University Hospital Southampton
NHS Foundation Trust

Management of Acute Thrombotic Thrombocytopenia Purpura (TTP) guideline, version 1

Trust reference		Version number	1
Description	Guideline on the diagnosis, acute management and follow-up of patients with TTP		
Level and type of document	Level 1: applicable across the Trust Clinical guideline – controlled document		
Target audience	Clinical teams that diagnose and contribute to the management of TTP		
List related documents / policies (do not include those listed as appendices)			
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Document sponsor	Dr Trevor Smith, Division B director		

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1 Version Control

Date		Author(s)	Version created	Approval committee	Date of approval	Date next review due	Key changes made to doc
18/2/22		S.Boyce	1	Drugs Committee	18/2/22		

Thames Valley and Wessex
TTP Network

2 Index

3 Introduction

Thrombotic thrombocytopenic purpura (TTP) is an acute and life-threatening condition that requires emergency plasma exchange within 4-8 hours of referral to a specialist centre. University Hospital Southampton is one of 9 specialist regional centres and 11 participating hospitals commissioned by the NHS to provide specialist treatment for TTP. As such there is no policy on the maximum number of cases that can be admitted, and this will have to be guided by the current case load. This protocol covers the investigation and management of TTP

Wessex TTP Network

University Hospital Southampton
Queen Alexandra Hospital, Portsmouth
St Richard's Hospital, Chichester
Basingstoke and North Hampshire Hospital
Royal Hampshire County Hospital, Winchester
St Mary's Hospital, Isle of Wight
Salisbury District Hospital
University Hospital Dorset, Bournemouth and Poole
Dorset County Hospital, Dorchester

3.1 Specialist Service Recognition For TTP (NHS England)

With the new service specification as per NHS England, all centres treating TTP will be formally funded by this route. As such, specific requirements need to be met, including:

1. The accepting centre (specialised centre) must have an 'automatic acceptance' policy. Patients must not be refused admission due to non-availability of beds

2. All patients must have started Plasma Exchange within 4-8 hours of referral to the specialist TTP centre**.**
3. 24/7 access to therapeutic apheresis
4. Level 3 Critical Care Facilities
5. Interventional Radiology/ IV Access Team access 24/7 for urgent line insertion for patients not entering ITU
6. Specialist Haematology Ward, with experience in treating TTP
7. Dedicated TMA Consultant Team with 24/7 on call availability
8. A named paediatric haematologist for congenital TTP delivered through the clinical partnership with the paediatric specialist centre
9. Intensive care specialists with experience in the management of this condition.
10. Support patient groups
11. Clinical Nurse Specialists for TTP
12. Trust Approved Patient Pathways, SOPs and Protocols based on the Clinical guideline that accompanies this service specification.
13. Ability to carry out the appropriate diagnostics, including access to ADAMTS13 testing 7 days a week.
14. Access to neurological, cardiac and other relevant services e.g., rheumatology, HIV, obstetrics
15. Access to a dedicated clinical psychologist.
16. Participate in national clinical forum

Participation in markers of quality indicators and activity for submission to NHSE (on a monthly basis) appendix 4

4 Scope

This guideline is for all staff at University Hospital Southampton who are involved in the care of patients with TTP and suspected TMAs.

5 Aim/Purpose

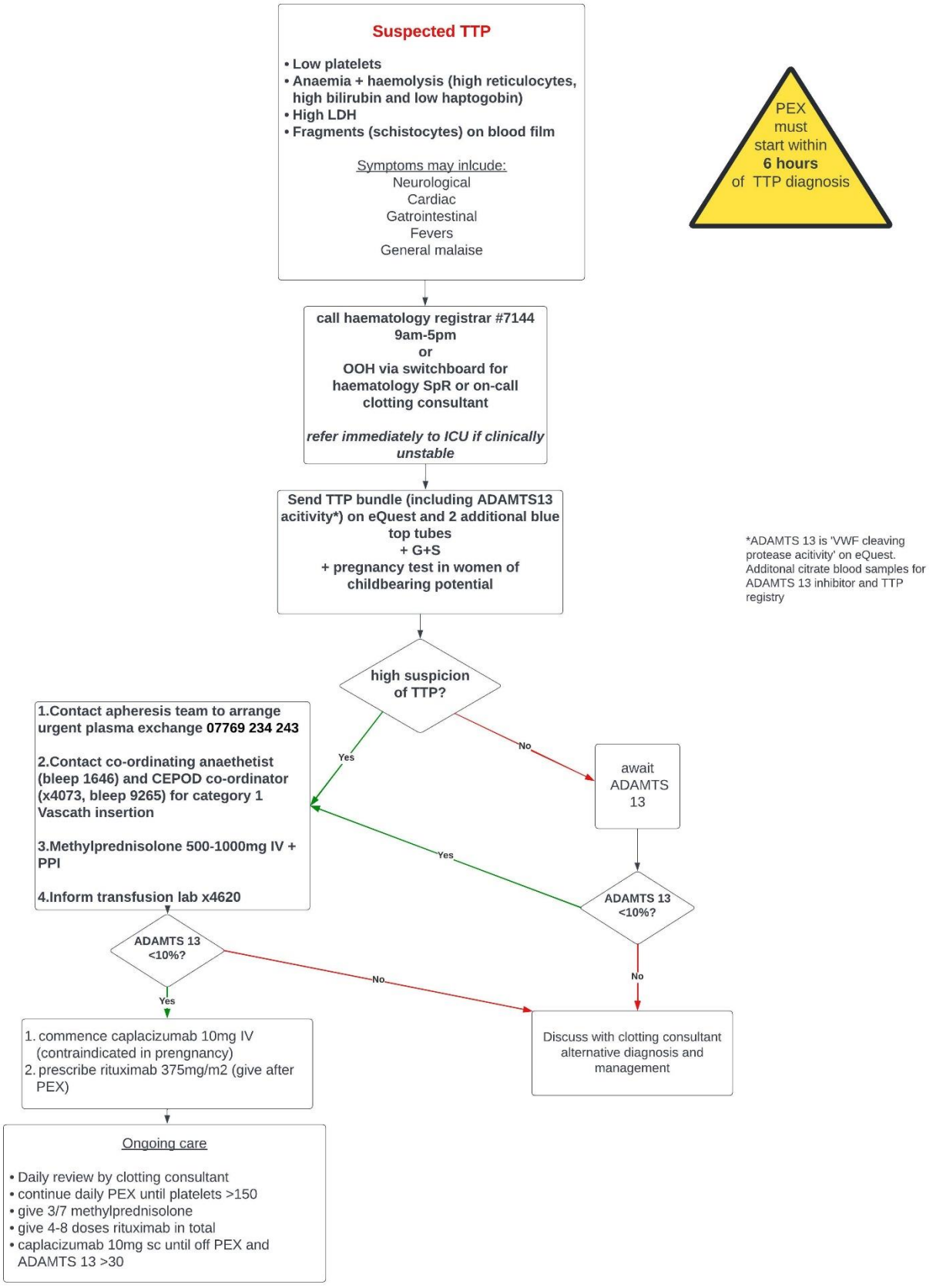
This document is to aid the rapid recognition and management of patients with thrombotic thrombocytopenia purpura to optimise patient outcomes

6 Definitions (If Necessary)

AOS:	Acute Oncology Service
CNS:	Clinical Nurse Specialist
FFP:	Fresh Frozen Plasma
HELLP:	Haemolysis, Elevated Liver Function and Low Platelets
HUS:	Haemolytic Uraemic Syndrome
ITU:	Intensive Therapy Unit
LMWH:	Low molecular weight heparin - enoxaparin
TMA:	Thrombotic Microangiopathy
TPE:	Therapeutic Plasma Exchange
TTP:	Thrombotic Thrombocytopaenic Purpura
UCLH:	University College London NHS Trust Hospitals
UHS:	University Hospital Southampton
CM HUS:	Complement mediated HUS
IA HUS:	Infection associated HUS
STEC:	Shiga toxin-producing Escherichia coli.
PEX:	Plasma exchange

7 Guideline On The Diagnosis And Management Of Thrombotic Thrombocytopenic Purpura

7.1 Acute TTP Management Pathway



7.2 New Patient Referral (Non-ICU Transfer)

All patients referred with suspected acute TTP should be accepted following urgent discussion with the on-call haemostasis consultant. The on-call haematology registrar (5pm-9am via switchboard) or the clotting registrar (9m-5pm #7144 or 07585880224) should do the following once accepted:

1. Confirm a bed either on C2 or AOS for patients being transferred to UHS from another hospital by contacting SPOC (bleep 2122) during normal working hours or the cancer care bleep holder (bleep 1102) out of working hours. From 8am to 8pm patients can go directly to C7 for plasma exchange; this is arranged by the apheresis team (below)

2. Call the Apheresis team to arrange emergency plasma exchange 07769 234 243

3. Arrange an emergency line insertion and ICU assessment via the anaesthetics co-ordinator (bleep 1646) and CEPOD co-ordinator (x4073 bleep 9265).

    - The haematology team must complete the consent form for line insertion
    - Vascath central venous catheters are provided from stock on C7
    - It is the responsibility of the haematology team to ensure the patient gets to theatres for the line insertion promptly
    - Post line-insertion CXR should be arranged by the haematology team

4. All patients not requiring intensive care need an inpatient bed on C2 haematology ward.

5. Call the TTP CNS if 9am-5pm Monday to Friday (x4047)

The 'Wessex Suspected TTP Referral Form' (APPENDIX 1) should be completed for the referred case, even if not accepted for transfer.

7.3 Transfer

The registrar at UHS accepting the referral should make arrangements via AOS and/or SPOC (bleep 2122, OOH cancer care bleep holder 2122), or with ITU if required on bleep 2110

Patients require transfer with a medical escort and review by the escorting team pre-transfer because of the risk of deterioration during transfer. It is the responsibility of the referring centre to assess the patient prior to transfer and to arrange appropriate supervision for the transfer.

A direct ITU transfer should be requested if the patient is haemodynamically and/or neurologically unstable. The patient must be reviewed by the ICU team at the referring centre and critical care transfer requested. There needs to be discussion with the UHS on call ITU consultant and ITU nurse in charge

In the event of multiple regional acute TTP referrals with lack of bed capacity regional patients can be referred to University College London, by the referring hospital, for direct transfer.

Patient Transfer From Referring Site

A doctor from the referring centre must organise for an immediate blue-light ambulance transfer direct to the UHS AOS/C2/C7 apheresis without avoidable delay.

TTP is now one of the specialist conditions that are part of the national critical care transfer list. Patients requiring immediate transfer should be discussed directly with South Central Ambulance Service (click here for pathway)

Methylprednisolone 1 gram intravenously and Fresh Frozen Plasma (FFP) infusion (preferably solvent detergent plasma (Octaplas) (10-15ml/kg)) should be given while awaiting transfer if there are any delays in cases of suspected TTP. This should not delay the transfer. The cancer care SPOC (bleep 2122) or bleep holder (bleep 1102), anaesthetics co-ordinator (bleep 1646 for duty consultant 8am-6pm, bleep 2265 for co-ordinating SpR 6pm-8am/weekends) the Apheresis Service (077 6923 4243) must be notified with an estimated time of arrival.

7.4 Admission

An admission checklist should be completed by the haematology registrar admitting the patient (APPENDIX 2)

On arrival, the clotting registrar must immediately assess the patient during day shift hours (07585 880224 or #7144) or the on-call registrar (contactable via switch board) out of hours. The registrar should contact the apheresis team (tel) immediately to arrange emergency plasma exchange. The anaesthetics co-ordinator (bleep 1646 for duty consultant 8-8, bleep 2265 for co-ordinating registrar) 6pm-8am/weekends) also must be contacted to confirm arrival; their team will arrange urgent Vascath insertion (section 7.4) and review the patient to ensure patients not immediately transferred to ICU are safe to manage on the ward.

Admission blood samples for baseline TTP assessment (detailed in section 7.6 must be taken immediately by requesting the TTP bundle on eQuest and by sending a transfusion Group and Screen. The blood film must be reviewed by the appropriate registrar. A group and save sample (and a second check sample if there is no historical blood group on record) must be sent immediately to Blood Transfusion and the Blood Transfusion laboratory contacted on x4620 to confirm blood group and the appropriate volume of plasma product ordered (60ml/kg for a 1.5 volume exchange).

If the patient is severely unstable (haemodynamically and/or neurologically) then the on-call haemostasis consultant will authorise the use of blood group AB Octaplas for the first plasma exchange. This will allow for the replacement fluid to be ordered before the patient arrives on the unit and for the therapeutic plasma exchange to commence without delay, whilst awaiting the patient's group and save and confirmation check group.

Patients should have urgent insertion of a Vascath. This should be inserted within 1 hour of arrival to UHS.

The anaesthetic/ITU team are aware of the urgent need for Vascath insertion in TTP patients and will give them appropriate priority. If at all possible the Vascath should be positioned in the neck as opposed to the groin to limit the risk of catheter-associated infection. However, acutely, a femoral line is the quickest position for access.

Platelet transfusions are contraindicated for Vascath insertion based on thrombocytopenia alone. Radiological guidance should be used to reduce bleeding risk and should be performed by an experienced clinician.

The procedure should be discussed with the on-call anaesthetic team (bleep 1646 for duty consultant 8-8, bleep 2265 for co-ordinating SpR 6pm-8am/weekends) and the patients name added to the respective theatre list.

7.5 Patient Assessment

The following should be elucidated:

- Possible precipitants e.g., infection, medication, pregnancy
- Family history of TTP (or any suggestive platelet disorder)
- Risk factors for HIV
- Associated illnesses (in particular SLE/autoimmune disease)
- Past/family history of venous thrombosis
- Evidence of malignancy

Clinical examination: Pay particular attention to cardiac and neurological status (cardiac ischemia, arrhythmias, status epilepticus and coma are recognised complications). Cardiac monitoring may be necessary.

7.6 Consent For Treatment

Consent should be obtained as per Trust policy. Verbal consent is sufficient for an out of hour's admission with written consent ('Consent Form 1') to be obtained at the earliest appropriate opportunity. The admitting registrar or Senior Apheresis Nurse performing the procedure must document the initial verbal consent in the patient notes.

If, as is often the case in the presence of severe neurological symptoms, the patient is lacking the capacity to give or withhold consent to treatment, the patient's significant others should be involved in the consent process. In the event of urgent lifesaving therapy then treatment will be started in the patient's best interests. However, you may still treat such a patient if the treatment would be in their best interests. Treating in a patient's 'Best interests' go wider than best medical interests, to include factors such as the wishes and beliefs of the patient when competent, their current wishes, their general well-being and their spiritual and religious welfare. People close to the patient may be able to give you information on some of these factors. Therefore, if the patient is not well enough to consent and there are no relatives the priority should be treating this life-threatening condition. In such cases a 'Consent Form 4' should be used.

If a child/young person requires treatment for TTP and cannot consent for the treatment themselves, a 'Consent Form 2 - Parental (or person with parental responsibility) agreement to investigation or treatment for a child or young person' should be completed.

7.7 Baseline Investigations

The following baseline investigations are required and should be taken BEFORE plasma exchange is started. They can be requested by selecting the TTP bundle on eQuest. There is NO indication to take post TPE samples and this should be discouraged, unless there is deterioration clinically in the patient.

ADAMTS 13 activity (VWF Cleaving Protease Activity on eQuest) should be processed as quickly as possible so there are no delays to initiating caplacizumab treatment

Blood Samples		
Transfusion	Group & Save (+/- check group) DAT	1 x pink EDTA
Haematology	FBC & Blood Film Reticulocytes Erythrocyte Sedimentation Rate (ESR) Anticardiolipin and anti-β2 glycoprotein-1 antibodies Lupus Anticoagulant Coagulation screen (includes fibrinogen) Vitamin B12 & Serum Folate	1 x EDTA 1 x SST Gel 1 x Citrate
Immunology	Rheumatoid Factors Connective tissue disease screen C3 & 4 (if renal impairment or autoimmune component) If a renal condition is considered, further testing may be required e.g. anti-GBM antibodies, ANCA	1 x Clotted (red)
Chemical Pathology	U&E, LFT, calcium & magnesium levels LDH, CRP, β-HCG (Females <60) Troponin I Iron Profile and Ferritin Thyroid function tests Protein-creatinine ratio	1 x SST Gel 1 X Clotted (red) Urine
Virology	HIV, syphilis screen, Hep A, Hep B, Hep C	1 x Clotted (red)
Haemostasis	ADAMTS13 ('VWF Cleaving Protease Activity' on eQuest) activity and antibody levels + coagulation frozen store sample for TTP registry (*antibody to be sent to Oxford University Hospital)*	3 x Citrate
Microbiology	Blood Cultures – sample both peripheral and central lines	Culture bottles
Other Samples / Investigations		
Microbiology	MRSA Screen Mid-Stream or Catheter Urine culture Stool sample if patient has history of diarrhoea for PCR testing for STEC. Gastro bacteria PCR if history of diarrhoea Urine for pneumococcal antigen	
Virology	NPA and respiratory virus screen – if patient has a history of cold or flu symptoms	
Imaging	Chest X-Ray	
Cardiac	ECG Baseline ECHO	

Bloods to be taken prior to each dose of Rituximab		
Pre-Rituximab Bloods	CD19 Screen 'Rituximab Monitoring' on eQuest Immunoglobulin (IgG, IgM & IgA) Levels	1 x SST Gel

Bloods/Further investigations to be taken in cases of suspected HUS/aHUS		
CM-HUS/IA-HUS	Urine dipstick and protein-creatinine ratio USS Abdomen: to review renal size Ophthalmic review for new/previous retinal changes relating to hypertension	Urine

7.8 Initial Management

Platelet transfusions are contra-indicated in TTP. If there is concomitant bleeding, please discuss with the on-call haemostasis consultant.

In the event of any sudden or unexpected deterioration in the patients' condition the on-call haemostasis consultant must be notified immediately.

Lines of therapy approved for use in TTP at UCLH NHS Trust

Acute TTP treatment

- Therapeutic Plasma Exchange (PEX) with ABO group compatible (or AB group) plasma replacement (Octaplas) utilising a blood cell separator.
- 1.5 plasma volumes (60mls/kg) PEX daily for first three procedures. Further PEX volume will be determined by patient's condition.
- Methylprednisolone pulsing/ steroid therapy (Dosage and duration to be determined by on call TMA consultant in view of patient's condition and risk/benefit analysis).
- Caplacizumab: 10mg IV pre PEX stat then 10mg daily SC post PEX following confirmation of ADAMTS13 deficiency (*on call pharmacist bleep*)
- Rituximab 375mg/m^2 by Intravenous Infusion (4 – 8 doses dependent on ADAMTS 13 activity and inhibitor results) immediately following TPE

  The first dose may be authorised by the TMA consultant prior to results.

TMA Clinical Trials

- UHS is active in many clinical trials, and patients may be offered participation in open clinical trials (if meets eligibility criteria).
- Enrolment in specific clinical trials may alter the acute management and treatment schedule (depending on trial protocols).

Therapy may be adjusted from First Line in view of underlying patient conditions as well as identified patient disease triggers. The following adjustments must be considered.

Rapidly deteriorating neurological status:
Commence 1.5 Plasma volumes PEX . Repeat PEX within a 24 hour period may be required.

Disease due to HIV: Review and commence antiretroviral treatment as soon as possible. Therapy should be prescribed post PEX.

Disease due to Pancreatitis: Discuss use of steroids as they are typically contraindicated in pancreatitis but they may be used in idiopathic disease.

Disease due to stem-cell transplant: There is no benefit of PEX

Medications should be given **after** PEX to ensure they are not cleared by the plasma exchange.

7.9 Therapeutic Plasma Exchange

Immediate 1.5 volume (60mls/kg) plasma exchange with Solvent Detergent plasma (Octaplas). If this is unavailable, standard FFP should be used. Prophylactic antihistamine premedication should be considered if an allergic reaction occurs, or if there is a history of previous allergic reactions.

Initially plasma exchange is routinely performed daily in the acute situation. In cases of severe disease (haemodynamically or neurologically unstable) or sudden deterioration, twice daily exchanges may be considered but should be implemented only after discussion with the haemostasis consultant (ideally there should be a minimum of 4 hours between exchanges however it may be sooner in view of clinical need).

Ensure that all patients with HIV related TTP receive their antiretroviral therapy following PEX where possible to ensure maximal drug bioavailability.

All patients undergoing PEX should have appropriate vascular access, which is usually in the form of a Vascath (please see Section 7.4) for local policy / requesting procedure agreed with Anaesthetics department.

Machine priming with cross matched red blood cells should be considered when Hb < 60g/L and systolic BP < 100 or Hb < 40g/L. If haemodynamically stable but Hb < 6g/dl and >4g/dl, transfuse during initial plasma exchange.

Once the patient is deemed to medically stable, they can be transferred to C2 haematology ward

7.10 Caplacizumab Therapy

Blueteq approval is required before prescribing caplacizumab – requests will be completed by the clotting consultant on call

Caplacizumab is humanised bivalent nanobody which targets the vWF A1 domain, thus inhibiting its interaction between vWF and platelets. This prevents UL-VWF mediated platelet adhesion which is direct pathophysiology implicated in autoimmune TTP pathophysiology.

Caplacizumab is an adjunct therapy, licensed for the treatment of adults and adolescents 12 years of age or older, weighing at least 40kg) for acquired (immune-mediated) TTP, in addition to standard treatments with plasma exchange and immunosuppression.

In adults < 40Kg or children, a dose of 5mg is used.

The licensed first dose of caplacizumab is administered as a single intravenous bolus injection of 10mg prior to plasma exchange, following confirmation of ADAMTS13 deficiency. Subsequent doses are administered daily by subcutaneous injection for the duration of plasma exchange and daily afterwards, guided by the ADAMTS13 activity by the haemostasis consultant. Typically it is continued for 30 days post PEX and a further 4 weeks can be considered based on ADAMTS 13 activity level. Stopping caplacuzimab is usually when ADAMTS 13 activity is > 30iu/dL x 2 analyses, assuming no recent PEX therapy. No dose adjustment is recommended for renal or liver impairment, or elderly patients (based on available data).

Caplacuzimab is contraindicated during pregnancy

In clinically significant bleeding (as determined by the haemostasis consultant), caplacizumab treatment should be interrupted and vWF concentrate may be required to correct haemostasis.

The concurrent use or anticoagulants or aspirin will increase bleeding risk. Aspirin should not be used without approval from the haemostasis consultant. Patients should be considered for LMWH thromboprophylaxis once platelet count is >50 (following approval by the haemostasis consultant)

7.11 Corticosteroid Therapy

Unless contra-indicated by pre-existing or suspected potential conditions, patients typically receive methylprednisolone e.g. 0.5-1g IV for 3 days.

In patients who are clinical stable with normal gastrointestinal absorption, oral prednisolone may be satisfactory.

The effect of methylprednisolone may wear off and further steroids, e.g. oral prednisolone, may be considered.

All doses to be given immediately after completing the first exchange.

7.12 Rituximab/Anti-CD20 Therapy

Blueteq approval is required before prescribing rituximab for TTP – requests will be completed by the clotting consultant on call

Rituximab has improved time to remission and reduces relapse risk in acute TTP. Currently doses of 375mg/m^2 are given every 3-4 days, because of the removal of rituximab by PEX.

Review of ADAMTS13 after 4 doses - a maximum of 8 are given, based on ADAMTS13 levels.

The benefit of rituximab given within 3 days of presentation has been proven, reducing number of PEX to remission, number of days in hospital and volumes of plasma required.

Rituximab should be given immediately following PEX. There should be a satisfactory gap between dosing and the next PEX. The minimum is 4 hours and the patient's clinical condition is paramount, therefore, if further PEX is indicated, this should proceed.

Anti-CD20 is also used routinely to prevent clinical relapse (see Section 7.16)

7.13 Supportive Measures

- Aspirin (enteric coated) 75mg once daily can be considered when the platelet count is > 50 x 10^9/L if the patients is not on caplacizumab.
- Transfuse to maintain haemoglobin level > 80g/L (unless underlying conditions require higher threshold)
- Folic acid 5mg once daily
- Lansoprazole 30mg/omeprazole 20mg once daily or famotidine 40mg once daily
- Calcichew tablets 2 three times a day until PEX treatment is completed
- Anti-hypertensives (if required) but ACE inhibitors should be avoided during PEX
- Thromboembolism is a recognised complication during rapid platelet recovery and all patients should wear TED stockings from admission until discharge
- Consider thromboprophylaxis with low molecular weight heparin (e.g. enoxaparin 40mg SC OD – depending on body weight). The first dose can be given when platelets > 50 x 10^9/L(for approval of haemostasis consultant if patient is on caplacizumab). This should be given in the abdomen or upper leg only.
- Treatment dose enoxaparin should be commenced in the presence of actual or suspected thromboembolism (the first dose to be given when platelets > 50 x 10^9/L) (for approval of haemostasis consultant if patient is on caplacizumab).

- Patients with previous evidence of Hepatitis B must start lamivudine 100mg once daily with rituximab to prevent reactivation. This must continue for 6 months post treatment. Monitoring of Hepatitis B viral load should be undertaken at follow up.

7.14 Antibiotic Therapy

Antibiotic therapy should only be prescribed if hypotensive or there is a high index of suspicion of clinical infection. Any infection will exacerbate acute TTP and therefore should be actively treated.

7.15 Daily Laboratory Monitoring And Line Care

FBC, reticulocyte count, blood film

Renal profile, calcium, liver function tests, LDH, CRP and Troponin I (if cardiac involvement)

Coagulation profile once a week unless on treatment dose anticoagulation or if there is clinical deterioration

Samples for ADAMTS13 activity, inhibitors and immunoglobulins should be taken prior to each dose of Rituximab and/or weekly (Monday AM) prior to PEX

CD19 Screen (Rituximab Monitoring on eQuest) and Immunoglobulins once a week prior to Rituximab

Ward medical staff are responsible for ensuring that bloods are taken so results are available by early-morning. This allows informed decision making re plasma exchange requirement and correction of any electrolytes prior to PEX. Hypokalaemia is common (~ 20% K+ reduction during exchange) and electrolytes MUST be checked and corrected pre-exchange.

Platelet counts: morning results are the most important prior to exchange. There is no need to perform routine post-exchange blood tests unless clinically indicated.

Line care must be meticulous: occult infection may prevent response to treatment or result in disease exacerbation and neck Vascaths are electively changed every week and femoral Vascaths after 3 days.

7.16 ADAMTS13 Activity And Inhibitor Samples

Samples for ADAMTS13 activity and inhibitors, and the TTP registry (total 3 x citrate/blue tubes) must be taken prior to the first PEX. The samples should be sent without delay to the coagulation laboratory.

Point of Sample	Samples required
On First Admission	3 x citrate samples (blue top)
Subsequent Admissions	2 x citrate samples (blue top) and 1 serum samples
Weekly Inpatient (Monday)	1 citrate sample
Outpatient	1 citrate sample

7.17 Refractory And/Or Multiply Replapsing Disease

Additional treatment may be indicated in the following situations:

- Refractory TTP, defined as not achieving a clinical response after 5 therapeutic plasma exchange session (clinical response defined at a sustained platelet count >150x10^9, and LDH <1.5time the ULN.
- Clinical Exacerbation: platelet count decreases to <150x10^9/L with or without evidence of new or progressive ischaemia organ injury, within 30days of stopping PEX or caplacizumab.
- Clinical Relapse: After a clinical remission platelet count decrease <150x109 (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischaemic organ injury. Clinical relapse must be confirmed by documentation of severe ADAMTS13 deficiency.

ADAMTS13 response is defined as:

- Complete ADAMTS13 remission: ADAMTS13 activity >LLN.
- Partial ADAMTS13 remission: ADAMTS13 activity >20% but <LLN.
- ADAMTS13 relapse: After an ADAMTS13 remission (partial or complete), the ADAMTS13 activity level increases to <20%

7.18 Management Of Refractory Disease

Further Treatment Options:

- Additional doses of Rituximab 375mg/m^2 by Intravenous Infusion (up to 6 – 8 doses weekly dependent on ADAMTS13 activity and inhibitor results). TTP MDT approval must be gained prior to initiation of therapy.
- Repeat pulsed methylprednisolone or high dose oral prednisolone at a dose of 1mg/kg.
- Further Immunosuppression: Consider Mycophenolate mofetil or Velcade (1mg/m^2 SC) to be determined by the haemostasis consultant/TTP MDT

7.19 Treatment Resolution

Plasma exchange is continued until the platelet count is within the normal range (>150 X 10^9/L) and increasing ADAMTS 13 activity.

7.20 Discharge

The patient will be discharged from inpatient admission once the haemostasis consultant in charge feels that inpatient therapy is no longer warranted.

Discharge letter “To Referred Consultant” and GP must be completed and sent at the earliest opportunity prior to or immediately following discharge. A TTP CNS will send the patient’s GP, the patient information leaflets on TTP.

Initial Follow–up: The patient should be booked for the next available TTP Clinic (Haemophilia Comprehensive Care Centre, level C) on Thursday afternoons. Any follow up prior to this should take place in C7 Day Unit. Bookings can be made phoning 5987 if review required within 48 hours or by submitting a C7 booking eQuest form.

Arrangements for follow-up, including shared care with referring hospital, will be arranged through the TTP Clinic, including ADAMTS13 (activity +/- antibody). The follow-up schedule is listed in Section:

The patient will receive information on TTP and related procedures/treatments and information for local hospitals if they require an urgent review. Contact numbers for 24/7 access in an emergency are given to all patients. This includes TTP CNS details during “office” hours, and Haematology urgent “out of hours” advice line number (AOS 24 hour emergency phone line 023 8120 1345).

Ensure follow-up investigations to include full assessment of end organ damage (including MRI head, echocardiogram) are organised. This should also include referral to the clinical psychologist service and if appropriate neurocognitive assessment

7.21 Follow-Up And Prevention Of Relapse

The risk of relapse remains significant despite treatment. All patients should be monitored as an outpatient with ADAMTS13 testing and offered rituximab pre-emptively to prevent clinical relapse occurring.

Follow-up schedule is listed below:

- Early: Weekly follow up in clinic for 4 weeks
- Intermediate: 2-4 weekly for the following 3 months
- Late: 3 monthly for 12 months
- Long term: 3-6 monthly thereafter
- Long term follow up should continue in the majority of patients indefinitely as late relapses may occur.

Monitoring ADAMTS13 activity is central to prevention of relapse of TTP, and if levels decrease from normal to <15%, rituximab can be given in the out-patient setting to prevent an acute presentation by restoring ADAMTS13 to normal levels.

All patients should be offered participation in the UK TTP Registry, including consenting (as applicable) for their acute episode, relapses, anti-CD20 treatment, pregnancy and follow-up.

All patients should have their individual psychological needs explored and offered referral to the TTP clinical psychologist, based at Oxford University Hospital.

7.22 Disease Related Death

In the event of a disease related death, the next of kin should be consulted for consent to a hospital autopsy.

The next of kin should also be given the opportunity for a meeting to discuss any matters that they feel relevant to the patient's condition, treatment and care the patients GP and the referring hospital should be notified promptly.

7.23 Congenital TTP

Congenital TTP is very rare, estimated 1/million of the population and primarily, but not exclusively, detected in women during pregnancy.

In the current era, all patients should be offered prophylaxis to prevent against subacute TTP events and long-term impact of organ damage.

Currently patients receive 10mls/kg Octaplas, every 1-3 weeks, dependant on symptoms and routine laboratory parameters. Alternative therapy includes BPL 8Y(10-25U/kg) and in the near future, recombinant ADAMTS 13.

Baseline investigations include routine lab parameters, USS kidneys, echocardiogram and MRI head

Escalation of therapy will be required following discussion with the on-call consultant with an acute TTP event, or to cover procedures/interventions.

During pregnancy, patients require increased therapy and monitoring and liaison with the combined haematology/obstetric clinic.

7.24 Haemolytic Uraemic Syndrome

HUS is a rare TMA associated with primarily renal involvement. Infection Associated HUS can be provoked by gastrointestinal, often toxin producing infections such as *E coli* and also *Campylobacter* and *Shigella*. Pneumococcal infection can produce a picture similar to HUS but often with significant extra renal organ involvement. Complement mediated HUS (CM-HUS) may have an associated triggering factor, but presents with acute MAHA, thrombocytopenia and renal impairment.

Patients with severe renal failure due to suspected HUS should be referred to their nearest renal unit for management, not the UHS TTP service.

Differentiation for the above causes is required. HUS typically has bloody diarrhoea, CM-HUS, there may be diarrhoea but not necessarily bloody. However STEC requires exclusion.

Differentiation from malignant hypertension in adults may be difficult, and a trial of complement inhibitor therapy may be suggested. However, a renal USS should present with normal sized kidneys and an ophthalmic review to exclude chronic hypertensive changes.

HUS may be difficult to distinguish from TTP, and daily plasma exchange is recommended until the diagnosis is confirmed. Other causes of TMA should be excluding including ADAMTS13 activity, STEC organisms, renal ultrasound, urinary protein creatinine ratio, ophthalmic review and autoimmune/lupus serology. C3 may be normal in HUS (it is reduced in 70% of cases),

Estimation of the protein leak from urine is helpful.

Patients may require haemofiltration, control of blood pressure and anaemia support during haemolysis.

All patients should receive daily single volume PEX until the diagnosis is clear

ADAMTS 13 testing at presentation is imperative to exclude congenital TTP primarily. The levels are typical normal or mid range in those with HUS.

Other secondary causes requiring admission for treatment are pregnancy, drugs and autoimmune disease. Extra renal manifestations may be present and require a similar work up as TTP cases including echocardiogram and MRI head if relevant.

Extra renal manifestations may be present and require a similar work up as TTP cases including echocardiogram and MRI head if relevant.

If the diagnosis of CM-HUS is deemed likely, referral for eculizumab should be made.

7.25 Referral For Eculizumab

Eculizumab therapy for CM HUS referral to Newcastle
https://www.atypicalhus.co.uk/emergency-referrals/

Referral forms:
https://www.atypicalhus.co.uk/emergency-referrals/forms-and-protocols/

Samples for genetic analysis should be forwarded to the Newcastle genetic service

Both therapy and genetics are nationally funded through NHS England.

Before patients receive eculizumab, entry to current clinical trials should be discussed. All patients must receive meningococcal vaccination (Bexsero) given prior to first dose and day 29 and tetravalent meningococcal vaccine (against A, C, Y and W-135).

A throat swab for meningococcus should be undertaken.

All patients require antibiotic prophylaxis against meningococcus. Initially this should be ciprofloxacin 500mg twice daily for 2 weeks, continuing Penicillin V 250mg twice daily for as long as patients are on eculizumab and for one month after stopping.

In patients allergic to penicillin, clarithromycin or ciprofloxacin at prophylactic doses can be used.

All patient must receive a safety card and present if unwell immediately. Despite the risk of meningococcus being low, it can be potentially life threatening.

In patients in whom complement inhibitor therapy is to be continued, ravuluzimab can be started and continued via a homecare service.

7.26 Ward Nursing Guidelines For Patients With TTP

7.26.1 Blood Investigations

Morning blood counts (0600 hours)

Required investigations:

- Full Blood Count
- Reticulocytes
- Urea & Electrolytes (including Mg,Ca+ & K+)
- LDH
- Coagulation profile (includes fibrinogen)
- Glucose (daily until 24 hours post steroid pulsing)
- CRP (daily in the presence of central vascular access or suspected infection.

7.26.2 Vital Signs Monitoring

All patients should have vital signs monitored as appropriate to their condition. i.e. if stable on admission then Blood Pressure, Pulse, Temperature & Respiration rate can be measured 4 hourly.

Alteration in frequency of vital signs monitoring should be in response to change in patient condition.

Neurological observations should be performed twice daily in the absence of symptoms increasing to an appropriate frequency if patient symptomatic.

Fluid Balance Charts must be accurately maintained for all patients from admission to discharge.

Daily Patient weight must be performed at admission and recorded.

Daily urinalysis must be performed for all patients until discharge, in addition to daily weights in patients with HUS.

In patients receiving steroids, particularly pulsed high dose, blood pressure and blood sugars should be monitored regularly each day during therapy.

7.27 Thromboprophylaxis

All patients should wear TED Stockings from admission through till discharge.

Patients should be assessed for pharmacological thromboprophylaxis when platelet count is >50x10^9/L.

If the patient has a femoral Vascath *in situ* then a daily review of the cannulated leg in comparison with the other leg, in particular monitoring for signs and symptoms of DVT, must occur and be documented in the patient notes. Femoral lines should be removed within 48-72 hrs of insertion and replaced with neck line, which should be changed every 7 days. If the Vascath is to be removed when the patient is on Caplacizumab then the Vascath should be removed immediately prior to Caplacizumab administration (to ensure maximum time to excretion of previous dose and reducing the bleeding risk). As Caplacizumab is known to increase bleeding risk it is important to provide direct pressure to the wound site for 20-30minutes and closely observe until bleeding has stopped.

Alert and orientated patients should be encouraged to mobilise as appropriate during the day.

Patients should be encouraged to drink 2 to 3 litres of fluid per day unless contraindicated by existing fluid restriction (i.e. patients in acute renal failure)

7.28 Red Cell Transfusions

Patients haemoglobin should be maintained > 80g/L or in appropriate patients >10g/dL (pregnancy, cardiac symptoms and/or past history and any other condition where the TTP clinical team deem it necessary).

Patients with TTP can decrease their Haemoglobin levels rapidly due to haemolysis, which may activate suddenly. Additionally, PEX can decrease haemoglobin levels post procedure by approximately 1g/dL.

It is important that prior to transfusion, an appropriate group & save sample for urgent cross matching is available. A second check group sample will be required if there is no historical blood group on record.

Patients with TTP are not to receive platelet transfusions under any circumstances.

7.27 Central Venous Access

If peripheral venous access is unsuitable for TPE, central venous access must be inserted. If clinical indications suggest the central venous site is infected it must be removed immediately and the site and line tip cultured to identify causative organisms. Line tips should also be cultured after all line removals.

If on admission a femoral Vascath is inserted then this must be changed within 48 hours due to the risk of infection and replaced with a neck Vascath.

Central venous access must be dressed, accessed and locked off as per unit policy.

The following sizes of apheresis lines should be used:

7.28.3 Femoral Access

Patient Size		Catheter Size (Fr)	Catheter length (mm)
Weight	Height		
10Kg or less	N/A	6.5	100
>10Kg,<20Kg	N/A	6.5	125
>20Kg,<30Kg	N/A	11	125
>30Kg	<160cm	11	150
>30Kg	161-178cm	11	200
>30Kg	>179cm	12	250

7.28.4 Internal Jugular & Subclavian Vascath Access

Patient Size		Catheter Size (Fr)	Catheter length (mm)
Weight	Height		
All Adults		11	200

7.29 Out Of Hours

- If patients with TTP contact the out of hours line, the on call SpR/haemostasis consultant **must be** contacted particularly if patients are unwell suggesting a relapse
- Any calls from TTP patients under UHS should be discussed with the on-call haemostasis consultant
- Any TTP patient that reports being unwell must have an urgent FBC and admitted if the platelet count is low

8 Roles And Responsibilities

Medical Staff
It is the consultant's responsibility to ensure the guideline is initiated for patients requiring emergency management on TTP
It is the doctor's responsibility to investigate patients appropriately, arrange rapid transfer to UHS (if a regional referral) and liaise with the apheresis, anaesthetics, ICU, bed management and transfusion team

Nursing staff
It is the apheresis team's responsibility to initiate carry out emergency plasma exchange and order Octaplas from the laboratory

Transfusion staff
It is the transfusion laboratory staff's responsibility to urgently distribute blood components, and allow AB Octaplas to be released if 2 x G+S samples are not available

Pharmacy staff
It is the responsibility of pharmacy staff to facilitate emergency access to caplacizumab and screen rituximab dosing

9 Document Review

This policy will be reviewed every 3 years, or sooner if there are major changes to BSH or ISTH guidelines on the management of TTP

10 Process For Monitoring Compliance

Element to be monitored	Time to plasma exchange from diagnosis
Lead (name/job title)	Dr Sara Boyce
Tool	Data reporting to commissioners
Frequency	monthly
Reporting arrangements	Standard reporting template

Where monitoring identifies deficiencies actions plans will be developed to address them.

11 Appendices

Appendix-1_Wessex Suspected TTP referral form

Appendix-2_UHS Haematology Admission checklist

Appendix-3_Wessex TTP referral pathway

Appendix-4_NHSE TTP quality indicators

11.1 Appendix 1: Wessex Suspected TTP Referral Form

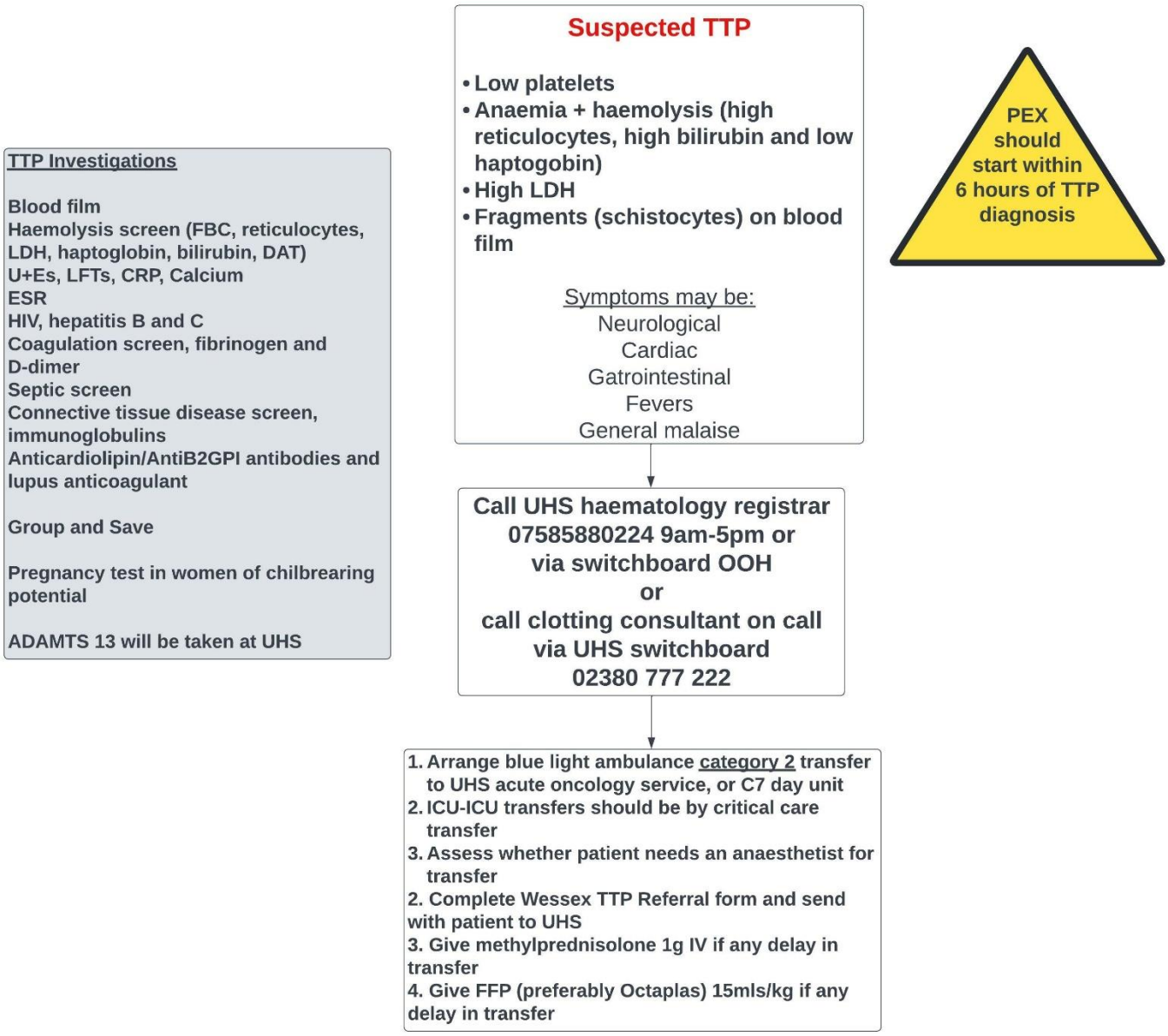
Patient name		**Date**	**Time**
NHS number		**Referring Hospital**	
Date of Birth		**Name of referrer**	
BP	**Pulse**	**Weight**	**EWS**
GCS	**Height**		
Current Clinical condition and level of care			
Time ambulance contacted		**Time of ambulance referral**	
Anaesthetic review Y N		**Anaesthetist escort required Y N**	
Co-morbidities			
Medications			
Allergies			

Recent vaccinations			
Current IV access central line peripheral cannula			
Investigations			
Hb	**platelets**	**Blood film**	**reticulocytes**
Creatinine	**LDH**	**Troponin**	
PT/INR	**APTT/APTR**	**Fibrinogen**	**D-dimer**
ADAMTS 13 taken Y N			
Blood components given*(platelet transfusion contraindicated)*			
Presenting symptoms			
Risk factors			
Pregnancy	**HIV**	**Autoimmune disease**	**Previous TTP**
Malignancy	**Pancreatic disease**		

11.2 Appendix 2: UHS TTP Haematology Admission Checklist

Date:	**Completed by:**
Time of referral for Vascath insertion:	Time of Vascath insertion:
TTP bundle including ADAMTS 13 sent prior to plasma infusion/exchange ☐	G+S sent ☐
Transfusion lab contracted to inform of TTP patient (volume of Octaplas 60 mls/kg) ☐	
Time plasma exchange commenced:	Location of first plasma exchange:
Inpatient bed on C2 (if non ICU patient) arranged ☐	
2nd check G+S (if needed) sent ☐	
Neuro observations chart ☐	
Prescriptions	
Caplacizumab 10mg IV stat (once confirmation with ADAMTS 13 <10%) can give before or after PEX ☐ (*consultant to complete Blueteq)* From day 2 capalacizumab 10mg s/c daily ☐	
Methylprednisolone 500mg-1000mg stat ☐	
Folic acid 5mg od ☐	
1st dose rituximab 375mg/m2 prescribed for after 1st PEX + consent ☐ (*consultant to complete Blueteq)*	
Calcichew D3 2 tablets TDS during plasma exchange ☐	
VTE prophylaxis	
TEDS ☐ Caplacizumab increases bleeding risk. Enoxaparin prophylaxis to be considered when platelets >50	

11.3 Appendix 3: Wessex TTP Referral Path



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11.4 Appendix 4: NHSE TTP quality indicators

NHSE TTP quality indicators Number	Indicator	Data Source	Outcome Framework Domain	CQC Key question
Clinical Outcomes				
101	% of emergency admissions receiving a specialist consultant review within 14 hours.	Trust to provide	1, 3, 4	effective, caring, responsive
102	% of patients starting PEX within 4 hours of referral to the specialist centre	Trust to provide	1, 3, 4	effective, caring, responsive
103	% of patients starting PEX within 6 hours of referral to the specialist centre	Trust to provide	1, 3, 4	effective, caring, responsive
104	% of patients starting PEX within 8 hours of referral to the specialist centre	Trust to provide	1, 3, 4	effective, caring, responsive
105	% of patients surviving for a year from the point of diagnosis. Expected level 80%	Trust to provide	1, 3, 4	Effective
106	% of patients will have a central line inserted within 1 hour of admission	Trust to provide	1, 3, 4	effective, caring, responsive
107	Clinical relapse	Trust to provide	1, 3, 4	effective, caring
108	Critical care availability	Trust to provide	1, 3, 4, 5	safe, effective, responsive

Patient Experience				
201	Patient feedback	Trust to provide	4	effective, caring, responsive
202	Review of complaints	Trust to provide	4	effective, caring, responsive
203	Support for patients	Trust to provide	4	effective, caring, responsive
Structure and Process				
301	Clinical lead	Self-declaration	4	well-led
302	Service requirements	Self-declaration	1, 3, 4	Safe, effective, caring, responsive
303	Infrastructure and facilities	Self-declaration	1, 3, 4, 5	Safe, effective, caring, responsive
304	24/7 access to therapeutic apheresis	Self-declaration	1, 3, 4, 5	Safe, effective, caring, responsive
305	Inpatient access to expert advice	Self-declaration	1, 3, 4, 5	Safe, effective, caring, responsive
306	TTP follow-up.	Self-declaration	1, 3, 4, 5	Safe, effective, caring, responsive
307	ADAMTS13 testing is available 24/7	Self-declaration	1, 3, 4, 5	Safe, effective, caring, responsive
308	Data collection	Self-declaration	1, 3	Safe, effective, caring, responsive
309	Clinical guidelines	Self-declaration	1, 2, 3, 4, 5	Safe, effective, caring, responsive
310	Patient pathways	Self-declaration	1, 2, 3, 4, 5	Safe, effective, caring, responsive
311	Patients referred to another centre	Self-declaration	1,2,3,4,5	Safe, effective, caring and responsive