fewer)	⨁⨁⨁⨁ HIGH	
Relapse[d] (follow **up: 28-30 days post treatment)**												
2 [1,3]	randomized trials	not serious	not serious	not serious	not serious [b]	none	14/108 (13.0%)	0/112 (0.0%)	OR 9.08 (3.06 to 26.89)	**Not estimable**	⨁⨁⨁⨁ HIGH	
Relapse (follow up: 1-12 months)												
1 [1]	Randomized trial	serious [e]	not serious	not serious	not serious [b]	none	11/36 (30.6%)	3/37 (8.1%)	OR 4.17 (1.31 to 13.27)	**188 more per 1,000** (from 23 more to 458 more)	⨁⨁⨁◯ MODERATE	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Caplacizumab	No caplacizumab	Relative (95% CI)	Absolute (95% CI)		
Time to relapse – not reported in the literature												
REGISTRY DATA (1 registry)[c]	(single arm, adding caplacizumab) 1st event [5]						(1/6 relapsed patients) Median 39.4 months					
REGISTRY DATA (3 registries)[c]	(single arm, any other therapy) 1st event [5,6]							(46/266 relapsed patients [4,5,6]) Median 19.8-24 months Total range across registries 2.3-120 months				
	(single arm, any other therapy) Relapse [5,6]							(42/98 relapsed patients [4,5,6]) Median 1-13.3 months Total range across registries 0-128.1 months				
Days in hospital (follow up: 28-30 days post treatment)												
1 [3]	randomized trials	not serious	not serious	not serious	not serious [b]	none	72	73	-	MD **4.5 lower** (7.32 lower to 1.68 lower)	⨁⨁⨁⨁ HIGH	
Days of plasma exchange (follow up: 28-30 days post treatment)												
2 [1,2]	randomized trials	not serious	not serious	not serious	not serious [b]	none	108	112	-	MD **3.69 lower** (5.35 lower to 2.02 lower)	⨁⨁⨁⨁ HIGH	
All CV events (follow up: 28-30 days post treatment)												
2 [2,3]	randomized trials	not serious	not serious	not serious	serious [a]	none	4/106 (3.8%)	3/110 (2.7%)	OR 1.39 (0.31 to 6.23)	**10 more per 1,000** (from 19 fewer to 121 more)	⨁⨁⨁◯ MODERATE	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Caplacizumab**	**No caplacizumab**	**Relative (95% CI)**	**Absolute (95% CI)**		
Stroke/TIA/clinically obvious neurological deficit (follow up: 28-30 days post treatment)												
2 [2,3]	randomized trials	not serious	not serious	not serious	serious [a]	none	3/106 (2.8%)	4/110 (3.6%)	OR 0.77 (0.17 to 3.47)	**8 fewer per 1,000** (from 30 fewer to 79 more)	⨁⨁⨁◯ MODERATE	
Acute kidney injury/dialysis – not reported in the literature												
REGISTRY DATA (1 registry)[c]	(single arm, adding caplacizumab) 1st event [5]						0/5 0.0%	-	-	-	-	-
REGISTRY DATA (3 registries)[c]	(single arm, any other therapy) 1st event [4,5,6]							11/86 Range 6.7%-25.0%				
	(single arm, any other therapy) Relapse [4,5,6]							2/30 0.0%-12.5%				
Adverse events (follow up: 28-30 days post treatment)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [a]	none	102/106 (93.6%)	102/106 (96.2%)	OR 1.73 (0.51 to 5.84)	**26 more per 1,000** (from 54 fewer to 52 more)	⨁⨁⨁◯ MODERATE	
Serious adverse events (follow up: 28-30 days post treatment)												
2 [1,3]	randomized trials	not serious	not serious	not serious	not serious [b]	none	36/106 (34%)	24/110 (21.8%)	OR 1.84 (1.01 to 3.34)	**121 more per 1,000** (from 2 more to 264 more)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Rated down for imprecision as confidence interval (CI) crosses clinical decision threshold between recommending and not recommending treatment.

b. Not rated down for imprecision. Small numbers of events and patients raises concerns that optimal information size (OIS) has not been achieved; however, absolute difference is considered potentially meaningful to patients and providers.
c. Panel originally sought to explore effect of caplacizumab in both first acute event and subsequent acute events; however, published data did not differentiate between these types of events. Data from registries did, in some cases, differentiate between these types of events, and are reported here where applicable.
d. *Recurrence* was defined as a new decrease in the platelet count that necessitated reinitiation of plasma exchange after normalization of the platelet count had occurred. *Exacerbation* was defined as a recurrence that occurred within 30 days after the last plasma exchange. *Relapse* was defined as a recurrence that occurred more than 30 days after cessation of plasma exchange. In both trials, all recurrences in placebo group occurred within 30 days after end of daily plasma exchange, and thus met the definition of exacerbation and not relapse.
e. Peyvandi 2016 was, by necessity, single blinded. Investigators were made aware of patient assignments to caplacizumab or no caplacizumab.

References

1. Peyvandi, F,Scully, M, Kremer Hovinga JA, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. NEJM 2016; 374(6): 511-522.
2. Peyvandi, F, Scully, M, Kremer Hovinga JA, et al. Caplacizumab reduces the frequency of major thromboembolic events, exacerbations, and death in patients with acquired thrombotic thrombocytopenic purpura. J Thromb Haemost 2017; 15:1448-1452.
3. Scully, M, Cataland, SR, Peyvandi, F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. NEJM 2019; 380(4):335-346

References for REGISTRY DATA:

4. Korea
5. Italy
6. Kansas (US)

G-6. Rituximab as prophylaxis vs no prophylaxis for patients with immune TTP currently in remission

G-6.1. EVIDENCE TO DECISION TABLE

Should rituximab as prophlaxis vs. no prophylaxis be used for patients with immune TTP currently in remission?	
POPULATION:	patients with immune TTP currently in remission
INTERVENTION:	rituximab as prophlaxis
COMPARISON:	no prophylaxis
MAIN OUTCOMES:	All-cause mortality, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, adverse events, quality of life, psychological state
SETTING:	Hospital, outpatient
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Rituximab has been used as prophylaxis during remission in patients with a history of TTP and deficient ADAMTS13 activity while in remission. The rationale for the treatment is that improvement in ADAMTS13 activity will prevent a relapse.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of prophylactic rituximab.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	See EPs.	Data from EPs and registries, indirect studies. Historical data - unclear if these are first remissions or subsequent remissions. Panel decided mortality was most important outcome.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	See EPs.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No published data on how individuals value the main outcomes of interest. **Panel members ranked the outcomes, from most to least important, as follows:** 1. Quality of life 2. All-cause mortality 3. Neurocognitive function and neurological deficits 4. Time to relapse 5. Psychological state 6. Relapse 7. Cardiovascular dysfunction 8. Days in hospital or days of TPE 9. Chronic kidney disease/dialysis 10. Live births (for pregnant patients) **Suggested considerations from panel members - interviews**	

	Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	3 of 4 studies gave rituximab in patients with low ADAMTS13. ** QUESTION MODIFICATION - prophylaxis in P (patients with low ADAMTS13)	Not useful to introduce rituximab in patients unless undetectable ADAMTS13. Data we pulled are mixed.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates of rituximab costs** · $2500 - $3000 CAD per dose · $2000 AUD per dose · 5616€ per 2400 mg dose (Denmark) · 4235€ per 2550 mg dose (France) o Truxima (biosimilar) is 47% less expensive · $2200 - $7000 USD per dose Panelists noted that in the U.S., costs for rituximab (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that rituximab was either available widely, or available in large and medium sized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction.	Societal costs not key here. This treatment creates individual costs. These patients are well, not all of them relapse. Cost incurred by testing / monitoring.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment,	

	Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient's ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between "haves" and "have nots."	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients' and providers' realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to rituximab's acceptability included concerns about cost and access (which is often limited to individuals with insurance, and individuals under the care of expert healthcare providers with experience giving the drug).	Need to factor in the time/resources needed for regular monitoring. Not all patients would want this treatment.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A “back to basics” strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. · Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	Need to factor in the time/resources needed for regular monitoring. Is it feasible to find the low ADAMTS13 and then give rituximab to all of these people? Some people are getting rituximab (too frequently) without ADAMTS13 monitoring - not data driven dosing – so is there possible overuse?

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For patients with immune TTP who are in remission *WITH LOW ADAMTS13* the panel **suggests for** using rituximab as prophylaxis versus no prophylaxis.

Justification

Subgroup considerations

We could not find data that differentiated initial and subsequent remissions - these patients may or may not be different.

Implementation considerations

Monitoring and evaluation

Research priorities

Need to understand how and how frequently people monitor.

G-6.2. Evidence Profile: Rituximab as prophylaxis compared to no prophylaxis

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with immune TTP currently in remission, what is the effect of **rituximab as prophylaxis** compared to **no prophylaxis** on all-cause mortality, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, adverse events, quality of life, psychological state?
Setting: Hospital, outpatient
Bibliography: See reference list below

Summary: Four studies informed the question of the use of rituximab as prophylaxis in patients with TTP in remission. All studies were observational cohort or case series. No RCTs were found to inform this question. Jestin, Westwood, and Bresin included patients with low ADAMTS13 levels. Fakhouri included 5 patients, 1 of whom had low ADAMTS13 levels, and the other 4 not reported.
One study (Jestin) was a comparative observational study with 115 patients comparing prophylactic rituximab to no rituximab. This study found fewer relapses in the patients using rituximab (OR 0.05, 95% CI 0.02-0.15) and no difference in mortality (OR 0.15, 95% CI 0.01-1.75). The median time to relapse in was much shorter in patients not receiving rituximab (median 2.7 years vs >11 years with rituximab).
Three single-arm observational studies with 54 patients receiving prophylactic rituximab saw no deaths and a pooled relapse rate of 2% (3 relapses in 54 patients).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab as prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: median 14-38 months)												
1[1] (115 patients)	observational study (comparative)	not serious	-	not serious	serious	none	2/92 (2%)	2/23 (9%)	OR 0.15 (0.01 to 1.75)	73 fewer per 1,000 (from 86 fewer to 56 more)	⊕◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rituximab as prophylaxis**	**no prophylaxis**	**Relative (95% CI)**	**Absolute (95% CI)**		
3[2-4] (54 patients)	observational study (single arm, rituximab prophylaxis only)	serious [a]	not serious	not serious	-	none	0/54 Pooled estimate: 0% (95% CI 0%-1%)	-	-	-	⨁◯◯◯ VERY LOW	
Relapse (follow up: range 6 months to 89 months)												
1[1] (115 patients)	observational study (comparative)	not serious	-	not serious	not serious	none	14/92 (15%)	17/23 (74%)	OR 0.05 (0.02 to 0.15)	615 fewer per 1,000 (from 686 fewer to 441 fewer)	⨁⨁◯◯ LOW	
3[2-4] (54 patients)	observational study (single arm, rituximab prophylaxis only)	serious [a]	not serious	not serious	-	none	3/54 Pooled estimate: 2% (95% CI 0%-10%)	-	-	-	⨁◯◯◯ VERY LOW	
Time to relapse (follow up: up to 89 months)												
1[1] (31 patients)*	observational study (comparative)	not serious	-	not serious	not serious	none	Median >11 years	Median 2.7 years	-	-	⨁⨁◯◯ LOW	
1[4] (1 patient)**	observational study (single arm, rituximab prophylaxis only)	serious [a]	-	not serious	-	none	1 patient 24 months	-	-	-	⨁◯◯◯ VERY LOW	
REGISTRY DATA (1 registry)[9]	(single arm, rituximab prophylaxis only)						(3/28 relapsed patients)¥ Median 19.1 months Range 19.1-49.8 months					

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab as prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)		
REGISTRY DATA (2 registries)[9,10]	(single arm, no prophylaxis)							(23/137 relapsed patients [8,9,10]) Median 18-20.9 months Range 3.6-116.7 months				
Cardiovascular dysfunction - not reported in the literature												
REGISTRY DATA (NO registry)	(single arm, rituximab prophylaxis only)						–					
REGISTRY DATA (2 registries)[8,10]	(single arm, no prophylaxis)							3/33 0.0%-15.0%				
Neurocognitive function (between acute events) and neurological deficits - not reported in the literature												
REGISTRY DATA (1 registry)[9]	(single arm, rituximab prophylaxis only)						0/12 0.0%					
REGISTRY DATA (3 registries)[8,9,10]	(single arm, no prophylaxis)							8/85 Range 0.0%-20.0%				
Chronic kidney disease / dialysis - not reported in the literature												
REGISTRY DATA (NO registry)	(single arm, rituximab prophylaxis only)						–					
REGISTRY DATA (2 registries)[8,10]	(single arm, no prophylaxis)							3/33 7.7%-10.0%				
Quality of life - not reported in the literature												
REGISTRY DATA (NO registry)	(single arm, rituximab prophylaxis only)						–					

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rituximab as prophylaxis**	**no prophylaxis**	**Relative (95% CI)**	**Absolute (95% CI)**		
REGISTRY DATA (1 registry)[10]	(single arm, no prophylaxis)							7/20 35.0%				
Psychological state - not reported in the literature												
REGISTRY DATA (1 registry)[9]	(single arm, rituximab prophylaxis only)						1/12 8.3%		-	-	-	
REGISTRY DATA (2 registries)[9,10]	(single arm, no prophylaxis)							12/119 8.1%-20.0%				
Adverse events (follow up: range 6 months to 38 months)												
2[1,2] (97 patients)	observational study (single arm, rituximab prophylaxis only)	serious [a]	not serious	not serious	-	none	19/97 Pooled estimate: 17% (95% CI 9%-26%)	-	-	-	⨁◯◯◯ VERY LOW	
Adverse events (in other non-TTP populations)												
3 [5-7]	Systematic reviews	not serious	not serious	serious [c]	not serious	none	Rituximab: 68/69 (98.6%)	-	-	-	⨁⨁⨁◯ MODERATE	
Serious adverse events (in other non-TTP populations)												
3 [5-7]	Systematic reviews	not serious	not serious	serious [c]	not serious	none	Rituximab: 367/1261 Range 13.0%-30.4%	-	-	-	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **OR:** odds ratio; **SD:** Standard deviation

* 31 patients in Jestin 2018 relapsed. All other patients were censored.

**One of 4 patients in Bresin relapsed, at 24 months after starting preemptive rituximab treatments. All other patients were censored.

¥ Data reported in the registry may also have been reported, in whole or in part, in published literature.

Explanations

a. Risk of bias assessed as serious for non-comparative studies, including case series and single arm studies, due to failure to adequately control confounding.
b. Note that a single estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as very low, due to serious concerns about risk of bias. Therefore, certainty in the body of evidence was not further downgraded for imprecision.
c. Adverse events and serious adverse events for TPE and for steroids were gathered from larger population studies including Cochrane reviews of uses of these treatments in other (non-TTP) populations. It is expected that adverse events of these treatments will be the same regardless of the indication for treatment

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4. Bresin E, Gastoldi S, Daina E, et al. Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. Thromb Haemost 2009, 101:233-238.

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5. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD008794. doi: 10.1002/14651858.CD008794.pub2. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Singh JA1, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R.
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7. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006552. doi: 10.1002/14651858.CD006552.pub2. Rituximab as maintenance therapy for patients with follicular lymphoma.Vidal L1, Gafter-Gvili A, Leibovici L, Shpilberg O.

References for REGISTRY DATA

8. Korea
9. Italy
10. Kansas (US)

G-7. Plasma infusion vs. a watch-and-wait strategy for patients with cTTP

G-7.1. EVIDENCE TO DECISION TABLE

Should plasma infusion vs. a watch and wait strategy be used for patients with cTTP?	
POPULATION:	patients with hereditary TTP
INTERVENTION:	plasma infusion
COMPARISON:	a watch and wait strategy
MAIN OUTCOMES:	All-cause mortality, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, adverse events, quality of life, psychological state
SETTING:	Hospital, outpatient
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Once in remission, treatment for hereditary TTP depends on the individual patient. Some require plasma infusions every 2-4 weeks, and some only require treatment when their condition worsens. Patients with hereditary TTP have a significant lifetime exposure to plasma, which may render them susceptible to the side effects of plasma.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of plasma infusion	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know		Mutation dictates phenotype, age of onset. Registry data and study data differ.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	A conference abstract discussed the derivation of a disease specific patient-reported outcome tool to assess patient burden and treatment outcomes in hereditary TTP. This tool - which has not been externally or internally validated - suggested the following patient-reported symptoms and impacts of treatment were potentially useful to patients: fatigue, pain, bruising, cognitive impairment, vision problems, headache, impact of symptoms on activities, and mood. (Oladapo, A., et al. Value in Health. Vol. 20. No. 5. 2017.) **Panel members ranked the outcomes, from most to least important, as follows:** 1. Quality of life 2. All-cause mortality 3. Neurocognitive function and neurological deficits 4. Time to relapse 5. Psychological state 6. Relapse 7. Cardiovascular dysfunction 8. Days in hospital or days of TPE	

	9. Chronic kidney disease/dialysis 10. Live births (for pregnant patients) **Suggested considerations from panel members - interviews** Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates of plasma infusion costs** · $440 to $560 USD per dose · 332€ to 498€ per dose (Denmark) · 360€ to 540€ per dose (France) Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that this treatment was either available widely or available in large and medium sized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Other costs** Patient panelists stated that hematologist and emergency department visits can involve a copay in the U.S. Patient panelists stated that laboratory tests are often fully covered by insurance, regardless of frequency or type of assay, if they go to a preferred laboratory in the U.S.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment, Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient’s ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma	Plasma infusion given every 2-3 weeks. Need to come in to large hospitals.

	exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between “haves” and “have nots.”	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients’ and providers’ realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to the acceptability of plasma included concerns around transfusion associated adverse effects, and special considerations for individuals who do not accept blood products (e.g., Jehovah’s Witnesses)	Vascular access - de novo every time versus a port? Time commitment, transfusion reactions, vascular access all impact acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise	

	awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A “back to basics” strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

For patients with hereditary TTP the panel **suggests either** plasma infusion or a watch and wait strategy.

Justification

Patients who have relapsed may feel more strongly about getting plasma.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Need more information on different phenotypes of TTP - severe, non-severe, early onset, late onset, amount of protein. They may respond differently.

G-7.2. Evidence profile: plasma infusion compared to a watch and wait strategy for cTTP

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with cTTP, what is the effect of **plasma infusion** compared to a **watch and wait strategy** on all-cause mortality, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, adverse events, quality of life, psychological state?
Setting: Hospital, outpatient
Bibliography: See reference list below

Summary: Three studies were found to inform the question of plasma infusion compared with a watch and wait strategy in patients with hereditary TTP.
Fujimura et al described a case series of 31 patients with cTTP in Japan, 25 of whom received FFP infusions. Further details on several patients were published in case series (Saitoh, Matsumoto). Aledort et al described 8 patients with cTTP receiving Factor VIII concentrate, who had previously received plasma infusions. Data were available for 3 of these patients on the frequency of cTTP relapses before starting therapy and while on FFP. The results were equivocal for cTTP events comparing no therapy to plasma infusions. Data on adverse events during FFP therapy were available for 7 patients. Three patients experienced serious adverse events (rash, anaphylaxis, vomiting/skin rash) while taking FFP.
Letowska reported data on adverse events in patients receiving pathogen-reduced blood components in Poland. Of seven patients with cTTP who received FFP, one patient experienced an adverse event (dyspnea and rash).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plasma infusion**	**Watch and wait**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality												
2[1,3-5§] (39 patients)	observational studies (comparative)	not serious	not serious	not serious	serious	none	3/32 (9%) †	0/14 (0%) *	OR 3.78 (0.19 to 73.21)	Not estimable	⨁◯◯◯ VERY LOW	
Relapse												
2[1,3-5§] (39 patients)	observational studies (comparative)	not serious	not serious	not serious	serious	none	6/28 (21%)	5/11 (45%)	OR 3.78 (0.19 to 73.21)	304 more per 1,000 (from 318 fewer to 529 more)	⨁◯◯◯ VERY LOW	
REGISTRY DATA (2 registries)[6,7]	(single arm, plasma infusion)						3/42 (7%)¥					
REGISTRY DATA (2 registries)[6,7]	(single arm, nothing)							1/31 (3%)¥				
Time to relapse / no registry data												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plasma infusion**	**Watch and wait**	**Relative (95% CI)**	**Absolute (95% CI)**		
1[1] (7 patients)	observational studies (comparative)	serious [a]	-	not serious	- [c]	none	Aledort et al reported on TTP episodes in 7 patients receiving plasma infusions and their episodes before starting therapy. The results were equivocal for TTP events comparing no therapy to plasma infusions (every 1-2 weeks vs every 1-3 weeks, 2 episodes over 2 months vs 2-3 episodes per year, every 8-12 weeks vs every 4 weeks).				⨁◯◯◯ VERY LOW	
Cardiovascular dysfunction												
1[3-5§] (31 patients)	observational studies (comparative)	not serious	-	not serious	serious	none	1/25 (4%) **†	0/6 (0%)**	OR 3.46 (0.02 to 493.21)	-	⨁◯◯◯ VERY LOW	
Neurocognitive function and neurological deficits												
1[3-5§] (31 patients)	observational studies (comparative)	not serious	-	not serious	serious	none	4/25 (16%) ***†	0/6 (0%)***	OR 3.97 (0.29 to 54.19)	-	⨁◯◯◯ VERY LOW	
Chronic kidney disease/dialysis												
1[3-5§] (31 patients)	observational studies (comparative)	not serious	-	not serious	serious	none	3/25 (12%)†‡	0/6 (0%)‡	OR 3.78 (0.19 to 73.21)	-	⨁◯◯◯ VERY LOW	
Quality of life – not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Psychological state – not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse events												
1[3-5§] (31 patients)	observational studies (comparative)	not serious	-	not serious	serious	none	2/25 (8%)	0/6 (0%)	OR 3.61 (0.10 to 127.82)	-	⨁◯◯◯ VERY LOW	
2[1,2] (14 patients)	observational studies (single arm, plasma infusion only)	serious [b]	not serious	not serious	-[c]	none	4/14* Pooled estimate: 28% (95% CI 6%-56%)	-	-	-	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** odds ratio

§ A series of 25 patients was most recently reported in Fujimura 2011[3]. Additional information on these patients was gathered from references 4-5.

† Three patients died in the Fujimura series: one of chronic heart failure, one from renal failure, one from stroke. These patients are reported in the outcome of all-cause mortality, in addition to cardiovascular dysfunction, neurocognitive function and neurological deficits, and chronic kidney disease/dialysis.

* Aledort et al reported 7 patients receiving FFP who had previously had no therapy, and many subsequently received FVIII. Data from the patients while on FFP and before therapy are presented here. Adverse events were not documented for patients before therapy.

** Fujimura et al reported 25 patients receiving FFP infusions and 6 patients receiving no infusions. One patient receiving FFP experienced decreased cardiac function (leading to eventual death from chronic heart failure†). No cardiac events were reported in the 6 patients not receiving prophylaxis.

*** Fujimura et al reported 25 patients receiving FFP infusions and 6 patients receiving no infusions. Three patients receiving FFP experienced neurological events (one right hemiparesis due to thrombosis of left carotid artery; one cerebellar bleed; one cerebral infarction). One additional patient suffered a fatal stroke. No neurological events were reported in the 6 patients receiving no prophylaxis.

‡ Fujimura et al reported 25 patients receiving FFP infusions and 6 patients receiving no infusions. Two patients (8%) experienced renal insufficiency leading to dialysis. One additional patient died of renal failure†. No renal events were reported in the 6 patients receiving no prophylaxis.

€ Three studies reported on adverse effects of plasma infusion. Aledort et al reported a series of 7 who received fresh frozen plasma infusions. Three of these patients had serious adverse events (anaphylaxis, rash, vomiting) while on fresh frozen plasma infusions (3/7, 43%). Letowska et al reported on 7 patients receiving fresh frozen plasma: 1/7 (14%) experienced an adverse event (rash and dyspnea). Fujimura et al reported 25 patients receiving FFP infusions and 6 patients receiving no infusions. Two patients on FFP (8%) reported one AE each (1 GI bleed, 1 hepatitis C contracted from plasma). No adverse events were reported (0%) in the 6 patients not receiving prophylaxis.
¥ Data reported in the registry may also have been reported, in whole or in part, in published literature.

Explanations

a. Risk of bias assessed as serious, due to inconsistent reporting of exposure and outcome

b. Risk of bias assessed as serious for non-comparative studies, including case series and single-arm studies, due to failure to adequately control confounding.
c. Note that a single estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as very low, due to serious concerns about risk of bias. Therefore, certainty in the body of evidence was not further downgraded for imprecision.

References

1. Aledort LM, Singleton TC, Ulsh PJ. Treatment of congenital thrombotic thrombocytopenia purpura: a new paradigm. J Pediatr Hematol Oncol 2017, 39:524-27.
2. Letowska M, Przybylska Z, Piotrowski, D, et al. Hemovigilance survey of pathogen-reduced blood components in the Warsaw Region in the 2009 to 2013 period. Transfusion 2016, 56:S39-44.
3. Fujimura Y, Matsumoto M, Isonishi A, Yagi H, Kokame K, Soejima K, Murata M, Miyata T. Natural history of Upshaw-Schulman syndrome based on ADAMTS13 gene analysis in Japan. Journal of Thrombosis and Haemostasis 9 (Suppl 1): 283-301.
4. Matsumoto M, Kokame K, Soejima K, et al. Molecular characterization of ADAMTS13 gene mutations in Japanese patients with Upshaw-Schulman syndrome. Blood 2004, 103(4): 1305-10.
5. Saitoh H, Murakami H, Mori C. Case report: Upshaw-Schulman syndrome in two siblings. Acta Paediatr Jpn 1990, 32:373-76.

References for REGISTRY DATA:

6. Japan
7. Italy

Note: The populations in G-9 and G-10 were not treated as subgroups of the populations in G-7 and G-8. Patients clearly identified as pregnant during the time of intervention were included in analyses for G-9 and G-10. Conversely, patients clearly identified as not pregnant during the intervention, or whose pregnancy status was unclear, were included in the analyses for G-7 and G-8. For this reason, the included papers and patients for these analyses are not identical.

G-8. Factor VIII concentrate infusion vs a watch-and-wait strategy for patients with cTTP

G-8.1. EVIDENCE TO DECISION TABLE

Should factor VIII concentrate infusion vs. a watch and wait strategy be used for patients with hereditary TTP?	
POPULATION:	patients with hereditary TTP
INTERVENTION:	factor VIII concentrate infusion
COMPARISON:	a watch and wait strategy
MAIN OUTCOMES:	All-cause mortality, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, adverse events, quality of life, psychological state
SETTING:	Hospital, outpatient
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Once in remission, treatment for hereditary TTP depends on the individual patient. Some require treatment every 2-4 weeks, and some only require treatment when their condition worsens. Some patients with hereditary TTP have been treated with intermediate purity FVIII concentrates, which contain a relatively high concentration of ADAMTS13.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of factor VIII concentrate	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know		

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		Potential thrombosis? Infection? No data.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	A conference abstract discussed the derivation of a disease specific patient-reported outcome tool to assess patient burden and treatment outcomes in hereditary TTP. This tool - which has not been externally or internally validated - suggested the following patient-reported symptoms and impacts of treatment were potentially useful to patients: fatigue, pain, bruising, cognitive impairment, vision problems, headache, impact of symptoms on activities, and mood. (Oladapo, A., et al. Value in Health. Vol. 20. No. 5. 2017.) **Panel members ranked the outcomes, from most to least important, as follows:** 1. Quality of life 2. All-cause mortality 3. Neurocognitive function and neurological deficits 4. Time to relapse 5. Psychological state 6. Relapse 7. Cardiovascular dysfunction 8. Days in hospital or days of TPE	

	9. Chronic kidney disease/dialysis 10. Live births (for pregnant patients) **Suggested considerations from panel members - interviews** Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates of Factor VIII cost** · $1500 to $3000 USD weekly · 1750€ to 3458€ weekly Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that this treatment was either available widely, available in large and medium sized hospitals, or available in only a few large, specialized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Other costs** Patient panelists stated that hematologist and emergency department visits can involve a copay in the U.S. Patient panelists stated that laboratory tests are often fully covered by insurance, regardless of frequency or type of assay, if they go to a preferred laboratory in the U.S.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment, Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient’s ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma	Product is shelf stable. Given at home. Unsure if licensed for this use.

	exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between “haves” and “have nots.”	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients’ and providers’ realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A “back to basics” strategy aimed	Availability of specific products have sufficient ADAMTS13 varies between countries. There is heterogeneity between products. There is far less ADAMTS13 in these products than in plasma.

	at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. · Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
			intervention or the comparison				
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

For patients with hereditary TTP the panel suggests against treating with either factor VIII concentrate infusions or a watch and wait strategy. (Lack of efficacy data, lack of harms data, lack of understanding of how much ADAMTS13 is in these preparations).

Justification

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

G-8.2. Evidence profile

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with hereditary TTP, what is the effect of **factor VIII concentrate infusion** compared to a **watch and wait strategy** on all-cause mortality, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, adverse events, quality of life, psychological state?
Setting: Hospital, outpatient
Bibliography: See reference list below

Summary: Two studies were found to inform the question of FVIII concentrate infusion compared with a watch and wait strategy in patients with hereditary TTP.
Aledort et al reported on TTP episodes in 8 patients receiving FVIII concentrate with data on these patients before starting any therapy for TTP. No patients died and all patients experienced relapses on treatment. Compared with no therapy, patients had fewer TTP episodes while on FVIII concentrate treatment. No serious adverse events were experienced while patients received FVIII.
Fujimura described six patients with hereditary TTP who were not treated with FFP. No deaths were observed in these patients.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	Factor VIII concentrate infusion	Watch and wait strategy	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
2[1] (8 patients)	observational studies (comparative)	not serious	not serious	not serious	-	none	0/8 (0%)*†	0/8 (0%)*†	-	-	⊕⊕◯◯ LOW	
1[2] (6 patients)	Observational studies (single arm, watch and wait strategy)	serious [a]	-	not serious	-	none	-	0/6‡ Pooled estimate 0% (95% CI 0%-39%)	-	-	⊕◯◯◯ VERY LOW	
Relapse (follow up: up to 10 years)												
1[1] (8 patients)	observational studies (comparative)	serious [b]	-	not serious	-	none	5/5 (100%)§	6/6 (100%)§	-	-	⊕◯◯◯ VERY LOW	
Time to relapse / (no registry data)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**Factor VIII concentrate infusion**	**Watch and wait strategy**	**Relative (95% CI)**	**Absolute (95% CI)**		
1[1] (8 patients)	observational studies (comparative)	serious [b]	-	not serious	-	none	Aledort et al reported on TTP episodes in 8 patients receiving FVIII concentrate and their episodes before starting therapy. Compared with no therapy, patients had fewer TTP episodes while on FVIII concentrate treatment (once in 5 years vs every 6 months, once in 10.5 years vs every 1-2 weeks, every 12 vs ever 4 weeks, once in 1 year vs 2 episodes in 2 months, 0-1 times per year vs ever 8-12 weeks).				⊕◯◯◯ VERY LOW	
Cardiovascular dysfunction - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Neurocognitive function and neurological deficits - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Chronic kidney disease/dialysis - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Quality of life – not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Psychological state – not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse events												
1[1] (8 patients)	observational studies (single arm, FVIII concentrate)	serious [b]	-	not serious	not serious	none	0/8** Pooled estimate 0% (95% CI 0%-32%)	-	-	-	⊕◯◯◯ VERY LOW	

CI: Confidence interval, **FVIII:** Factor eight

* Aledort et al reported 8 patients receiving FVIII who had previously had plasma infusions, and before that no therapy. Data from the patients while on FVIII and before therapy are presented here.

** Aledort et al reported a series of 8 patients taking FVIII. None of the 8 patients experienced a serious adverse event. Data on adverse events were not provided for patients while receiving no therapy.

† Aledort et al reported no deaths in their series of 8 patients.

‡ Fujimura et al reported six patients receiving no infusions or prophylaxis and reported no deaths.
§ Aledort et al reported 8 patients receiving FVIII who had previously had plasma infusions, and before that no therapy. Available data from the patients while on FVIII and before therapy are presented here.

Explanations

a. Risk of bias assessed as serious for non-comparative studies, including case series and single-arm studies, due to failure to adequately control confounding.
b. Risk of bias assessed as serious, due to inconsistent reporting of exposure and outcome
c. Note that a single estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as low to very very low, due to serious concerns about risk of bias and study design. Therefore, certainty in the body of evidence was not further downgraded for imprecision.

References

8. Aledort LM, Singleton TC, Ulsh PJ. Treatment of congenital thrombotic thrombocytopenia purpura: a new paradigm. J Pediatr Hematol Oncol 2017, 39:524-27.
9. Fujimura Y, Matsumoto M, Isonishi A, Yagi H, Kokame K, Soejima K, Murata M, Miyata T. Natural history of Upshaw-Schulman syndrome based on ADAMTS13 gene analysis in Japan. Journal of Thrombosis and Haemostasis 9 (Suppl 1): 283-301.

Note: The populations in G-9 and G-10 were not treated as subgroups of the populations in G-7 and G-8. Patients clearly identified as pregnant during the time of intervention were included in analyses for G-9 and G-10. Conversely, patients clearly identified as not pregnant during the intervention, or whose pregnancy status was unclear, were included in the analyses for G-7 and G-8. For this reason, the included papers and patients for these analyses are not identical.

G-9. Prophylactic immunosuppression vs a watch-and-wait strategy for patients with iTTP who are pregnant, have decreased ADAMTS13, but without other signs of TMA

G-9.1. EVIDENCE TO DECISION TABLE

Should prophylactic immunosuppression vs. a watch and wait strategy be used for patients with immune TTP who are pregnant, have decreased ADAMTS13, and without other signs of TMA?	
POPULATION:	patients with immune TTP who are pregnant, have decreased ADAMTS13, and without other signs of TMA
INTERVENTION:	prophylactic immunosuppression
COMPARISON:	a watch and wait strategy
MAIN OUTCOMES:	All-cause mortality, days in hospital/days of TPE, live births, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, quality of life, psychological state
SETTING:	Hospital, outpatient
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Relapse of TTP is a risk in patients that have had a previous episode of immune TTP that become pregnant. ADAMTS13 levels are typically actively monitored in these patients. The role of immunosuppressive treatments during pregnancy for low ADAMTS13 levels is currently unclear.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of prophylactic immunosuppressive treatment in pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	See EPs.	No comparative published data. Registry data was scant. No expert observations.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	See EPs.	Known pregnancy toxicities of of many drugs (e.g., rituximab, steroids) TPE data exists in pregnant women.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No published data on how individuals value the main outcomes of interest. **Panel members ranked the outcomes, from most to least important, as follows:** 1. Quality of life 2. All-cause mortality 3. Neurocognitive function and neurological deficits 4. Time to relapse 5. Psychological state 6. Relapse 7. Cardiovascular dysfunction 8. Days in hospital or days of TPE 9. Chronic kidney disease/dialysis 10. Live births (for pregnant patients) **Suggested considerations from panel members - interviews**	

	Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Rituximab** · $2500 - $3000 CAD per dose · $2000 AUD per dose · 5616€ per 2400 mg dose (Denmark) · 4235€ per 2550 mg dose (France) o Truxima (biosimilar) is 47% less expensive · $2200 - $7000 USD per dose Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that rituximab was either available widely, or available in large and medium sized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Steroids** · $16.35 CAD daily · $12 USD daily · 26€ to 60€ daily (Denmark) · 11€ daily (France) Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that steroid treatment was available widely in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment, Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient’s ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma	

	exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between “haves” and “have nots.”	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients’ and providers’ realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to rituximab’s acceptability included concerns about cost and access (which is often limited to individuals with insurance, and individuals under the care of expert healthcare providers with experience giving the drug). Threats to steroids’ acceptability included concerns around long term side effects, however patients acknowledged that the tapering schedule used in TTP minimized exposure to side effects.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation:	

	· Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A “back to basics” strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. · Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

For patients with immune TTP who are pregnant, have decreased ADAMTS13, and without other signs of TMA, the panel recommends treatment versus no treatment.

Justification

Panel agreement is that pregnant women with low ADAMTS13 have poor outcomes. There is a lack of data to support what regimen should be used. There is real concern about low ADAMTS13 levels in pregnancy portending a poor outcome .The panel has provided non-graded good practice statements in this area, as there is no data to support a GRADEd recommendation.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

No synthesized data exist. Imperative to pool data from global registries - huge need for data! Also imperative to discuss role of ADAMTS13 testing (and how to implement it widely for pregnant patients) to both collect data and direct care.

G-9.2. Evidence profile: prophylactic immunosuppression compared to a watch-and-wait strategy for iTTP during pregnancy

Author(s): McMaster Methodology Team
Date: May 10, 2019
Question: For patients with immune TTP who are pregnant, have decreased ADAMTS13, and without other signs of TMA, what is the effect of **prophylactic immunosuppression** compared to **a watch and wait strategy** on all-cause mortality, days in hospital/days of TPE, live births, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, quality of life, psychological state?
Setting: Hospital, outpatient
Bibliography: See reference list below

Summary: Three studies included patients with immune TTP experiencing a pregnancy. No study reported on the ADAMTS13 level of included patients during pregnancy. Four pregnancies of a total 37 were associated with use of immunosuppressive treatment (one receiving steroids and TPE for low ADAMTS13 during pregnancy, one treated for lupus, one receiving azathioprine, one receiving highly active antiretroviral treatment for HIV). Six pregnancies ended in fetal death. Five patients relapsed and none died. It is not clear whether immunosuppressive treatments were associated with outcomes.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**Prophylactic immunosuppression (of any treatment)**	**Watch and wait**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (follow up: during pregnancy and immediate postpartum period)												
3[1-3] (27 women, 37 pregnancies)	observational studies	serious [a]	not serious	serious [b]	-	none	Outcomes were reported for 27 women with 37 pregnancies. Three pregnancies were associated with immunosuppressive treatments. No maternal deaths were reported. Outcomes were not clearly linked to treatment status.				⨁◯◯◯ VERY LOW	
Days in hospital/days of TPE - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Live births (follow up: during pregnancy and immediate postpartum period)												
3[1-3] (27 women, 37 pregnancies)	observational studies	serious [a]	not serious	serious [b]	-	none	Outcomes were reported for 27 women with 37 pregnancies. Three pregnancies were associated with immunosuppressive treatments. 33 live births were reported*. Outcomes were not clearly linked to treatment status**†‡				⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [c]	**Other considerations**	**Prophylactic immunosuppression (of any treatment)**	**Watch and wait**	**Relative (95% CI)**	**Absolute (95% CI)**		
Relapse (follow up: not reported)												
3[1-3] (27 women, 37 pregnancies)	observational studies	serious [a]	not serious	serious [b]	-	none	Outcomes were reported for 27 women with 37 pregnancies. Three pregnancies were associated with immunosuppressive treatments. 7 relapses were observed in 5 patients. Outcomes were not clearly linked to treatment status[§]				⊕◯◯◯ VERY LOW	
REGISTRY DATA (1 registry)[18]	(single arm, prophylactic immunosuppression of any treatment)						0/1 (0%)					
REGISTRY DATA (1 registry)[18]	(single arm, watch and wait)							3/13 (23%)				
Time to relapse - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular dysfunction - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Neurocognitive function and neurological deficits - not reported in the literature												
REGISTRY DATA (1 registry)[18]	(single arm, prophylactic immunosuppression of any treatment)						0/1 (0%)					
REGISTRY DATA (1 registry)[18]	(single arm, watch and wait)							0/13 (0%)				
Chronic kidney disease / dialysis - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Quality of life - not reported in the literature or registry												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [c]	Other considerations	Prophylactic immunosuppression (of any treatment)	Watch and wait	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	
Psychological state - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Adverse events (in other non-TTP populations)												
11 [7-17]	Systematic reviews	not serious	not serious	serious [d]	not serious	none	Rituximab: 68/69 (98.6%) Steroids: 335/867 Range 31%-51%		-	-	⨁⨁⨁◯ MODERATE	
Serious adverse events (in other non-TTP populations)												
11 [7-17]	Systematic reviews	not serious	not serious	serious [d]	not serious	none	Rituximab: 367/1261 Range 13.0%-30.4% Steroids: 257/2183 Range 1.8%-37.0%		-	-	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **TPE:** Plasma exchange; **TMA:** Thrombotic microangiopathy

* The 33 live births include 2 sets of twins. There were 6 fetal deaths in 37 pregnancies.

** One fetal loss in Scully 2014 was attributed to β-hemolytic *Streptococcus* infection.

† Four patients in Scully 2014 were reported to receive immunosuppressive treatments. One patient had reduced ADAMTS13 during pregnancy and was treated with TPE and steroids. The patient had a live birth but relapsed one week after delivery. A second patient developed acute lupus during pregnancy and was treated with immunosuppressives for lupus. A third patient received azathioprine throughout pregnancy. It is not clearly reported whether a live birth was associated with these three patients. A fourth patient had HIV-related TTP and continued to receive highly active antiretroviral therapy throughout pregnancy, associated with “no complications”. Many pregnancies (25/37, 68%) were prophylactically treated with aspirin and/or low molecular weight heparin as prophylaxis.

‡ One pregnancy in Scully 2006 resulted in a miscarriage. It was not reported whether this pregnancy was associated with immunosuppressives or other prophylaxis of any kind.

§ It is possible but not clearly reported that one relapse in Scully 2014 was associated with the patient who received azathioprine.

Explanations

a. Risk of bias assessed as serious for non-comparative studies, including case series and single-arm studies, due to failure to adequately control confounding.
b. In Scully 2014, ADAMTS13 measurements during pregnancy ranged from 9-89%. Ducloy-Bouthors reported ADAMTS13 activity in only 1 of 6 pregnancies as <5%. Scully 2006 reports one patient with consistent levels of ≥89% before and during pregnancy, 3 patients with activity levels <5% before pregnancy, but during pregnancy levels were not measured or were measured between 16-85%.
c. Note that a single estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as very low, due to serious concerns about risk of bias. Therefore, certainty in the body of evidence was not further downgraded for imprecision.
d. Adverse events and serious adverse events for TPE and for steroids were gathered from larger population studies including Cochrane reviews of uses of these treatments in other (non-TTP) populations. It is expected that adverse events of these treatments will be the same regardless of the indication for treatment

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Note: The populations in G-9 and G-10 were not treated as subgroups of the populations in G-7 and G-8. Patients clearly identified as pregnant during the time of intervention were included in analyses for G-9 and G-10. Conversely, patients clearly identified as not pregnant during the intervention, or whose pregnancy status was unclear, were included in the analyses for G-7 and G-8. For this reason, the included papers and patients for these analyses are not identical.

G-10. Plasma infusion vs factor VIII concentrate infusion for patients with cTTP who are pregnant

G-10.1. EVIDENCE TO DECISION TABLE

Should plasma infusion vs. factor VIII concentrate infusion be used for patients with hereditary TTP who are pregnant?	
POPULATION:	patients with hereditary TTP who are pregnant
INTERVENTION:	plasma infusion
COMPARISON:	factor VIII concentrate infusion
MAIN OUTCOMES:	All-cause mortality, days in hospital/days of TPE, live births, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, quality of life, psychological state
SETTING:	Hospital, outpatient
PERSPECTIVE:	Clinical considerations - population perspective
BACKGROUND:	Prophylactic plasma infusions are required in pregnant women with hereditary TTP to prevent relapses that can be deleterious for the mother and the fetus. Some patients, including pregnant patients, with hereditary TTP have been treated with intermediate purity FVIII concentrates, which contains a relatively high concentration of ADAMTS13. Factor VIII concentrate has several potential advantages over plasma: small volume, virally inactivated product, and the ability to be administered for prophylactic therapy in the outpatient setting.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The panel felt this question was important because of perceived variability in practice, and the need for synthesized data on the value of plasma infusion and factor VIII concentrate in pregnancy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See EPs.	No difference in mortality or live births. Small numbers. No information on relapse from fVIII arm. Panel views there is no difference in benefits when compared to non-pregnant patients.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	See EPs. ** New reference: Mannucci, levels of fVIII, VWF and ADAMTS13 by trimester.	No evidence here. Panel raised concerns that pregnant patients have baseline three-fold higher levels of fVIII than non-pregnant patients. Adding fVIII could theoretically increase risk of thrombosis. Moreover, intermediate purity fVIII concentrates have unclear fVIII concentrations.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	A conference abstract discussed the derivation of a disease specific patient-reported outcome tool to assess patient burden and treatment outcomes in hereditary TTP. This tool - which has not been externally or internally validated - suggested the following patient-reported symptoms and impacts of treatment were potentially useful to patients: fatigue, pain, bruising, cognitive impairment, vision problems, headache, impact of symptoms on activities, and mood. (Oladapo, A., et al. Value in Health. Vol. 20. No. 5. 2017.) **Panel members ranked the outcomes, from most to least important, as follows:** 1. Quality of life 2. All-cause mortality 3. Neurocognitive function and neurological deficits 4. Time to relapse 5. Psychological state 6. Relapse 7. Cardiovascular dysfunction 8. Days in hospital or days of TPE	The value placed on live birth, versus patient's survival, may differ between provider and patient perspective. Risk tolerance may differ as well. Panel surveyed during the meeting and re-ranked outcomes for this PICO: 1. All cause mortality 2. Live births at term 3. Neurocognitive function for mom 4. Infant morbidity (including neurocognitive function) - theoretically due to placental insufficiency, premature delivery - baby alive but not healthy. Panel emphasized that there is little data on infant morbidity in these patients, and it is not commonly seen. 5. Relapse Other outcomes felt to be less important: CV dysfunction CKD

	9. Chronic kidney disease/dialysis 10. Live births (for pregnant patients) **Suggested considerations from panel members - interviews** Patients consistently valued mortality and neurocognitive function as important outcomes of interest, in the setting of both an acute event and remission. Minor adverse drug effects (e.g., fatigue, nausea) were identified as less important outcomes, particularly in the setting of an acute event. Outcomes related to the length of treatment and the time to recovery (e.g., length of stay in hospital, days of TPE, days to platelet recovery) were identified as less important in the setting of an acute event. Patients expressed that if they had good clinical outcomes, they would be willing to accept that the treatment process took more time. Patients acknowledged that outcomes may be valued differently based on stage of life and experiences (i.e., factors that drive situational values, which are tied to a specific context). For example, functional outcomes may be more important to younger patients, and less important to older patients. Patients also acknowledged that global values (i.e., core personal values, which are tied to underlying personality) could influence the importance that patients place on outcomes. For example, individuals who are more risk averse with regards to relapse may place more importance on the ADAMTS13 level during remission.	Other outcomes felt to be unimportant: Days in hospitall Days of TPE The panel emphasized the importance of maternal mortality (currently a subset of all-cause mortality) The panel discussed possibility that there could be long term effects of TTP - particularly neuropsychiatric – that would be concerning for pregnant patients. No data on this in the published literature. Difficult to make judgement about longterm neurological outcomes during acute event due to confounding factors. Shortterm priority: neurovascular event prevention. That is, behavioural and cognitive measures more meaningful in chronic phase. However, focus on prevention of stroke and TIA acutely is most important.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	** Favour plasma	No data. But concerns about theoretical harm from fVIII in pregnant patients with higher baseline fVIII and potential thrombosis risk. (Indirect evidence taken from other populations in terms of healthy pregnant women and patients with thrombosis.)

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	**Estimates of plasma infusion costs** · $440 to $560 USD per dose · 332€ to 498€ per dose (Denmark) · 360€ to 540€ per dose (France) Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that plasma infusion was either available widely or available in large and medium sized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Estimates of Factor VIII cost** · $1500 to $3000 USD weekly · 1750€ to 3458€ weekly Panelists noted that in the U.S., costs for this treatment (particularly patients' out of pocket costs) could vary significantly, depending on the insurance provider, the price negotiated with individual hospitals, and the individual patient's insurance coverage. Panelists stated that factor VIII concentrate was either available widely, available in large and medium sized hospitals, or available in only a few large, specialized hospitals in their countries. This treatment was paid for by government (public health insurance), private health insurance, or the patient (out of pocket cost), depending on the jurisdiction. **Other costs** Patient panelists stated that hematologist and emergency department visits can involve a copay in the U.S. Patient panelists stated that laboratory tests are often fully covered by insurance, regardless of frequency or type of assay, if they go to a preferred laboratory in the U.S.	In some jurisdictions, fVIII cost borne by different stakeholders. Generally more expensive than plasma by four- to six-fold.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no published data on cost-effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	There are no published data on impact on health equity. **Structured interviews with patient panelists explored existing inequities in the diagnosis and treatment of TTP.** They felt inequity in diagnosis was tied to a lack of awareness of TTP; providers in more remote areas, with less access to specialist hematologists, may not have TTP on their differential diagnosis of a patient with an unusual presentation. Inequity may also be impacted by patient gender, race, and/or socioeconomic status; individuals with a subtler presentation of TTP (as opposed to the typical “Pentad”) may have their complaints dismissed. Inequity in treatment was felt to be a major problem. Patients suggested that it was often “luck” that determined if a patient presented to a hospital with access to healthcare providers who recognized their disease, understood best practices around treatment, and also had access to that treatment. Patients in rural areas, or areas not well served by a tertiary care hospital with plasmapheresis capabilities were felt to receive inequitable treatment, Cost of treatment was felt to be the greatest driver of inequity, particularly in countries without robust public healthcare / pharmacare. In some jurisdictions, insurance status could impact a patient’s ability to see appropriate doctors or go to appropriate hospitals (which may not be in their insurance network). Patients related anecdotes that insurance company requirements prior authorizations often delayed treatment. Modifiers of inequity may include telehealth, outreach clinics (for patients in remission), educating local healthcare providers to improve the awareness and early diagnosis of TTP, broader access to TTP expertise (e.g., through appropriate implementation of evidence based recommendations that set a baseline standard of care, pathways to consult more expert healthcare providers), and broader access to TTP treatments (e.g., by decreasing barriers set up by insurers around cost, co-pays, and requirement for prior authorizations). Healthcare providers were encouraged to take a broadly consultative approach when managing TTP, due to its rarity, and the concentration of expertise and experience in a few centres worldwide. Structured interviews with patient panelists also explored if the intervention and comparator in this PICO question could have an impact on health equity. They stated that the addition of treatments that were more costly, required more expertise to administer (e.g., plasma	Infusion "easier" to get - these patients may not be as comfortable with self infusion as individuals with hemophilia.

	exchange), and/or were more difficult to access (e.g., plasma exchange, factor concentrates, caplacizumab, rituximab) could increase inequity, widening the gap between “haves” and “have nots.”	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are no published data on acceptability to key stakeholders. **Structured interviews with patient panelists explored acceptability in the treatment of TTP.** In general, acceptability was enhanced by treatments that had a major impact on the outcomes of mortality and relapse prevention. All treatments addressed in these guidelines were perceived to be acceptable to key stakeholders, as they confirmed to patients’ and providers’ realistic wishes and expectations around efficacy, balance of risks and benefits, and route of administration. Threats to the acceptability of plasma included concerns around transfusion associated adverse effects, and special considerations for individuals who do not accept blood products (e.g., Jehovah’s Witnesses)	Time limited therapy might be easier to accept during pregnancy, even if it requires partients to negotiate schedule (time/travel). Less acceptable if patient had allergic reactions to plasma. Patient has already demonstrated that they are committed to pregnancy - they are likely willing to take the extra step to ensure a good pregnancy outcome. Discussion around individual patient feasibility, scheduling, etc that may change acceptability.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There are no published data on feasibility. **Structured interviews with patient panelists explored feasibility of implementation.** A general acknowledgement was made that TTP is a rare and expensive disease, which requires significant institutional and intellectual resources for both diagnosis and treatment. Patient panelists identified potential barriers and facilitators to implementation: · Professional factors: knowledge and skills of health care providers remains a barrier to implementation. There is an opportunity to raise	As above.

	awareness of this rare disease with evidence based recommendations with different knowledge translation strategies. · System factors: many centers are not resourced to implement costly or expertise-intensive diagnostic or treatment strategies, particularly for a rarely encountered disease like TTP. A “back to basics” strategy aimed at first line providers might be useful; for example, the CBC, cheap and rapid test, can be informative in a patient with vague symptoms. Creating an environment where non-experts can connect to experts is also important, to accelerate and optimize TTP care. · Patient factors: patients also have a lack of awareness of TTP, and can feel overwhelmed and unsupported. Patients often trade information online, but this information is not always reliable. Better partnerships between MDs and patients (particularly patient support groups), and targeted patient education may enhance uptake of this intervention.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

For patients with hereditary TTP who are pregnant, the panel **recommends treatment versus no treatment. (Strong recommendation...)**

For patients with hereditary TTP who are pregnant, the panel **suggests for treatment with plasma versus fVIII. (Conditional recommendation...)**

Justification

Subgroup considerations

Implementation considerations

The panel suggests that in pregnant patients in particular, viral inactivated plasma would be preferable. This plasma not available everywhere, is more expensive, and based on indirect evidence, has less reactions. (There is low certainty evidence that there are less side effects associated with SD plasma than quarantined plasma, for example.) Pathogen inactivation is achieved by various methods, including SD and UV. The panel also noted that cryosupernatant plasma has lower fVIII concentrations.

Monitoring and evaluation

Research priorities

The panel felt it is a priority to explore the long term effects of TTP - particularly neuropsychiatric – for pregnant and non-pregnant patients.

G-10.2. Evidence profile: **plasma infusion** vs. **factor VIII concentrate infusion**

Author(s): McMaster Methodology Team

Date: May 10, 2019
Question: For patients with hereditary TTP who are pregnant, what is the effect of **plasma infusion** versus **factor VIII concentrate infusion** on all-cause mortality, days in hospital/days of TPE, live births, relapse, time to relapse, cardiovascular dysfunction, neurocognitive function and neurological deficits, chronic kidney disease/dialysis, quality of life, psychological state?
Setting: Hospital, outpatient
Bibliography: See reference list below

Summary: Scully included ten women with TTP who had 15 pregnancies subsequent to the diagnosis of hereditary TTP. All women were actively monitored and treated throughout pregnancy. Two women received FVIII during one pregnancy each, and eight other women were treated with FFP for 13 pregnancies. All pregnancies resulted in a live infant and no maternal mortality was observed in the series of 10 women.
Three patients in Moatti-Cohen (and followed up in Delmas) had pregnancies treated with FFP. All pregnancies resulted in a live birth with no maternal mortality or relapse.
Four women in Fujimura had a total of six pregnancies subsequent to a diagnosis of hereditary TTP and received infusions of FFP. Further details on several patients were published in case series (Kato, Matsumoto). No maternal deaths were reported. One patient relapsed during pregnancy. Five live births were reported. One patient who had two subsequent pregnancies received FFP during both pregnancies. Her first pregnancy ended with spontaneous abortion at 5 weeks, and the second resulted in a live birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [b]	**Other considerations**	**Plasma infusion**	**Factor VIII concentrate infusion**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (follow up: during pregnancy and immediate postpartum period)												
1[1] (10 women, 15 pregnancies)	Observational study (comparative)	not serious	-	not serious	-	none	0/8 (0%) (8 women, 13 pregnancies)	0/2 (0%) (2 women, 2 pregnancies)	-	-	⊕⊕◯◯ LOW	
2[2-7§†] (7 women, 10 pregnancies)	observational studies (single arm, plasma infusion)	serious [a]	not serious	not serious	-	none	0/10 Pooled estimate 0% (95% CI 0%-19%)	-	-	-	⊕◯◯◯ VERY LOW	
Days in hospital/days of TPE- not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Live births (assessed with: per pregnancy) (follow up: during pregnancy and immediate postpartum period)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision** [b]	**Other considerations**	**Plasma infusion**	**Factor VIII concentrate infusion**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [1] (10 women, 15 pregnancies)	Observational study (comparative)	not serious	-	not serious	-	none	13/13 (100%) (8 women, 13 pregnancies) [‡]	2/2 (100%) (2 women, 2 pregnancies) [‡]	-	-	⨁⨁◯◯ LOW	
2[2-7§†] (7 women, 10 pregnancies)	observational studies (single arm, plasma infusion)	serious [a]	not serious	not serious	-	none	9/10 Pooled estimate 93% (95% CI 63%-100%)	-	-	-	⨁◯◯◯ VERY LOW	
Relapse (follow up:)												
2[2-7§†] (7 women, 10 pregnancies)	observational studies (single arm, plasma infusion)	serious [a]	not serious	not serious	-	none	1/10 Pooled estimate 7% (95% CI 0%-37%)	-	-	-	⨁◯◯◯ VERY LOW	
REGISTRY DATA (1 registry)[8]	(single arm, plasma infusion)						0/7 0.0%					
REGISTRY DATA (NO registry)	(single arm, plasma derived fVIII concentrates)							–				
Time to relapse - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular dysfunction - not reported in the literature												
REGISTRY DATA (1 registry)[8]	(single arm, plasma infusion)						0/7 0.0%					
REGISTRY DATA (NO registry)	(single arm, plasma derived fVIII concentrates)							–				

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision [b]	Other considerations	Plasma infusion	Factor VIII concentrate infusion	Relative (95% CI)	Absolute (95% CI)		
Neurocognitive function + neurological deficits - not reported in the literature												
REGISTRY DATA (1 registry)[8]	(single arm, plasma infusion)						0/7 0.0%					
REGISTRY DATA (NO registry)	(single arm, plasma derived fVIII concentrates)							_				
Chronic kidney disease / dialysis - not reported in the literature												
REGISTRY DATA (1 registry)[8]	(single arm, plasma infusion)						0/7 0.0%					
REGISTRY DATA (NO registry)	(single arm, plasma derived fVIII concentrates)							_				
Quality of life - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	
Psychological state - not reported in the literature or registry												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **TPE:** Plasma exchange

† A series of 10 patients was reported in Moatti-Cohen 2012, with supplemental data on these patients presented in Delmas 2015.

§ A series of 10 Japanese patients was most recently reported in Fujimura 2011[1]. Additional information on these patients was gathered from references 4-6.

‡Twenty-three pregnancies were treated prophylactically with fresh frozen plasma infusions. Of these, 22 (96%) resulted in a live birth. Two pregnancies were managed with FVIII. Both of these pregnancies (100%) resulted in a live birth.
Of additional interest: In these three series of patients (Moatti-Cohen/Delmas, Fujimura, Scully), forty-three women had a total of 91 pregnancies. Sixty-two pregnancies in 42 women occurred before diagnosis with hereditary TTP (the precipitating event, or misdiagnoses). Of these 62 pregnancies, 32[†] (52%) resulted

in a live birth. Four pregnancies in 3 women occurred after the diagnosis of hereditary TTP and were treated with no prophylaxis (n=3) or aspirin as prophylaxis (n=1). Of these, 2 (50%, 1 aspirin, 1 no prophylaxis) resulted in a live birth.

Explanations

a. Risk of bias assessed as serious for non-comparative studies, including case series and single-arm studies, due to failure to adequately control confounding.
b. Note that a single estimate of effect could not be calculated for several outcomes. In these cases, the small number of events and subjects in included studies raises concerns about imprecision. However, certainty in evidence was already assessed as low to very low, due to serious concerns about risk of bias and study design. Therefore, certainty in the body of evidence was not further downgraded for imprecision.

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7. Fujimura Y, Matsumoto M, Kokame K, et al. Pregnancy-induced thrombocytopenia and TTP, and the risk of fetal death, in Upshaw-Schulman syndrome: a series of 15 pregnancies in 9 genotyped patients. British Journal of Haematology 2008, 144:742-54.

References for REGISTRY DATA

8. Japan

Note: The populations in G-9 and G-10 were not treated as subgroups of the populations in G-7 and G-8. Patients clearly identified as pregnant during the time of intervention were included in analyses for G-9 and G-10. Conversely, patients clearly identified as not pregnant during the intervention, or whose pregnancy status was unclear, were included in the analyses for G-7 and G-8. For this reason, the included papers and patients for these analyses are not identical.

APPENDIX H: Outcome definitions

Outcome	Definition
All-cause mortality	Death from any cause
All cardiovascular events	A composite outcome including acute myocardial infarction, CV ischemic events, CV mortality, and arrhythmia (fatal or non-fatal).
Stroke / TIA / clinically obvious neurologic deficit	A composite outcome including stroke, transient ischemic attack, and impairments of nerve, spinal cord, or brain function affecting a specific region of the body.
Platelet count recovery	Sustained normalization of platelet counts above the lower limit of the established reference range (e.g., 150 x 10^9/L) for 3 or more days after cessation of plasma exchange.
Relapse	A fall in platelet count to below the lower limit of the established reference range, with or without clinical symptoms, > 30 days after stopping of plasma exchange for an acute TTP episode, requiring re-initiation of therapy
Time to relapse	Time in between cessation of TPE and relapse.
Acute kidney injury / dialysis	Number of patients with acute kidney injury as classified using the Kidney Disease Improving Global Outcomes (KDIGO) or alternate criteria, or requiring dialysis while on active treatment.
Days in hospital or days of TPE	Number of days spent as an inpatient in a hospital; or the number of days spent receiving TPE.
Exacerbation	A reduction in platelet count to below the lower limit of the established reference range (e.g., 150 x 10^9/L), an increased lactate dehydrogenase (LDH) level, and the need to restart plasma exchange within 30 days of the last plasma exchange after a clinical response to plasma exchange.
Normal ADAMTS13 level after TPE complete	ADAMTS13 levels at or above the normal reference range after cessation of therapeutic plasma exchange.
Quality of life	General wellbeing and life satisfaction. This may be captured by a quality of life measure score.
Neurocognitive function (between acute events) + neurological deficits	Worsened neurocognitive function (between acute events) and/or neurological deficit (e.g., memory loss). This may be measured by a neurological or cognitive outcome measure score (e.g., Montreal Cognitive Assessment (MoCA), mini mental status exam (MMSE)).
Psychological state	Anxiety, depression, or other psychological conditions.
Cardiovascular dysfunction	Systolic or diastolic dysfunction of either the left or right ventricles, and/or persistent arrhythmia.
Chronic kidney disease / dialysis	Number of patients with chronic kidney injury as classified by the Kidney Disease Improving Global Outcomes (KDIGO) or alternate criteria (e.g., CrCl <30 mL/min or eGFR <30 mL/min/1.73 m^2), or requiring dialysis between events.
Live births	A birth at which a child is born alive, irrespective pregnancy duration.

APPENDIX I: ADVERSE EVENTS

Table I-1: Specific populations enrolled in systematic reviews and original studies used to inform treatment adverse events

Rituximab - adverse events in others (non-TTP) populations
Populations considered in Cochrane reviews: • Rheumatoid arthritis • Relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis • Follicular and mantle cell lymphoma, large- B cell lymphoma, lymphoplasmacytic lymphoma, relapsing or refractory aggressive lymphoma, indolent non-Hodgkin's lymphoma, low-grade non-Hodgkin's lymphoma • Induction in renal transplantation
TPE - adverse events in others (non-TTP) populations and in TTP
Populations considered in Cochrane reviews: • Guillan-Barré syndrome • Inflammatory demyelinating polyradiculoneuropathy • Generalized myasthenia gravis Populations considered in other original studies: • TTP
Steroids - adverse events in others (non-TTP) populations and in TTP
Populations considered in Cochrane reviews: • Relapses in multiple sclerosis • Systemic lupus erythematosus • Guillain-Barre syndrome • Spinal cord injury • Exacerbations of chronic obstructive pulmonary disease • Pneumonia • Acute asthma • Nephrotic syndrome • Acute bacterial meningitis • Haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura

Table I-2: Adverse events for rituximab

	RITUXIMAB		PLACEBO	
	Σ (n/N)	**% (range)**	**Σ (n/N)**	**% (range)**
Any AEs	68/69	98.6%	35/35	100%
Any SEVERE AEs	367/1261	13.0%-30.4%	34/195	14.3%-18.1%

Withdrawals due to adverse events	41/1108	3.7%-4.3%	2/35	5.7%
SERIOUS infections	106/1428	2.9%-8.1%	9/362	2.1%-5.7%
All infections	87/389	12.2%-69.6%	45/362	6.1%-71.4%
Infusion-associated adverse events	54/69	78.3%	14/35	40%

Rituximab: only indirect evidence (adverse events in other diseases)

Table I-3: Adverse events for TPE

	TPE		SHAM EXCHANGE	
	Σ (n/N)	**% (range)**	**Σ (n/N)**	**% (range)**
Any AEs per procedure	18321 procedures (3646 patients treated)	3.9-17%	-	-
Any AEs	**55/124** *12/53* 43/71	**19.5%-60.6%** *19.5%-33.3%* 60.6%	-	-
Any SEVERE AEs	93/373	23.8%-29.6%	-	-
Discontinuation due to poor hemodynamic tolerance	*62/605*	*4.9%-12.8%*	-	-
SEVERE infections	**188/1022** *94/288* 94/734	**8.3%-33.7%** *8.3%-33.7%* 8.4%-16.9%	*104/280*	*37.1%*
SEVERE allergic reactions	14/508	0.3%-6.3%	-	-
Blood pressure instability	**65/702** *56/329* 9/373	**2.3%-18.8%** *4.9%-18.8%* 2.3%-2.8%	*60/280*	*21.4%*
Cardiac Arrhythmias	*58/276*	*21%*	*79/280*	*28.2%*
Venus thrombosis	**18/787** *2/53* 16/734	**1.7%-8.3%** *2.4%-8.3%* 1.7%-2.8%	-	-

Bold: direct + indirect evidence
Italic: only indirect evidence (adverse events in other diseases)
Underline: only direct evidence (adverse events in TTP)

Table I-4: Adverse events for steroids

	STEROIDS		PLACEBO	
	Σ (n/N)	**% (range)**	**Σ (n/N)**	**% (range)**
Any adverse events	*335/867*	*31%-51%*	*228/796*	*26%-34%*
Any SEVERE adverse events*	*257/2183*	*1.8%-37.0%*	*93/2276*	*1.7%-25%*
SEVERE infections	**190/1166** *173/1120* 17/46	**7.9%-37%** *7.9%-19.1%* 37%	**177/992** *165/944* 12/48	**14.7%-26%** *14.7%-26%* 25%
Hypertension	*54/798*	*0%-15%*	*31/342*	*3.6%-11.7%*
Hyperglycemia	*299/1241*	*0%-44.2%*	*99/971*	*2%-12.3%*
Diabetes Mellitus requiring insulin	*29/236*	*12.3%*	*13/231*	*5.6%*
Gastrointestinal Hemorrhage – bleeding	*63/2317*	*2.5%-9.1%*	*36/2065*	*1.7%-2.2%*
Psychological or psychiatric disturbances	*57/966*	*1.7%-31.8%*	*8/688*	*0.9%-2.7%*
Adverse cardiac events	*14/623*	*2.2%*	*24/626*	*3.8%*

Bold: direct + indirect evidence
Italic: only indirect evidence (adverse events in other diseases)
Underline: only direct evidence (adverse events in TTP)
*including severe infections, diabetes mellitus requiring insulin, gastrointestinal hemorrhage, psychological/psychiatric disturbance, adverse cardiac events