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RECOMMENDATIONS AND GUIDELINES

Good practice statements (GPS) for the clinical care of patients with thrombotic thrombocytopenic purpura

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1 | METHODS

Upon setting the Population, Intervention, Comparison, and Outcome questions for the guidelines, the panel identified a number of topics that might be well suited to non-Grading of Recommendations Assessment, Development, and Evaluation Good Practice Statements (GPSs). The McMaster team drafted an initial set of statements for distribution to the panelists before our second in-person meeting. The panelists reviewed the statements for relevance and accuracy.

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["Correction Statement added on October 18, 2020: an abstract was included by mistake and has since been removed."]

The GPSs were then revised based on feedbacks that were redistributed to the panelists for further revisions and finalization.

2 | COMMENT

The Guidelines panel discussed a number of additional considerations to support good clinical care of patients with thrombotic thrombocytopenic purpura (TTP). The "GPSs" are not evidence-based recommendations. Specifically, they are not based on systematic search or formal review of the evidence. These statements are intended to provide a "snapshot" of the care provided to patients with TTP by expert health care providers. They address scenarios in which there is very limited high-certainty evidence, yet there is a body of indirect evidence and/or clinical experience that suggests the net benefit of certain actions. GPSs are intended to guide health care providers who have limited experience in treating TTP. They should be used with caution; the provider's own clinical judgment, in combination with the individual patient's clinical situation, values, and preferences, should all be considered.

3 | SUPPORTIVE CARE

The following statements pertain to initial emergency care and general supportive care of patients with TTP.

3.1 | Statement 1

Clinicians generally consider a diagnosis of TTP in individuals presenting with thrombocytopenia and microangiopathic hemolytic anemia.[1-4] Patients may be critically ill, or may have relatively minor and nonspecific complaints. Importantly, the classic signs of TTP (eg, hemolytic anemia, thrombocytopenia, fever, neurologic abnormalities, and renal abnormalities) also known as "Raynaud's Pentad" are present in only 40% of patients; therefore, the historical pentad only are only seen in the more severe forms of the disease, or in patients left without appropriate treatment resulting from a delayed diagnosis. The prevalence of this catastrophic presentation has decreased in past few decades as the result of better awareness of the disease among practitioners.[4-7] Therefore, the presence of thrombocytopenia and microangiopathic hemolytic anemia without other explanation should prompt a suspicion of TTP in the differential diagnosis.[8]

3.2 | Statement 2

We did not systematically search and review the evidence on different clinical or laboratory approaches for diagnostic workup of a patient with suspected TTP. However, an initial laboratory evaluation of presumptive TTP should include a complete blood count with careful review of a peripheral blood film for lack of platelets and presence of fragmented red blood cells (or schistocytes), serum lactate dehydrogenase, and creatinine, testing to demonstrate hemolysis (eg, low haptoglobin, increased indirect bilirubin), coagulation testing (which is expected to be relatively normal in TTP unless it is a severe form of the disease[5] and there is a concomitant disseminated intravascular coagulation).[9] A direct Coombs test is expected to be negative in TTP, but may be positive in autoimmune hemolytic anemia. Troponin I and electrocardiogram should be systematically performed to identify subclinical cardiac involvement.[5,10,11] Computed tomography/magnetic resonance imaging of the brain may also be included in the initial evaluation for TTP if there are symptoms and signs, suggestive of brain injury.[12-16]

3.3 | Statement 3

If the index of suspicion for TTP is high, clinicians should consider the emergency initiation of therapeutic plasma exchange (TPE) and corticosteroids. Because of the severity and instability of their illness, and the foundational role of TPE in the treatment of TTP, patients experiencing an acute event of TTP are usually urgently transferred to a facility that can perform TPE, ideally overseen by a clinician who has expertise in the management of TTP. Most of these patients (>95%) if plasma ADAMTS13 activity is less than 10 IU/dL (or <10% of normal) are immune-mediated TTP or iTTP.

For a suspected iTTP, a blood sample should be obtained for plasma ADAMTS13 testing (eg, activity and inhibitors or anti-ADAMTS13 IgG, etc.) before the initiation of TPE. Daily TPE is generally initiated as soon as possible with fresh frozen plasma (FFP), or cryopoor plasma, or solvent detergent-treated (SD) plasma as a replacement fluid. The volume of the replacement fluid is usually 1.0 to 1.5 times of patient's plasma volume (ie, 40-60 mL/kg) every 24 hours until normalization of patient's platelet counts and serum lactate dehydrogenase.

Patients with a suspected or confirmed hereditary or congenital TTP (cTTP) are generally treated with plasma infusion (10 to 15 mL/kg) at a frequency of every 1 to 3 weeks for maintenance therapy or daily for a symptomatic patient until the symptoms resolve and normalization of platelet counts.[17-19]

3.4 | Statement 4

Because of the severity and instability of their illness, TTP patients experiencing an acute event are often managed in a setting with critical/intensive care capabilities, including continuous monitoring of neurologic status, cardiac status, and oxygen saturation. Initial management in a critical/intensive care setting is considered appropriate on the grounds that TTP patients may deteriorate quickly, and have a high risk of severe organ dysfunction such as coma, ischemic stroke, seizures, myocardial infarction, congestive heart failure, arrhythmias, mesenteric ischemia, pancreatitis, and acute kidney injury. All

of these complications require early detection, intensive care monitoring, and rapid therapeutic interventions; furthermore, TPE is associated with rare adverse effects, such as anaphylactic reactions, that are best managed in the critical/intensive care setting.[20,21]

3.5 | Statement 5

We did not systematically search and review the evidence on different modalities of monitoring in TTP patients. In general, the clinical evaluation of TTP patients at the time of hospital admission, and regularly thereafter, emphasizes cardiac and neurological assessment. Specifically, cardiac troponin levels are measured at diagnosis, followed by serial troponin levels, electrocardiography, and echocardiography as clinically indicated.[22] Increased cardiac troponin (>0.25 μg/L) appears to be associated with increased cardiac and cerebral involvement, ischemic stroke, and mortality in TTP,[5] although most patients with an increased level of cardiac troponin remain asymptomatic.[5,10,23,24]

3.6 | Statement 6

TTP patients often need a central venous access secured urgently. Rapid placement of central venous access allows TPE to be initiated as soon as possible. The type of central venous access depends on the modality of TPE: centrifugal apheresis vs membrane filtration. Centrifugal apheresis involves lower blood flow rates, and enables the use of catheters with smaller diameters, and more flexible walls (such as peripheral catheters or standard triple lumen central venous catheters. Conversely, membrane filtration involves higher blood flow rates, which requires the use of larger diameter, stiffer catheters (such as standard dialysis catheters or single lumen central venous catheters).[25-29] Clinicians should be aware of, or consult the appropriate service for what modality of TPE is used at their center, so appropriate central venous access can be secured before initiation of TPE.

3.7 | Statement 7

The risk of catheter-related complications such as bleeding, thrombosis, and sepsis are increased in patients with TTP.[30] We did not systematically search and review the evidence on strategies to reduce the risk of bleeding around catheter placement. Depending on local practice and resource availability, procedures to minimize the risk of bleeding may be considered, including placement by an experienced clinician, ultrasound-guided placement, and internal jugular vein or femoral vein access (rather than subclavian vein access).[31-33] Once the platelet count increases and the patient is stable, clinicians usually regularly review whether lines need to be changed and whether venous thromboembolism prophylaxis should be considered.

3.8 | Statement 8

We did not systematically search and review the evidence on the beneficial or harmful effects of platelet transfusions in TTP. Platelet transfusions are usually avoided and considered unnecessary in most cases of TTP. However, platelet transfusion is often carried out before a correct diagnosis of TTP has been made. There are case reports in TTP patients of the association between platelet transfusions and arterial thrombosis, clinical deterioration, and increased relapse rate.[33-35] However, the causative role of platelet transfusion is not clear. In general, prophylactic platelet transfusions are avoided in nonbleeding TTP patients because their effect is not clear and they carry the potential risk of adverse events, especially when transfusions are repeated. However, platelet transfusions are sometimes used in TTP patients with serious bleedings, or in TTP patients undergoing invasive procedures with a high risk of bleeding.[35] However, whether platelet transfusion should be performed before central line placement depends on the experience of the individual placing the line and the patient's overall bleeding risk.

3.9 | Statement 9

Based on indirect evidence in other critically ill patients, patients with TTP usually receive venous thromboembolism (VTE) prophylaxis. Nonpharmacologic VTE prophylaxis (ie, ambulation as tolerated, graduated compression stockings, intermittent pneumatic compression devices) is usually used while the platelet count is $<50 \times 10^9$/L. Once the platelet count is $>50 \times 10^9$/L, pharmacologic VTE prophylaxis such as low molecular weight heparin should be considered.

3.10 | Statement 10

We did not systematically search and review the evidence on long-term complications of TTP. In patients that have recovered from an acute TTP episode, the panel acknowledged the importance of monitoring for the development of mood disorders, neurocognitive symptoms (including short-term memory issues), and hypertension, which may develop during remission. Specific recommendations regarding screening for long-term complications cannot be made at this time, but serial follow-up and monitoring for these complications should be considered part of routine follow-up.

3.11 | Statement 11

We did not systematically search and review the evidence on the role of support groups for TTP patients. Health care providers may consider offering patients with TTP professional online resources and/or support groups for this rare disease. A number of established support groups exist for individuals with TTP who are going through or have gone through similar experiences. These are listed in Table 1.

4 | RELAPSE PREVENTION

In this section, the panel provides statements pertaining to the relapse prevention beyond what has provided in Recommendations 3-5.

4.1 | Statement 12

We did not systematically review the evidence on triggers for relapse. However, a number of potential triggers for relapse have been suggested in patients with TTP who have achieved clinical remission.[17,36,37] Any illness or a special health condition can trigger a relapse; however, the most commonly discussed triggers include:

- Infections, including influenza, community-acquired pneumonia, periodontal and dental infections, and gastroenteritis
- Pregnancy
- Major trauma or surgery
- Intake of oral contraceptives
- Cocaine and other recreational drugs
- Intake of other drugs including quinine, ticlopidine, clopidogrel, check point inhibitors, cyclosporine, and tacrolimus, etc.
- Pancreatitis

Clinicians usually counsel patients on triggers for relapse and encourage them to seek medical attention for concerning signs and symptoms of any illness.

4.2 | Statement 13

We did not systematically search and review the evidence on the role of ADAMTS13 monitoring in TTP patients in remission. Patients in remission are usually assessed regularly during follow-up (typically every month for the first 3 months, then every 3 months for the first year, then every 6-12 months if stable). If available, ADAMTS13 activity is usually measured serially during each follow-up assessment, and more frequently if levels begin to drop. Durably stable ADAMTS13 activity close to the lower limit of normal is usually a reassuring finding. Conversely, patients with persistently low ADAMTS13 activity (<10 IU/dL or 10% of normal) may be at risk for relapse, which may be prevented by administration of rituximab.[38,39]

5 | OTHER TREATMENT AGENTS FOR TTP

The following nine statements pertain to the use of TTP treatment strategies that fall outside of the panel's prespecified Population, Intervention, Comparison, Outcome questions.

5.1 | Statement 14

We did not systematically search and review the evidence on vincristine for TTP patients. Patients with refractory TTP unresponsive to standard treatments may be considered for other immunosuppressive treatments (with scant supporting evidence), such as vincristine.[40-43] In these cases, vincristine (2 mg) is usually administered intravenously, at a slow rate of infusion. Typically, a single dose is used because additional doses can cause neurotoxicity and bone marrow suppression.[44]

5.2 | Statement 15

We did not systematically search and review the evidence on cyclosporine A for TTP patients. Patients with refractory TTP unresponsive to standard treatments may be considered for other immunosuppressive treatments (with scant supporting evidence), such as cyclosporine A. In these cases, cyclosporine A is usually administered orally (300 mg/day) or intravenously (2-3 mg/kg/day, divided twice daily). The appropriate duration of therapy is unknown, although administration of this drug for several months, followed by tapering, has been reported.[45-51]

TABLE 1 A list of TTP professional online resources and/or support group

Group name	Region/Country	Website
Answering TTP	Canada	https://www.answeringttp.org/
Association ADAMTS13	France	https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=FR&Expert=96406
Associazione Nazionale Porpora Trombotica Trombocitopenica (ANPTT)	Italy	http://www.anptt.org/
Japanese group for cTTP patients	Japan	https://www.facebook.com/uss.ttp/
Oklahoma TTP-HUS Support Group Meetings	Oklahoma, USA	https://ouhsc.edu/platelets/TTP/pt%20group%20meetings.html
The Rhee Wynn Foundation	New Jersey, USA	https://www.reewynn.org/

5.3 | Statement 16

We did not systematically search and review the evidence on cyclophosphamide for TTP patients. Patients with refractory TTP unresponsive to standard treatments may be considered for other immunosuppressive treatments (with scant supporting evidence), such as cyclophosphamide. In these cases, cyclophosphamide (500 mg/day) is usually administered intravenously over a 2-hour period. Typically, a single dose is used because additional doses may cause severe bone marrow suppression.[8,44,51-53]

5.4 | Statement 17

We did not systematically search and review the evidence on splenectomy for TTP patients. This procedure has been largely superseded by other treatments such as rituximab. It is generally not used, but may still have a role in selected TTP patients as a prophylactic/treatment strategy.[54-58]

5.5 | Statement 18

We did not systematically search and review the evidence on azathioprine for TTP patients. Clinicians sometimes may consider azathioprine to inhibit anti-ADAMTS13 autoantibody production, which leads to normalization of plasma ADAMTS13 activity and prevents relapse in patients with refractory disease unresponsive to standard treatments.[59]

5.6 | Statement 19

We did not systematically search and review the evidence on antiplatelet agents for TTP patients. Antiplatelet agents have been used in nonpregnant patients with TTP,[60-65] particularly in the setting of macrothrombotic complications (eg, ischemic stroke and myocardial infarction). Otherwise, antiplatelets are not generally recommended in TTP; their role in preventing relapse is not supported in the literature, and they may be harmful in the acute phase of TTP when the platelet count is low (eg, $<50 \times 10^9$/L). Inputs from cardiologists, neurologists, and/or other vascular medicine specialists are usually sought if antiplatelet agents are considered in the treatment of TTP-related complications.

5.7 | Statement 20

We did not systematically search and review the evidence on anti-C5 monoclonal antibody (eg, eculizumab) for TTP patients. Increased complement activation has been demonstrated in patients with acute TTP. Therefore, clinicians sometimes consider eculizumab in very selected patients with refractory disease or those unresponsive to all other treatment options.[66,67] This strategy should be pursued with caution.

5.8 | Statement 21

We did not systematically search and review the evidence on intravenous immunoglobulin (IVIG) for TTP patients. IVIG is generally not used in TTP. Its efficacy is unknown, and adverse reactions to this product mimic thrombotic, neurologic, and renal manifestations of TTP.[68,69]

5.9 | Statement 22

We did not systematically search and review the evidence on corticosteroid dosage, dose adjustment, or tapering in TTP. In patients with TTP, high dose cocorticosteroids (eg, prednisone, 1 mg/kg per day, orally, or methylprednisolone, 125 mg, IV, two to four times daily) are usually used as the initial regimen.[3,4,45,70] If the platelet count does not increase within 3 to 4 days of treatment, a higher dose of corticoteroids is usually used. High doses of corticosteriods are usually continued until the platelet count is recovered and TPE is stopped. When platelet count recovery is sustained (eg, after 5-7 days), corticosteroids are usually tapered and discontinued over a 3-week period. Tapering may be delayed or slowed based on platelet count, ADAMTS13 test results, and/or neurological symptoms.[44,70]

6 | TTP AND WOMEN'S HEALTH

The following statements pertain to women's health issues in patients with history of TTP: perinatal care; contraception; and pregnancy counseling.

6.1 | Statement 23

Women with a history of TTP who are planning for pregnancy usually receive preconception counseling. The panel acknowledged the importance of offering counseling to all women with a history of TTP who are considering for pregnancy. The risks of TTP with a somewhat unpredictable course must be discussed during the counseling. The patient's individual values and preferences must also be considered. Pregnancy can trigger TTP relapse, resulting in an increased risk of maternal and fetal mortality and morbidity. It is difficult to predict who may experience a relapse during pregnancy. A normal plasma ADAMTS13 activity at the onset of pregnancy in patients with a history of TTP may be associated with a reduced risk of immediate relapse, while a low (eg, <10 IU/dL) plasma ADAMTS13 activity at the onset of pregnancy may be associated with an increased risk of relapse.[71]

6.2 | Statement 24

In some institutions, women with a decreased ADAMTS13 activity (eg, <10 IU/dL) before or at the onset of pregnancy are offered an prophylactic rituximab therapy, with a goal to eliminate anti-ADAMTS13 autoantibodies and normalize plasma ADAMTS13 activity before conception. Evidence of normal ADAMTS13 activity may be associated with a lower risk of relapse in women with a history of TTP.[71,72]

6.3 | Statement 25

Patients treated with rituximab are usually asked to wait for 6 to 12 months following rituximab administration before trying to conceive; normalization of CD19 lymphocyte levels and undetectable serum rituximab levels are often used as the evidence of "drug washout."[19,73] Global drug safety databases suggest that rituximab is associated with few congenital malformations or neonatal infections. However, scant case reports of its use in patients with TTP did not report maternal or neonatal toxicity.[74,75] Nevertheless, women should be informed that the evidence about the safety and efficacy of rituximab in pregnancy is extremely limited and inconclusive.

6.4 | Statement 26

Pregnant women with a history of TTP are usually closely monitored by a hematologist and an obstetrician with experience in maternal fetal medicine/perinatology. The panel supports the involvement of clinicians with expertise in TTP in the care of pregnant women with a history of TTP. Complete blood counts are usually monitored at least monthly. Plasma ADAMTS13 activity is usually monitored monthly or every 2 to 3 months at least. (More frequent monitoring tends to occur if the ADAMTS13 activity begins to drop during pregnancy).

6.5 | Statement 27

TTP presenting in pregnancy generally merits a transfer to a more specialized center with hematologist, obstetrician, and transfusion medicine specialists, and TPE capabilities, for comprehensive and definitive care. As in the case of TTP in nonpregnant patients, daily TPE is generally needed as soon as possible with FFP, or cryopoor plasma, or SD plasma as a replacement fluid. The volume of replacement fluid is usually 1.0 to 1.5 times of patient's plasma volume (ie, 40-60 mL/kg) every 24 hours.[74,76]

6.6 | Statement 28

Women with a history of TTP require close monitoring by a hematologist with experience in TTP and maternal fetal medicine throughout pregnancy. Their risk of relapse is generally considered to be high if they enter pregnancy with plasma ADAMTS13 activity below the normal range. If plasma ADAMTS13 activity falls significantly (eg, usually < 30 IU/dL or 30% of normal) even in the absence of clinical signs/symptoms, TPE and corticosteroids (or azathioprine) are often considered.

It is a good practice to monitor ADAMTS13 activity throughout pregnancy and during the postpartum period. Induction of labor at 36 to 37 weeks' gestation is commonly suggested.[77,78] In the absence of other obstetrical indications for cesarean section, vaginal delivery is considered a preferred method of delivery in pregnant women with a history of TTP. This statement also applies to women with a history of either cTTP or iTTP.

6.7 | Statement 29

Women with a history of TTP who are planning pregnancy usually receive preconception counseling. Pregnant women with a history of TTP have a high risk of serious complications during pregnancy.[78] They receive plasma infusion, at a dose of 10 to 15 mL/kg weekly or every 2 weeks, or TPE, depending on the symptoms. Beginning in the second or early third trimester, the frequency of infusion is usually increased to weekly or twice weekly or TPE. Women with a history of TTP require close monitoring by a hematologist with experience in maternal fetal medicine throughout pregnancy. Induction of labor at 36 to 37 weeks' gestation is commonly suggested.[77] In the absence of other obstetrical indications for cesarean section, vaginal delivery is considered the preferred method of delivery in pregnant women with a history of TTP. These statements apply to women with a history of either cTTP or iTTP.

6.8 | Statement 30

We did not systematically search and review the evidence on the effect of aspirin in pregnant women with TTP. Largely based on indirect evidence from other populations, pregnant women with a history of TTP are usually not offered low-dose aspirin throughout pregnancy.[19]

6.9 | Statement 31

We did not systematically search and review the evidence on the effect of antithrombotic therapy in pregnant women with TTP. Largely based on indirect evidence from other populations, pregnant women with a history of TTP, and a history of venous thrombosis, are usually offered low molecular weight heparin at prophylactic doses throughout pregnancy, with the goal of preventing the formation of placental microthrombi and insufficiency, as well as preventing recurrent venous thrombosis.[19] Offering antithrombotic therapy to women with a history of TTP-associated pregnancy loss, but not venous thrombosis, remains controversial.

6.10 | Statement 32

We did not systematically search and review the evidence on the effect of hormonal preparations, particularly those containing estrogen, as a potential trigger for relapse in women with TTP. Women with a history of TTP are usually counseled that nonhormonal methods of contraception and progestin-only preparations are preferred over estrogen-containing preparations that may promote production of autoantibodies against ADAMTS13.[79-84]

7 | REFUSAL OF BLOOD PRODUCTS

The following statement pertains to care of TTP in patients who refuse blood products.

7.1 | Statement 32

We did not systematically search and review the evidence on alternatives to blood products in TTP patients. Patients with TTP refusing blood products (eg, Jehovah's Witnesses) generally will not accept TPE with replacement of plasma. Clinicians should explore patients' values and preferences to determine if they will accept albumin and other purified protein fractions because these products are sometimes acceptable. This strategy can, at minimum, help remove ADAMTS13 autoantibodies and other potential harmful inflammatory mediators. Clinicians may empirically consider the use of corticosteroids, rituximab, and caplacizumab as well as erythropoietin and folic acid (to promote erythropoiesis).[85-92] If the patient will accept plasma derivatives, factor VIII concentrates containing sufficient amounts of ADAMTS13 may be considered instead of plasma.[90,91] If the patient will accept albumin, TPE with albumin as the replacement fluid may be considered. [88,90]

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CONFLICT OF INTEREST

Dr. Zheng is a speaker and consultant for Alexion, Sanofi-Genzyme, and Takeda, as well as the cofounder of Clotsolution; Dr. Vesely is a biostatistician for the Oklahoma TTP registry; Dr. Cataland is a consultant for Sanofi-Genzyme and Takeda and served on an advisory board for Alexion; Dr. Coppo is a consultant for Sanofi-Genzyme, Alexion, and Takeda; Dr. Matsumoto has received royalty interest from Alfressa Pharma; Dr. Peyvandi is a speaker for Spark Therapeutics, Sobi, Bioverativ, Grifols, Takeda, and Sanofi-Genzyme; Dr. Geldziler is an employee of Merck Pharmaceuticals. Dr. Iorio declare no conflict of interest, but reports that his institution has received project-based funding via research or service agreements from Bayer, CSL, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark, and Takeda; Dr. Pai and other authors whose names are not specifically mentioned in this section declare no conflict of interest.

AUTHOR CONTRIBUTIONS

X. L. Zheng, Sara K. Vesely, Menaka Pai, and Flora Peyvandi reviewed the literature and wrote manuscript; all other authors revised and approved the final version of the manuscript.

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