NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Thrombotic Thrombocytopaenic Purpura, Clinical Management Guideline

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Clinical Management Guideline for Thrombotic Thrombocytopaenic Purpura

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Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is a rare, non-malignant but potentially lethal autoimmune blood disorder. There is a reported incidence of 6 per million per year in the UK although TTP may be under-diagnosed. It is an extremely important diagnosis to make as the untreated mortality is 90%, while prompt appropriate treatment can reduce this to 10% or less. There is also a risk of residual end-organ damage (particularly neurological problems) in a minority of patients, and again this risk can be reduced with prompt diagnosis and treatment. The current BSH guideline gives the full background to these issues (https://b-s-h.org.uk/guidelines/).

The root cause of TTP is deficiency of the enzyme ADAMTS13, which leads to endothelial platelet adhesion via accumulation of high-molecular-weight multimers of von Willebrand Factor (vWF). Accumulation of platelet-rich thrombi in the microvasculature impairs blood flow to critical organs, including the brain, the spinal cord, the heart and (more rarely) the kidneys. Strands of platelet-rich thrombi lead to mechanical damage to red blood cells with resultant microangiopathic haemolytic anaemia.

Most TTP cases are autoimmune, with an antibody against ADAMTS13 blocking enzyme activity. A small proportion of cases are genetic, due to mutations in the ADAMTS13 gene, and these cases tend to present in childhood or adolescence.

Differential Diagnoses: other Thrombotic Microangiopathies.

There is some clinical overlap between TTP and Haemolytic Uraemic Syndrome (HUS), as well as some overlap with the pregnancy complication of “HELLP” syndrome. Significant renal involvement in TTP is relatively rare, and presenting platelet counts are typically below 30 (in contrast with HUS where renal impairment is common and presenting platelet counts are usually above 30). However, the initial treatment of all three conditions in adults is similar, and where there is clinical doubt, patients should be treated as having TTP pending confirmation of the diagnosis.

Transplant-associated thrombotic microangiopathy (TMA) (usually following allogeneic haemopoietic stem cell [HPC] transplant) and cancer-associated thrombotic microangiopathy (in patients with known metastatic cancer) may mimic TTP clinically. However, these conditions are not typically associated with reduced ADAMTS13 levels and there is lack of evidence to support the use of therapeutic plasma exchange (TPE) in these patient groups.
Rituximab is also ineffective in cancer-associated TMA. It is currently unclear whether rituximab is effective in transplant-associated TMA and various other pharmacological options are still being studied, including eculizimab and defibrotide (Khosla J et al, 2018).
Drug-associated TMA may also mimic TTP. While several drugs have been reported, the most commonly implicated include: clopidogrel, calcineurin

inhibitors, oestrogen/progesterone, gemcitabine, interferon, mitomycin, quinine and ticlodipine. Recent case reports have also implicated oxymorphone, bevacizumab, carfilizomab, ixazomib, and palbociclib. Of these, ticlodipine is the only implicated drug that results in severely diminished ADAMTS13 levels with inhibitors present and is the only drug-induced TMA association where evidence for the benefit of TPE exists. Other drug-induced TMAs are typically associated with normal ADAMTS13 levels and there is no evidence to support the use of TPE in these instances.

Guidance on the diagnosis and management of other recognised syndromes of TMA can be found in the guidelines of the American Society for Apheresis (ASFA). (Padmanabhan, 2019).

Diagnostic features

The minimum criteria for a diagnosis of TTP are:

- **Microangiopathic haemolytic anaemia (MAHA) on blood film microscopy**

AND

- **Thrombocytopenia**

Some patients may have other features of the "classic pentad" which may further support the diagnosis, but these **do not have to be present** to make the diagnosis. These are:

- Fever
- Neurological features (seizures; confusion; focal neurological signs)
- Renal impairment (note: most TTP patients have normal or only mildly abnormal renal function at presentation. Severe renal failure should suggest an alternative diagnosis of HUS)

Additionally, virtually all patients have a **significantly elevated LDH** at presentation, reflecting significant active haemolysis.

Initial evaluation

- FBC and film
- U&Es, LFTs, Ca++
- LDH
- Coagulation screen (often normal in TTP)
- D-Dimers
- Sample for "Group and Save"
- 2 x citrate (blue-top Vacutainer) blood samples sent **immediately** to the haemostasis laboratory at Glasgow Royal Infirmary for ADAMTS13 activity levels. (samples will be forwarded for antibody testing if ADAMTS13 activity levels are low)
- ECG (beware silent cardiac involvement)
- Troponin T (for all patients, regardless of clinical evidence of cardiac involvement)
- HIV test (HIV is a known cause of TTP although most cases are HIV negative)
- Pregnancy test for women of childbearing age
- Review of pre-existing medication (some drugs can trigger TTP – calcineurin inhibitors, ticlopidine, clopidogrel, quinine, simvastatin)
- Review for potential underlying malignancy

Initial treatment

- The patient should be transferred **immediately** to the care (or joint care in the case of GRI) of a **Haematology Consultant.** See guidance below ('Transfer of patients with TTP from outlying hospitals for plasma exchange')
- **AVOID PLATELET TRANSFUSION unless the patient has severe haemorrhage**
- Patients should be admitted to a critical care unit and remain there for at least the first 48 hours and ideally until ADAMTS13 levels are improving and the patient is clinically stable.
- The SNBTS apheresis team at the BOC must be contacted immediately (for telephone numbers - see below) and **daily plasma exchange** with Octaplas (SD-FFP) must be started **immediately (including out of hours).**
- Exchange 1.5x plasma volumes for at least 3 days. Exchange volume may be dropped to 1 plasma volume thereafter, providing platelet count has risen significantly.
- **Central venous access**, with a non-tunnelled dialysis-type line, should be established **immediately** by an experienced operator for patients whose peripheral veins are inadequate for apheresis. Platelet transfusion is **not** indicated prior to line insertion irrespective of platelet count
- The patient should also receive **corticosteroids**: EITHER IV Methylprednisolone 1 gram daily for 3 days OR oral Prednisolone 1 mg/kg daily for 7 days, with P.P.I. cover
- **Caplacizumab** should be prescribed for all patients with a clinical presentation of TTP and who have a **confirmed ADAMTS13 activity level <10%**, unless clinical contraindications exist (see SMC caplacizumab 10mg powder and solvent for injection (Cablivi) published 07 September 2020).
- Caplacizumab inhibits the interaction between von Willebrand Factor and platelets thereby preventing platelet adhesion mediated by ultra-large vWF (UL-vWF) multimers that bind to platelets and induce adhesion. This results in an acquired VWF disease phenomenon and a potential bleeding risk. Please see below for management of bleeding symptoms.
  Please contact your pharmacist to arrange delivery of the drug to the clinical area.
  - Administration of caplacizumab
    - First dose 10mg <u>intravenous</u> injection **prior** to exchange.
    - Subsequent doses 10mg <u>subcutaneously</u> daily **after** completion of each plasma exchange.
    - Continue daily for the duration of plasma exchange, followed by a further 30 days of caplacizumab 10mg SC injection daily from day two onwards.
- All patients should be considered for 4 doses of **Rituximab** 375 mg/m^2, every 3 to 4 days and started as soon as feasible, unless contra-indications exist (NB - important to investigate for underlying

malignancy). Note that a recent study showed efficacy of lower dose rituximab (100mg/m^2 IV once weekly for 4 weeks) (Zwicker at al, 2018), however randomised controlled trials comparing the two dosing regimens have not yet been performed. Furthermore, whilst the study reported similar efficacy, there was no reduction in adverse events, suggesting that the main benefits of reduced dose rituximab would be financial rather than clinical.

Daily plasma exchange should **not** be interrupted but rituximab should be given immediately after that day's plasma exchange with the next day's exchange delayed until the afternoon if feasible.

- TTP is often associated with hypertension, and blood pressure should be controlled with anti-hypertensives as necessary and increased blood sugars, which may also require treatment, both due to steroid therapy.
- Aspirin may be considered, only for patients NOT receiving Caplacizumab and upon platelet count recovery.

Ongoing Treatment

- Patients must have daily blood samples checked for:
    - FBC (haemoglobin and platelets)
    - LDH
    - U&Es, LFTs and Calcium
- Normalisation of the **platelet count** was previously used as a marker of recovery, however, caplacizumab will increase the platelet count, while the underlying pathological process due to low ADAMTS13 persists.
  Platelet count recovery is therefore not a reliable marker of true "remission" in a patient receiving caplacizumab, in the sense that the TTP may relapse rapidly if caplacizumab is stopped before adequate recovery of ADAMTS13 levels.
  However, platelet recovery (with or without caplacizumab) is still associated with significant reduction in mortality and in end-organ damage.
- **Red cell fragmentation** can persist for up to 2 weeks in patients in remission and is not a reliable marker of response.
- **ADAMTS13 assay, and (if present at diagnosis) anti-ADAMTS13 antibody,** should be repeated after a minimum of 7 days, and a maximum of 10 days, after starting plasma exchange.
- Plasma exchange may be discontinued once the platelet count is normalised. Caplacizumab should be continued until ADAMTS13 levels of >30% are confirmed and increasing. It is expected that the majority of patients will start **rituximab** at the outset of treatment. Despite caplacizumab normalising the platelet count, it has no effect on ADAMTS13.Therefore, to ensure patients do not relapse, rituximab is essential to switch off production of ADAMTS 13 antibodies and aid normalisation of ADAMTS 13 activity.
- **Folic acid 5 mg PO daily** should be started at diagnosis.
- Blood transfusion may be needed depending on Hb levels.
- For all patients, including those on Caplacizumab, consider starting **prophylactic dose LMW Heparin** once the platelet count is greater than 50 x 10^9/litre.
- HIV positive patients must receive prompt HAART. Otherwise treatment is the same as for idiopathic / autoimmune TTP.
- All new TTP patients should be entered into the UK TTP Registry if they are willing. Please contact the Apheresis Consultant for Registry Consent paperwork and for details of specimen requirements.

Management of Bleeding complications on Caplacizumab:

Caplacizumb results in an acquired VWD phenomenon. For this reason, patients are at increased risk of bleeding. Minor mucosal bleeding is common (65%). However major bleeding is rare.
Recommended management
Minor bleeding symptoms

- Withhold caplazicumab
- Check VWF activity (request VWF screen)
- Consider tranexamic acid 1g tds

Major bleeding symptoms

- Withhold caplazicumab
- Urgently check VWF activity if recent result not available
- If VWF activity <20%, administer Veyvondi 30 IU/kg
- If VWF activity 20-40%, administer Veyvondi 20 IU/kg
- Consider tranexamic acid 1g tds

Transfer of patients with TTP from outlying hospitals for plasma exchange

Patients in the West of Scotland presenting with TTP outwith GG&C catchment area **must** be transferred to a hospital in GG&C for plasma exchange, since this is not available locally. Once a patient has been identified the following pathway should be followed:

1. Referring clinician contacts the SNBTS on-call Consultant Haematologist (via SNBTS switchboard on 0141 433 5800, or during office hours directly to CAU on 0141 301 7014) with patient details including investigations performed.

2. SNBTS Consultant contacts the Haematology Consultant on call for the Queen Elizabeth University Hospital (QEUH) with a request for a bed for the patient.

3. QEUH Consultant is responsible for arranging an appropriate critical care bed for the patient. This will involve discussion with the ICU referrals Consultant (Extension 83081). Ideally this will be a bed in ICU. Once a bed has been identified the QEUH consultant will contact the following people:
    - Referring Consultant, with details of bed availability **OR** if there are no beds available on that site, explain that patient details have been passed to the Consultant on call for GRI and provide their name and contact details
    - SNBTS Consultant, with details of location of patient. SNBTS Consultant is then responsible for organising transfer of appropriate exchange fluid to QEUH blood bank, informing blood bank staff of this, and arranging transfer of cell separator machine. The on-call nurse for CAU will assist with some of these tasks where appropriate.

- Haematology junior doctor on call, who is responsible for seeing the patient on their arrival and arranging any relevant blood tests in consultation with CAU doctor and ensuring blood bank have request form for exchange fluid.

IF there are no beds available at QEUH, the Consultant on call for QEUH will contact the Consultant Haematologist on call for GRI who will work through the steps above.

Treatment of Refractory and Relapsed TTP

Refractory TTP is defined as "**progression of clinical symptoms despite plasma exchange, or failure of thrombocytopenia to normalise after 7 days of plasma exchange"**.

Relapsed TTP is defined as **"recurrence of thrombocytopenia and MAHA after initial treatment response".**

- If, at the end of the 30-day post-plasma exchange Caplacizumab therapy, there is evidence of unresolved immunological disease, it is recommended to optimise the immunosuppression regimen and continue daily caplacizumab 10mg SC administration until the signs of underlying immunological disease are resolved (for example, normalisation of ADAMTS13 activity level to >30%). In the clinical development program, caplacizumab has been administered for up to 65 days. No data on re-treatment with caplacizumab are available.
- **Rituximab 375 mg/m^2 weekly for 4 weeks** must now be given if it has not already been started. Daily plasma exchange should **not** be interrupted but rituximab should be given immediately after that day's plasma exchange with the next day's exchange delayed until the afternoon if feasible.
- **Plasma exchange should continue** or be re-started. If re-started, consider 1.5 plasma volume exchange for first 3 days.
- **Fresh citrated plasma should be sent for ADAMTS13 assays**, even if already done at first presentation**.**
- **Consider increasing frequency of plasma exchange to twice daily** for patients with progressive clinical symptoms, especially progressive neurology.
- **Consider alternative diagnoses**: cancer-associated thrombotic microangiopathy (consider check tumour markers, D-Dimers, CT neck, chest, abdomen, pelvis & bone marrow biopsy); HUS (check stool cultures and serology for E. coli O157; consider complement co-factor assays if renal function is significantly abnormal and VTEC HUS has been excluded – discuss with Apheresis Consultant); pancreatitis (another common association: check amylase if patient has abdominal pain)
- Third-line treatment is usually oral ciclosporin/MMF/azathioprine.
- Fourth-line treatment options include cyclophosphamide and splenectomy: however, the advice of the CAU consultant should be sought before initiating any fourth-line treatments.

Patient Information

A patient information leaflet on TTP is available from the Clinical Apheresis Unit at the Beatson West of Scotland Cancer Centre, or on the GG&C staff intranet.

Contact telephone Numbers

Beatson West of Scotland Cancer Centre
Clinical Apheresis Unit: 0141 301 7013 / 7014
(Out of hours contact apheresis team via SNBTS RTC 0141 433 5800)

Queen Elizabeth University Hospital, haematology consultant on call:
contact via hospital switchboard 0141 201 1100

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Caplacizumab Prescribing Information:

https://www.medicines.org.uk/emc/product/10347#gref

https://www.scottishmedicines.org.uk/medicines-advice/caplacizumab-cablivi-full-smc2266/