Trust Guideline for the Management of Thrombotic Thrombocytopenic Purpura (TTP) in adults

A Clinical Guideline

For use in:	All departments of Norfolk & Norwich University Hospital
By:	Medical, Nursing and Laboratory staff NNUH
For:	Suspected thrombotic thrombocytopenic purpura in adults
Division responsible for document:	Medical
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Description of changes:	BCSH guidance on FFP incorporated, adjunct to PEX, refractory and relapsed disease updated
Compliance links: *(is there any NICE related to guidance)*	None
If Yes - does the strategy/policy deviate from the recommendations of NICE? If so why?	N/A

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.

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Quick Reference

Suspect TTP in all cases of thrombocytopenia and microangiopathic haemolytic anaemia

History and examination:

Consider underlying causes and predisposing factors (see below)
Conduct and record full neurological examination including accurate recording of Glasgow coma scale (GCS) and mini mental test.

Investigations at presentation:

FBC, blood film, reticulocyte count, coagulation screen, fibrinogen, D-Dimer, direct antiglobulin test, U&E, LFT, group & screen, pregnancy test, HIV test, ANA, ECG, stool culture for E.coli 0157 (if diarrhoea), Hepatitis B and C full septic screen (blood cultures MSU and throat swab) ADAMTS-13 assay, C3/C4

Consider predisposing or exacerbating factors:

- Pregnancy
- Infection
- HIV
- SLE and other auto-immune diseases
- Medications

If TTP is suspected or diagnosed, inform on-call haematology consultant, on-call nephrologist and blood bank.
Discuss with ICU if haemodynamic, cardiac or neurological compromise.
Patients should be managed on renal or haematology ward (unless ICU care required).

Consider alternative diagnoses:

- Haemolytic Uraemic Syndrome (HUS)
- HELLP syndrome
- Pre-eclampsia
- Disseminated intravascular coagulation (DIC)
- Catastrophic antiphospholipid syndrome
- Evan's syndrome
- Heparin induced thrombocytopenia (HIT)
- Small Vessel Vasculitis
- Systemic lupus erythematosus (SLE)
- ITP
- Malignancy

Initial Management:

TTP is a medical emergency. Do not delay treatment.
Treatment is plasma therapy. If plasma exchange is not immediately available give 30mL/kg Octaplas (solvent detergent FFP) by IV infusion (rate 10ml/kg/hr or as clinically tolerated).
Plasma exchange with Octaplas should be initiated within 4-8 hours of presentation where possible.
Use FFP if Octaplas is unavailable.
Exchanges should continue daily until remission has been achieved. PEx volume is as per Renal Protocol
Monitor FBC, Blood film, UE, calcium and LDH daily.
Remission defined as platelets >150x10^9/l

Supportive management:

Methylprednisolone 1g IV daily for 3 days followed by oral prednisolone 1mg/kg OD until remission is achieved then tapered (reducing course till stop over 6 weeks).
Aspirin 75mg OD once platelets >50x10^9/L
Prophylactic low molecular weight heparin once platelets >50x10^9/L
Blood transfusion as clinically indicated
Platelet transfusions are contraindicated unless major bleeding

Discuss refractory cases with UCH TTP centre, Department of Haemostasis, University College London

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Objectives

To aid the timely investigation, diagnosis and management of adult patients with suspected TTP.

Rationale

TTP is a rare, life-threatening condition caused by deficiency of von Willebrand factor cleaving protease enzyme (ADAMTS-13). This results in the accumulation of ultra-high molecular weight von Willebrand factor multimers which trap platelets in the microcirculation. The resulting microthrombi cause end organ damage, frequently to the brain, kidneys, heart and gut. Deficiency of the enzyme is usually autoantibody mediated.

Without treatment, TTP has a >90% mortality. Treatment with plasma exchange results in <10% mortality. The prognosis is worse if there is delay in commencing treatment.

This guideline has been adapted from the British Committee for Standards in Haematology (BCSH) guideline: diagnosis and management of thrombotic thrombocytopenic purpura and other microangiopathies (2012). This is available at www.bcshguidelines.com

Broad recommendations

Background:

TTP is characterised by:

- **microangiopathic haemolytic anaemia (MAHA)**
- **thrombocytopenia**

Associated end organ damage may manifest as:

- Renal failure,
- CNS involvement (headache, altered mental state, transient ischaemic attack (TIA), seizure, coma)
- Bowel involvement (ischaemia),
- Liver involvement (transaminitis)
- Heart involvement (chest pain, myocardial infarction, heart failure).

Fever is frequently present. This may be a feature of TTP or concomitant infection.

Note that **not** all features are necessary to make the diagnosis of TTP. The diagnosis should be considered in the presence of thrombocytopenia and MAHA alone.

Other conditions that may mimic TTP are:

- Haemolytic Uraemic Syndrome (HUS)
- HELLP syndrome
- Pre-eclampsia

- Disseminated intravascular coagulation (DIC)
- Catastrophic antiphospholipid syndrome
- Evans syndrome (Haemolytic anaemia and ITP)
- Heparin induced thrombocytopenia (HIT)
- Small vessel vasculitis
- Systemic lupus erythematosus (SLE)
- Idiopathic thrombocytopenic purpura or Immune thrombocytopenia (ITP)
- Malignancy

If there is any doubt as to whether a patient has TTP they should be managed as if they have TTP until proven otherwise.

TTP may be either familial or acquired.

Underlying causes of acquired TTP should always be considered. (Pregnancy Infection, HIV, SLE and other auto-immune diseases), Medications (quinine, OCP, ticlodipine, mitomycin-c, clopidogrel, calcineurin inhibitors - ciclosporin, tacrolimus).

Familial forms usually present in childhood but may present later in life. Familial TTP can be precipitated by other events such as pregnancy, medications and co-morbid conditions.

Investigations:

Investigation	**Rationale**
FBC	Thrombocytopenia and anaemia
Blood film	Evidence of MAHA
Reticulocyte count	Evidence of haemolysis
Direct Antiglobulin Test (DAT)	Positive in Evan's syndrome
Group and Screen	Determine blood group for plasma
PT, APTT, Fibrinogen, D-Dimer	To differentiate from DIC
ADAMTS-13 assay (**1 x blue top citrate)**	Confirms diagnosis
U&E	Renal failure
LFT	Haemolysis, transaminitis
LDH	Marker of haemolysis and tissue ischaemia
Troponin	Myocardial damage
ANA, anticardiolipin antibodies	SLE can precipitate TTP
C3/C4	Differentiate from aHUS
Pregnancy test	Pregnancy can precipitate TTP
Hepatitis serology (HBsAg, anti-Hep C)	Required by Renal team (isolate dialysis machine if positive)
HIV Test	HIV can precipitate TTP
Stool culture for E.coli 0157 (if diarrhoea)	HUS associated with E.coli 0157
ECG + 2D Echocardiography	Cardiac manifestations of TTP

NB:
The blood film does not always show the classical picture of fragmentation and polychromasia immediately. It can take 24-48 hours to develop.

The coagulation screen is typically normal in TTP and this will help to differentiate TTP from DIC.

TTP is associated with HIV in 1.4-7% cases. Prompt initiation of anti-retroviral therapy in patients with HIV and TTP is associated with improved outcomes. HIV testing (with informed consent) should therefore be part of routine assessment.

ADAMTS-13
It is essential that a sample for ADAMTS 13 activity and antibody testing is sent prior to plasma exchange. Discuss with a Haematologist who will liaise with the referral laboratory and discuss turnaround times. Request on webICE. **One blue top Vacutainer (citrate) needs to be sent – this is used to test for both the ADAMTS-13 level and inhibitory antibody.**

Haemolytic Uraemic Syndrome is a notifiable disease.

Atypical HUS predominantly affects children but may present in adult patients. This is characterised by acute renal failure and MAHA without a history of infective diarrhoea. In patients with this phenotype, samples for deficiency of complement pathways should be sent as per instructions in current national guidelines (Taylor et al reference 7). These will be requested by a Haematology or Renal consultant.

Initial Management:
Patients with confirmed or suspected TTP should be immediately discussed with the duty Consultant Haematologist and Nephrologist. Inform Blood Bank as early as possible. Patients should be managed on either the haematology or renal wards. Inform ICU early if there is haemodynamic instability, cardiac or neurological impairment.

Plasma exchange should commence within 4-8 hours of diagnosis. If this is not possible plasma infusion (30mL/kg IV) has been proven to reduce mortality although is not as effective as plasma exchange.

The NNUHFT plasma exchange regimen is weight-based volume exchange performed by plasma filtration every 24 hours according to Renal guidelines, and performed by the Renal department. If there is no response after 7 days, or if there is clinical deterioration, plasma exchange can be increased, subject to availability. Centrifugal plasma exchange is not available.

Venous access will be supervised by the renal unit.

The plasma of choice for plasma exchange is imported solvent detergent FFP (SDFFP - Octaplas). This has been implemented following a directive by the Department of Health. The intended benefit is reduced risk of contracting new variant CJD. There may also be a reduced risk of viral transmission and transfusion reactions. If there is no solvent

detergent FFP available, conventional FFP may be used until Octaplas becomes available.

There is great variability in the number of exchanges required to achieve remission. The average number of exchanges required is 16, but this may be fewer if caplacizumab treatment is given (see below). Plasma exchange should be continued until 2 days after remission has been achieved (defined as platelet count >150 x 10^9/L)

Once remission is achieved exchanges can be stopped, and the patient observed to ensure remission is maintained

Daily blood tests should include FBC, LDH, U&Es.

Adjunctive treatments:

- 1g methylprednisolone IV daily for three days. This should be followed by prednisolone 1mg/kg tapered rapidly (over 6 weeks) once remission has been achieved.
- Once platelet count > 50x10^9/L commence aspirin 75mg OD.
- Prophylactic low molecular weight heparin should be started when platelet count is above 50x10^9/L.
- Rituximab is usually required as part of initial therapy. If patient has cardiac or neurological features at presentation (associated with poor prognosis) give first dose immediately after 1st plasma exchange. In lower risk patients can consider giving after plasma exchanges stopped as an adjunct to prevent relapse.
- Caplacizumab (subject to funding and availability) – this is a bivalent nanobody that inhibits the vWF-platelet interaction, and can be used alongside plasma exchange and immunosuppression to decrease microvascular thrombosis and shorten the period of thrombocytopenia. If this is drug is used consider withholding aspirin and LMWH.

Platelet transfusions are contraindicated. Platelets should only be considered if there is catastrophic bleeding or a requirement for urgent surgery that cannot wait until after plasma exchange. Red cell transfusions should be administered according to clinical need.

Management of refractory or relapsing disease:
Refractory disease is defined as persistent thrombocytopenia or progression in symptoms despite plasma exchange. Rituximab should be added if not already given. Other agents that may have efficacy include ciclosporin, cyclophosphamide, vincristine and bortezomib and should be considered on an individual case basis.

Following remission ADAMTS13 should be monitored for detection of pre-symptomatic relapse. Consider Rituximab to prevent relapse if level falls to < 10-20%.

Clinical audit standards
This is a rare disease. No audits are planned.

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Summary of development and consultation process undertaken before registration and dissemination

This 2019 update has been agreed by the authors prior to submission to the Clinical Guidelines Assessment Panel.

This version has been endorsed by the Clinical Guidelines Assessment Panel.

Distribution list / dissemination method

Trust intranet

References / source documents

BCSH Guidelines: Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies 2012. www.bcshguidelines.com

BCSH Guidelines: Guideline on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding 2018
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Glossary

ADAMTS 13	A Disintegrin and Metalloprotease with ThromboSpondin Type 1 motif-13
BCSH	British Committee for Standards in Haematology
DIC	Disseminated intravascular coagulation
FFP	Plasma exchange imported solvent detergent FFP (Octaplas).
GCS	Glasgow coma scale
HELLP	Haemolysis Elevated Liver Enzymes and Low Platelets
HIT	Heparin induced thrombocytopenia
HUS	Haemolytic Uraemic Syndrome
ITP	Idiopathic thrombocytopenic purpura or Immune thrombocytopenia
MAHA	Microangiopathic haemolytic anaemia
SLE	Systemic lupus erythematosus
TIA	Transient ischaemic attack
TTP	Thrombotic thrombocytopenic purpura