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A British Society for Haematology Guideline: Diagnosis and Management of Thrombotic Thrombocytopenic Purpura and Thrombotic Microangiopathies.

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TITLE

A British Society for Haematology Guideline: Diagnosis and Management of Thrombotic Thrombocytopenic Purpura and Thrombotic Microangiopathies.

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Methodology

This guideline was compiled according to the BSH process at [https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. A literature search was carried out using the terms given in Appendix S1 until June 2022

Review of the manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haemostasis and Thrombosis Taskforce, the BSH Guidelines Committee and BSH sounding board. It has been reviewed by UK TTP forum, Intensive Care Society (ICS), Faculty of Intensive Care Medicine (FICM) and the TTPNetwork.

Abstract

The objective of this guideline is to provide healthcare professionals with clear, up-to-date and practical guidance on the management of thrombotic thrombocytopenic purpura (TTP) and related thrombotic microangiopathies (TMAs), including complement-mediated haemolytic uraemic syndrome (CM HUS); these are defined by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and small vessel thrombosis. Within England, all TTP cases should be managed within designated regional centres as per NHSE commissioning for highly specialised services.

Pathogenesis of TTP

TTP is a Thrombotic Microangiopathy (TMA), an umbrella term for several disorders characterised clinically by the presence of a microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia, with pathological features including occlusive microvascular/macrovascular disease (1).

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening medical emergency caused by a severe deficiency of the metalloproteinase, ADAMTS13 (2). ADAMTS13 has 14 domains (3), and is synthesised principally in the liver and cleaves Von Willebrand factor (VWF) at Tyr1605-Met1606 within the A2 domain (4). The ADAMTS13 cleavage site of VWF is exposed under conditions of shear stress facilitating clearance of high molecular weight VWF multimers, which would otherwise spontaneously bind platelets and cause widespread microthrombi (5-9) Deficiency of ADAMTS13 results in platelet-rich thrombi in the microvasculature, red cell fragmentation/haemolysis and end organ damage predominantly affecting the brain, heart and kidneys. Untreated, TTP has a high mortality due to sudden neurological and cardiac dysfunction. A mild deficiency of ADAMTS13 can occur in thrombotic microangiopathic anaemias (TMA) such as disseminated intravascular coagulation (DIC) and Haemolytic Uraemic Syndrome (HUS), which may present with similar features to TTP (Table 1). However, TTP is associated with severe deficiency, with ADAMTS13 activity levels, usually <10 IU/dL.

The majority of cases of TTP are acquired, immune mediated TTP (iTTP), with autoantibodies against ADAMTS13 (10). iTTP is usually idiopathic, or associated

with autoimmune disease, pregnancy, drugs or infection, particularly HIV. Auto-antibodies are usually IgG class primarily directed against N-terminal (spacer) domain (11). Antibodies may cause increased clearance of ADAMTS13, although anti-spacer domain autoantibodies are usually inhibitory (12).

Congenital TTP (cTTP) is caused by bi-allelic recessive variants in the ADAMTS13 gene resulting in severe deficiency of the enzyme (13). Pathogenic variants span the 31 exons and there is some evidence for a correlation between genotype and clinical phenotype (14). The ADAMTS13 gene (OMIM accession number 604134) is located on chromosome 9q34.2 and pathogenic variants are missense (55%), or frameshift (28%) (15-17). The gene variants can determine both the level and the conformation of ADAMTS13 (18).

Diagnosis of TTP

The differential diagnosis of TMA is variable, and these disorders can have similar clinical presentation (Table 1).

International consensus defines TTP as: MAHA with moderate or severe thrombocytopenia, with associated organ dysfunction – this can include neurological, cardiac, gastrointestinal and renal involvement. The presence of specific organ dysfunction is not a prerequisite for diagnosis, which is confirmed by demonstrating a severe deficiency of ADAMTS13 (<10 IU/dL) (1)

TTP remains a diagnosis suspected from the clinical history, examination and laboratory parameters including the blood film to aid exclusion of other TMAs. Assays for ADAMTS13 help to confirm the diagnosis and monitor the course of the disease and requirement for additional treatments.

Presenting symptoms and signs are summarized in Table 2. Neurological symptoms are the commonest presenting symptoms in acute TTP, but may be transient and vary from headaches to seizures, paraesthesia or altered speech; coma is a poor prognostic sign. Cardiac involvement is usually defined by a raised troponin level. Ischaemic change on ECG is uncommon and associated with a poor outcome, therefore early TTP therapy is considered a priority. Acute renal failure requiring haemodialysis is rare in TTP and highly suggestive of HUS (19, 20). Additional

ischaemic complications may occur, including intestinal ischaemia causing abdominal pain.

Consumption of platelets in platelet-rich thrombi results in thrombocytopenia, with a median platelet count typically 10–30x10^9/L at presentation (19-23). Mechanical fragmentation of erythrocytes during flow through partially occluded, high shear small vessels causes a MAHA. Median haemoglobin levels on admission are typically 80–100 g/L. The combination of haemolysis and tissue ischaemia produces elevated lactate dehydrogenase (LDH) values.

The coagulation screen is typically normal. A virology screen pre-treatment is necessary to exclude Human Immunodeficiency Virus (HIV) and hepatitis viruses especially as a baseline prior to plasma exposure, including hepatitis B pre rituximab. Troponin levels are raised in more than 50% of acute iTTP cases (24-26), highlighting that cardiac involvement is common. Elevated troponin has been associated with a sixfold increase in mortality (12.1% vs 2%, p=0.04) compared to those having normal troponin (26), and has also been found to be a risk factor for poor outcome when combined with increased anti-ADAMTS13 IgG levels (Table 3).

Two scoring systems, the French score (27) and the PLASMIC score (28) have been developed to aid identification of patients presenting with a TMA who are likely to have TTP and therefore benefit from urgent plasma exchange (PEX). These scoring systems have variable sensitivity/specificity, may decrease with increasing age (29) and have not been validated prospectively.

In practice, it may be difficult to differentiate between TTP and other TMAs using clinical and laboratory features alone (30). Treatment with PEX should be initiated where TTP is suspected on clinical grounds, pending confirmation of results of urgent ADAMTS13 testing.

ADAMTS13 assays

ADAMTS13 assays are essential in confirming the diagnosis of TTP, samples should be taken prior to PEX but treatment should not be delayed pending results. ADAMTS13 activity <10 IU/dL +/- presence of IgG antibodies or an inhibitor, confirms the diagnosis of TTP. ADAMTS13 activity <10 IU/dL has a high sensitivity (97%) and specificity (100%) in distinguishing TTP from other TMAs (31) . Decreased

ADAMTS13 activity can be seen in various conditions including metastatic cancer, sepsis, DIC, liver disease and pregnancy (32).

ADAMTS13 assays include those measuring activity, antigen and anti-ADAMTS13 autoantibodies (these can be neutralizing or non-neutralizing). ADAMTS13 activity assays rely on testing patient's plasma with either a full-length, or more commonly a synthetic VWF substrate; activity is determined by measuring ADAMTS13 cleavage products using either an ELISA based method, or by fluorescence resonance energy transfer (FRETS). More recently, a fully-automated chemiluminescence ADAMTS13 assay has been developed (AcuStar ®) (33, 34)), and a semi-quantitative (point of care) assay (35). Variation has been reported in ADAMTS13 activity results across different testing platforms. The finding of a low ADAMTS13 activity based on an automated or semi-quantitative assay may therefore require confirmation using a FRETS based assay, in particular where the clinical index of suspicion for TTP is low.

Anti-ADAMTS13 antibodies are usually measured via an ELISA based method (detecting both inhibitory and non-inhibitory antibodies). Bethesda-style assays are sometimes used, although these will only detect inhibitory anti-ADAMTS13 antibodies. ADAMTS13 antigen can be measured via an ELISA method, and appears to have prognostic value, although is not in widespread clinical use (26).

Recommendation

1. The initial diagnosis of TTP and treatment decisions should be made on clinical history, examination and laboratory testing including blood film (1A).
2. Pre-treatment samples should be obtained to measure ADAMTS13 activity levels and to detect anti-ADAMTS13 antibodies (1A).
3 The early measurement of ADAMTS13 activity is recommended over using scoring systems. (2C).
4 Serological tests for HIV, HBV and HCV, autoantibody screen and when appropriate, a pregnancy test, should be performed at presentation (1A).

5 A low ADAMTS13 activity level based on a fully-automated assay/semi-quantitative assay may require confirmation (by a FRETS based assay) depending on the index of clinical suspicion for TTP (2C)

Treatment of acute TTP

A summary of referral and treatment protocol Figure 1

Initial Management of Acute TTP

The suspected diagnosis of TTP is a medical emergency requiring urgent referral and time-critical transfer to a dedicated centre. Ideally, PEX should be commenced within four hours but certainly by eight hours of a suspected diagnosis to reduce the high risk of mortality. Pre-transfer review, preferably from anaesthetics or intensive care, should be considered to facilitate safe transfer. Intubation may be required during the acute presentation (36), therefore ideally transfer should be with an airway escort. Plasma exchange often requires insertion of a Vascath. Platelet transfusion in TTP is associated with significant increase in mortality and should be avoided (37). Priority should be to initiate PEX over investigations such as neuroimaging.

Recommendations:

- TTP is a medical emergency requiring time critical transfer to a dedicated treatment centre (1A)
- Pre-transfer review should be undertaken by an appropriately skilled medical team. Intubation should be considered for clinically unstable patients (1B)
- From referral of a suspected diagnosis of TTP and transfer, PEX should be initiated within four to eight hours (1A).
- Platelet transfusion should be avoided (1B)

Therapies and evidence for use in TTP

Caplacizumab

Caplacizumab is a monoclonal, bivalent humanised Immunoglobulin fragment. It binds to the A1 region of VWF, preventing platelet binding to the GpIb-IX-V receptor(38), (39), (40). On confirmation of TTP, either clinically, as in the pivotal studies, or by confirmation of severe ADAMTS13 deficiency (<10 IU/dL), an intravenous dose of caplacizumab 10mg is given pre PEX. A once daily 10mg subcutaneous dose is continued up to 30 days following completion of PEX. Caplacizumab reduces duration of thrombocytopenia, exacerbations, refractory disease (36, 41, 42), admission duration, PEX procedures and volume of plasma used (39, 40). Caplacizumab prevents a fall in platelet count associated with ADAMTS13 deficiency but does not modify the underlying immune disease process. Persistence of severe ADAMTS13 deficiency is associated with clinical relapse, therefore caplacizumab may be continued beyond 30 days following cessation of PEX if ADAMTS 13 activity levels remain <10iu/dL (40).
Caplacizumab is being used in acute TTP without the need for PEX (43) and alternate day regimens (44)
Caplacizumab causes a significant reduction in VWF activity and is associated with bleeding, which is rarely severe. Major bleeding can be managed with VWF concentrate (40). The half-life of caplacizumab is approximately 24 hours and it is partially renally eliminated (45). If invasive procedures are required, the subsequent caplacizumab dose can be delayed to allow this, but in the acute setting, treatment should not be stopped. In those with body weight < 40 kg, a 5mg daily dosing should be used(46).

Plasma therapy

Daily PEX, typically with spun apheresis, reduces mortality, from 90% to 10–20%. It repletes ADAMTS13 and removes autoantibodies. Plasma infusions are only indicated if there is an unavoidable delay in commencing PEX, which is superior to plasma infusion (47). In this RCT, daily 1.5x plasma volume (PV) exchange was performed on the first three days followed by 1.0x PV exchange thereafter. More intensive exchange, such as twice daily PEX, may be required in refractory cases particularly with new neurological or cardiac events (1). Daily exchanges should continue to clinical remission, defined as a normal platelet count (>150× 10^9/L).

Previous guidance recommended two PEX following clinical remission, but caplacizumab has allowed stopping of PEX on normalisation of the platelet count. Tapering (reducing frequency and/or volume of PEX) has not been shown to reduce relapse rates (48).

In the UK, solvent/detergent-treated (S/D) plasma (OctaplasLG) is used for PEX/ADAMTS13 replacement. UK regulatory bodies recommended the use of solvent/detergent-treated (S/D) plasma (49) in TTP patients to reduce the risk of transfusion-transmitted infection and adverse immune responses (50-52). The addition of a prion reduction step to Octaplas is associated with comparable efficacy in treating TTP (51). Due to the high volumes of plasma in young patients, OctaplasLG remains the primary plasma to be used in TTP (53).

Insertion of central venous catheters does not require platelet transfusion. The vascath should be removed as soon as practical to reduce known risks such as infection and thrombosis. Direct pressure should be applied at the site of removal for sufficient time to minimise the risk of bleeding. We do not recommend the use of haemostatic agents to reverse the effects of caplacizumab.

4.1.2 Jehovah's Witness patients/unable to receive blood products

In acute TTP, this has been a therapeutic challenge but PEX with albumin (54) or cryosupernatant (55) have been used. More recently, treatment with steroids, caplacizumab and rituximab has been successfully reported (43, 56).

Steroids:

There remains limited data on the use of steroids in acute TTP. However, early studies of patients with milder disease demonstrated remission with steroids (57, 58). Use of high dose methylprednisolone (10 mg/kg/day for three days followed by 2.5 mg/kg/day) yields higher remission rates than standard dose methylprednisolone (1mg/kg/day), 76.6%) vs 46.6% (59). Prolonged steroid exposure should be avoided,

and doses titrated to the clinical response. Steroid tapering should be considered once the platelet count is in the normal laboratory range (60).

Rituximab

Rituximab is a chimeric anti CD 20 monoclonal antibody. Its use in relapsed or refractory TTP is well established (50, 61, 62) . Early use of rituximab (within 3 days of admission for iTTP) alongside standard care reduces: number of PEX, days on ICU, relapse rates and mortality. ADAMTS13 activity levels are normalised, resulting in increased remission rates (63-65) (66). Most publications cite a dose of 375mg/m^2 rituximab. At least four infusions are given, but further immunosuppression may be required where there is delayed normalisation of ADAMTS13 activity. During PEX therapy, rituximab is infused every three to four days because of associated monoclonal antibody clearance (67).

An alternative anti-CD20 therapy, such as obinutuzumab, can be offered to patients who have anaphylaxis or acute serum sickness with rituximab, if ADAMTS13 activity levels do not improve or fall within 12 months of rituximab (68-70). If obinutuzumab is used, following a test dose 1g is given weekly, for two to four treatments.

Plasma cell directed therapy

This is considered in refractory iTTP or in those who (following a clinical remission) have ongoing ADAMTS13 activity <10 IU/dL and detectable anti-ADAMTS13 antibodies, despite anti CD20 therapy. Daratumumab (71) and bortezomib (72-78) have both been used.

Additional immunosuppressive therapies

Mycophenolate Mofetil (MMF): use in TTP is anecdotal (79-84), although it is widely used in other autoimmune conditions such as SLE. (85, 86).
Ciclosporin: A randomised controlled study compared with steroids was stopped because of improved ADAMTS13 recovery in the steroid group (87)
Azathioprine: There are few publications in iTTP (88, 89), but it may be useful in pregnancy and breast feeding.

Alternate immunomodulatory therapies.

Vincristine: Vincristine has been used in the past in either acute TTP (less than three days from admission (90)) or in refractory/relapsed cases (91, 92). However, because of its toxicity, its use has been superseded by rituximab.

Cyclophosphamide: The use of cyclophosphamide has been reduced since the use of rituximab but may be beneficial in refractory/ relapsing TTP (93). Used acutely, with steroids, it may increase the risk of infection.

Splenectomy: several case series suggest splenectomy may be useful in refractory or relapsing TTP (93-96).

Supportive therapy Antiplatelet agents and thromboprophylaxis

The Italian Co-operative Group randomized 72 TTP patients to PEX and steroids with and without aspirin and dipyridomole (97). There was no difference in response rate or excessive haemorrhage and a non-significant decreased rate of early death in the first 15 days in the anti-platelet-treated group (13·5% vs. 2·8%)(97). An increased thrombotic rate has not been reported in acute TTP cases where thromboprophylaxis with low molecular weight heparin (LMWH) and low dose aspirin was used routinely once the platelet count was >50 × 10^9/L(98). With the use of caplacuzimab, low dose aspirin (75mg) is avoided until therapy has been completed. As VTE remains a risk(99) , thromboprophylaxis is given when the platelet count is >50 10^9/L.

Recommendations:

1. Caplacizumab should be initiated on confirmation of acute iTTP and for up to 30 days following completion of PEX. In patients who remain severely ADAMTS13 deficient (<20 IU/dL) caplacizumab therapy may be continued (1A).
2. Intravenous daily methylprednisolone (e.g. 1 g/day for three consecutive days – adult dose) or high dose oral prednisolone (e.g. 1 mg/kg/day) should be considered, with tapering when there is a sustained increase in ADAMTS 13 activity levels(1B).

3. PEX, with OctaplasLG should be started with 1·5 PV exchanges, and reassessed daily, reducing to 1.0V when the clinical picture and laboratory tests are stabilising (1A).
4. Intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases (1B).
5. Daily PEX should stop when the platelet count is sustained >150 × 10^9/l (2B)
6. Monoclonal anti-CD20 therapy should be initiated within three days of acute iTTP admission (1B).
7. In patients who have refractory iTTP, or have severe ADAMTS13 deficiency despite anti CD20 therapy, alternative immunosuppressive therapy should be considered (2B).
8. Alternate immunomodulatory therapies, such as azathioprine, cyclophosphamide, splenectomy may be alternative options in patients with refractory or relapsing iTTP (2C).
9. All hospitalised/immobilised patients should receive thromboprophylaxis once platelet counts are ≥ 50x10^9/L, even when treated with caplacizumab (1B).

Prognostic Markers in TTP

Prognosis in TTP includes the risk of mortality, exacerbation of TTP or relapse. Since the last BSH guideline (100), several studies have reported prognostic indicators in iTTP (Table 4). However, it is important to note these were published in the era prior to the routine use of caplacizumab.

Clinical Features . Older age at presentation is an independent risk factor for poor outcome (101, 102) whilst younger age is predictive of relapse (103). Ethnicity may be linked to outcome (104-106). Arterial thrombosis, renal failure and neurological involvement may all predict mortality (101, 102, 104).

Laboratory Features, Increased mortality and treatment refractoriness have been associated with a raised troponin (107) (25).

ADAMTS13 activity, antigen and antibody titre at presentation may predict mortality and relapse whilst ADAMTS13 activity 3 months from diagnosis may

also predict the risk of subsequent relapse (103). ADAMTS13 antigen <1.5% (lowest quartile) compared to >10% (highest quartile) is associated with increased mortality (26, 108).

Follow up after an acute TTP episode

Discharge from hospital to out patient follow up following a sustained normalisation of the platelet count. All patients and their relatives should be taught how to administer caplacizumab. If this is not possible, community nursing support should be arranged. Patients should be reviewed at least weekly until completion of immunosuppressive therapy, and to monitor ADAMTS 13 activity levels and re-prescribe caplacizumab. Patients and their relatives should receive information and education about TTP, anticipated adverse events, including relapse and 24/7 contact details.

Long term follow up

TTP is a chronic condition requiring long-term follow-up after an acute episode in order to identify and manage the physical and psychological sequelae as well as to monitor ADAMTS13 activity so as to prevent subsequent clinical relapse.

Monitoring of end organ damage-including the brain, heart and renal function. This includes, but is not exhaustive -MRI head, echocardiogram, renal function, assessment of urine protein: creatinine ratio, blood pressure and autoimmune screen (109). Memory issues, specifically short-term memory can be assessed with questionnaires and if available, formal neurocognitive assessment should be considered. Strokes may require long-term antiplatelet therapy and review of ongoing anti-epileptic therapy.

Assessment of anxiety/depression-This may be aided by questionnaires, and assessment by clinical psychology services. Anxiety and depression have been recorded in up to 60% of patients following acute iTTP (110), but also posttraumatic stress disorder, (PTSD) in 35% of patients(111) and a lower quality of life (111-113). In remission, 27% report persistent cognitive symptoms (114): specifically, impaired memory (66%), difficulty concentrating (26%), and word-finding difficulties unrelated

to acute stroke (26%). The frontal lobe is disproportionally affected in patients with intellectual impairment. The primary MRI finding in these patients was hyperintense white matter lesions. An abnormal MRI was associated with a lower median verbal IQ and performance IQ. Whilst neurocognitive impairment seems to correlate with changes on imaging, a similar finding is not seen when considering the presence of anxiety and depression (115). Patients should be signposted to peer support, for example from the UK TTPNetwork (https://www.ttpnetwork.org.uk) and if available, local TTP/Haematology groups. Cognitive testing and input from psychology services should be arranged where appropriate.

Medical Follow up of iTTP

The risk of relapse is 30-50% (62, 63, 116, 117) and ADAMTS13 <10IU/dL or persistence of anti-ADAMTS13 antibodies are associated with a three-fold higher risk of relapse (118). Clinical relapse can be prevented by monitoring ADAMTS13 activity levels and when reduced from normal levels, to 15-20 IU/dL or based on clinical symptoms, elective rituximab/anti CD20 therapy should be initiated (116, 119, 120). The current optimal dose is undergoing investigation and currently ranges from low dose (fixed doses of 100mg-200mg weekly for four doses) to standard therapy (375mg/m^2 weekly for four doses) with the intention to normalise ADAMTS13 activity (119). ADAMTS13 activity levels below the normal laboratory range confer an increased risk of stroke, compared to a comparable non-TTP cohort (121).

In patients who have had repeated rituximab doses, there may be a risk of

(i) Hypogammaglobulinaemia- immunoglobulin levels should be checked.

(ii) Serum sickness to rituximab. This has been associated with the presence of human anti-chimeric antibodies (HACA) (122). Alternative human anti-human CD20 therapy should be considered (68).

Frequency of monitoring can be reduced as the ADAMTS13 activity stabilises.

Recommendations:

1.Patients should have lifelong follow up including ADAMTS13 assay monitoring (1B)

2.Neurocognitive assessment and psychology support for anxiety/depression should be offered (1C)

3.Pre-emptive therapy with Rituximab should be given when ADAMTS13 activity < 20 IU/dL or higher levels associated with clinical symptoms. (1B)

Congenital TTP

cTTP, also known as Upshaw-Schulman syndrome, is defined by:

i. ADAMTS13 activity < 10IU/dL
ii. No anti-ADAMTS13 autoantibodies.
iii. Confirmatory variants in the ADAMTS13 gene

cTTP accounts for 2 to 10% of all TTP cases, with an incidence of 1/million (20). Presentation can occur in neonates/childhood with severe neonatal jaundice, thrombocytopenia and red cell fragmentation on blood film. Diagnosis in adulthood is seen in 62% (n=45) of patients listed on the UK TTP Registry and the median age of diagnosis was 18 years in the International Hereditary TTP Registry(123). Inheritance of cTTP is autosomal recessive.

cTTP patients can remain asymptomatic until a precipitating event results in a frank TTP episode. Congenital TTP can be misdiagnosed as chronic immune thrombocytopenia, Evans syndrome or atypical HUS. Only half of the cTTP patients (n=37, 51%) on the UK TTP Registry were diagnosed at the time of first symptom onset (16). Late recognition is associated with medical co-morbidities, from obstetric complications to stroke (124).

a. Childhood onset cTTP -accounted for 38% of all cases in the UK TTP Registry publication(16). In 40%, infection was the most common precipitant. 36% of childhood cases had neonatal onset of TTP.
b. Adult onset cTTP -should be considered with thrombocytopenia, neurological signs and thrombosis. Approximately 10% of patients were diagnosed between 40 and 70 years of age(16).

Pregnancy was the most common trigger of cTTP in the UK Registry (69% of adult presentations(15). Precipitating events also include febrile episodes, infections and vaccinations.

More than 150 genetic variants have been described(18), the most frequent being a missense variant in exon 24 R1060W (rs142572218)(125), associated with later-age disease onset.

Treatment of congenital TTP

Replacement of deficient ADAMTS13 is either with plasma infusion or virally-inactivated intermediate purity factor VIII concentrate containing ADAMTS13, such as 8Y (BPL; BioProducts Laboratory, Elstree, Herts;(126, 127)). Efficacy has been demonstrated in both acute correction of thrombocytopenia, prophylaxis in preventing relapse of TTP and can be administered as home therapy.

Plasma infusion is a more reliable ADAMTS13 source than 8Y, with higher post-treatment ADAMTS13 activity (Lester, et al 2002, Peyvandi, et al 2013,Scully et al, 2006, Taylor et al 2019) , giving 10-15mls/kg every one to two weeks (16). Factor VIII concentrate dosing regimens are typically a weekly dose of 15-30U/kg. There is a more variable ADAMTS13 content(128), but antibodies to ADAMTS13 have not been detected following the use of 8Y. Recombinant human ADAMTS13 is now in phase 3 clinical trial with phase 1 trials confirming safety and tolerability. Proposed advantages include significantly higher ADAMTS13 levels and ease of administration compared to plasma infusion (129-131).

Recent data suggest patients may benefit from prophylaxis, since non-overt symptoms may represent subacute microvascular thrombi. The International cTTP Registry found 50% of cTTP patients at least 40 years of age not on prophylaxis had more than one arterial thromboembolic event(123), while the UK Registry showed symptom resolution in 88% of the 24 patients commencing regular prophylaxis for headaches, lethargy and abdominal pain without laboratory evidence of TTP or end-organ damage(16).

The half-life of ADAMTS13 was initially reported as three days, more recently revised to between three and eight days; according to individual rates of elimination, body weight and basal metabolism(132), (133).

Recommendations

1. cTTP should be considered in severe neonatal jaundice with thrombocytopenia and in children with unexplained thrombocytopenia. (1B)

2. Siblings of confirmed cTTP cases should be screened, including ADAMTS13 activity and genetic analysis. (1C)

3. The diagnosis of congenital TTP is confirmed by ADAMTS13 activity <10IU/dL, no anti-ADAMTS13 antibody and confirmation of homozygous or compound heterozygous variants in the ADAMTS13 gene. (1B)

4. For an acute cTTP episode, solvent detergent plasma infusion is recommended. Intermediate purity factor VIII (eg BPL8Y) can be considered. (1B)

5. ADAMTS13 prophylaxis should be considered for all patients with cTTP, with an individualised approach to dose and frequency according to symptoms, whether overt or non-overt. (1B)

Pregnancy associated TTP

Both cTTP and iTTP can first present during pregnancy. It may present in any trimester but is most common in the third trimester and postpartum. Aside from maternal morbidity and mortality, the risk of fetal loss can be >40%, most commonly in the second trimester in untreated women (15).

There are other causes of TMA in pregnancy, including haemolysis elevated liver enzymes low platelet count (HELLP), atypical haemolytic uraemic syndrome (aHUS) and pre-eclampsia (PET). Distinguishing between TTP and other TMAs can be very difficult and ADAMTS13 activity assays can differentiate (134).

Patients with de novo TTP in pregnancy should initially be treated with PEX and steroids. If a diagnosis of cTTP is subsequently made, regular solvent/detergent fresh frozen plasma (SD-FFP) infusions or PEX should continue throughout pregnancy and post-partum. cTTP associated with the variant C3178T (R1060W) is the commonest underlying variant defect described.

Caplacizumab in pregnancy is currently not recommended; it is a small sized molecule which can cross the placenta and there is an unquantified risk of pregnancy-specific bleeding associated with the severe reduction in VWF activity levels. However, a case report of Caplacizumab use in pregnancy has been published (135). Low dose aspirin and prophylactic LMWH should be considered for all women with acute TTP in pregnancy when the platelet count is >50x10^9/L.

In the event of refractory or relapsing iTTP additional immunosuppression may be required. Options include prednisolone, azathioprine, ciclosporin and rituximab. There is no specific pattern of adverse outcome from case series of women exposed to rituximab in pregnancy (136-138). Low levels of rituximab have been detected in breast milk (139).

Termination of pregnancy is not required in most cases. Careful fetal monitoring with regular assessment of fetal growth and placental function is recommended. Ongoing antenatal management and delivery should take place in a tertiary obstetric and fetomaternal specialist units and TTP regional centre. Fetal thrombocytopenia would not be expected.

8.1 Subsequent pregnancy in women with prior TTP

In women with prior iTTP, normal ADAMTS13 activity levels at onset of pregnancy predict a successful outcome in most cases (15). ADAMTS13 activity should be monitored at least in each trimester and more regularly if levels decrease.

Women should continue to be counselled to avoid pregnancy for at least six months (ideally 12 months) after rituximab (15, 136).

For women with falling ADAMTS13 activity in pregnancy (ADAMTS13 relapse), options include prednisolone, azathioprine, ciclosporin, PEX or rituximab.

In women with cTTP, plasma infusion or exchange should be initiated as prophylaxis to achieve sufficient ADAMTS13 activity levels to avoid clinical relapse. Infusion therapy has been recommended at least every other week initially, then weekly from the second trimester onwards (15, 140). Women with known cTTP already on

prophylaxis with 8Y prior to pregnancy could be switched to SD-FFP replacement due to the low ADAMTS13 recovery and the potentially pro-thrombotic risks of intermediate purity factor VIII concentrate in pregnancy.

Recommendations

1.Patients presenting for the first time with TTP in pregnancy should initially be treated as per iTTP with PEX and steroids (1A)

2.Women presenting with TTP in pregnancy should have investigations to determine whether they have iTTP or a first presentation of cTTP (1B)

3. For pregnant women with iTTP refractory to PEX and steroids or who relapse, additional treatment options include ciclosporin, azathioprine and rituximab (2C)

4. For pregnant women with cTTP, regular SD-FFP replacement therapy should be given prophylactically to prevent clinical TTP relapse (1B)

5. For women with iTTP, normalisation of ADAMTS13 activity prior to pregnancy is recommended (1B)

TMA Subgroups

In recent years, there has been clarification of TMAs and TTP as a defined differential, which thus impacts on much of the previously published/historical data. We must therefore exercise caution when considering TMAs that are associated with other disorders, and whether the association and management strategies are relating to TMA or “true” TTP. It is likely that cases that responded to PEX were TTP, whereas those that did not were non-TTP TMA, but the data is heterogeneous and beyond the scope of this guideline.

HIV associated TTP

TMA may be multifactorial in the setting of HIV infection. However, TTP is associated with HIV (141, 142) associated with a high viral load(143). Presentation with TTP de

novo and relapse may also occur for those treated with antiretroviral therapy and may indicate non-compliance or drug resistance. The majority of cases appear to respond to PEX/corticosteroids and HAART (143), therefore additional immunomodulatory therapy may not be required. Where TTP occurs with undetectable viral loads, or if unresponsive to first line therapy, treatment with rituximab can be used (143). Early engagement with the infectious diseases team is advisable and to ensure robust follow up. As with other medications for those receiving PEX, the timing of HAART administration and PEX should aim to ensure maximum drug exposure.

Recommendations:

- HIV associated iTTP should be treated with HAART and plasma exchange/steroids/caplacizumab.(1B)
- In patients with low/undetectable viral load, ADAMTS13 relapse or clinical relapse should be treated as standard iTTP (1C)

Co-existing autoimmune conditions

Immune TTP may present in the setting of other autoimmune disorders (e.g. SLE/Sjogrens) and is frequently associated with the presence of other autoantibodies (144). Management of acute TTP will not be altered in this setting, however longer term, management and monitoring will require input from other relevant medical specialists (e.g. rheumatologist/renal physician)

Cancer

People with cancer have a number of reasons for developing TMA – including DI-TMA (see below). The commonest histology is adenocarcinoma, typically gastric, breast, prostate and lung, and in the majority of cases these were metastatic (145). ADAMTS13 activity is not severely reduced in patients with cancer associated TMA and therefore there is no role for PEX in this patient group(146).

Pancreatitis associated TMA

The pathogenesis of MAHA in association with severe pancreatitis poorly understood. There is often no obvious precipitant for the pancreatitis and the TMA

occurs a number of days after presentation. ADAMTS13 activity levels are not severely reduced and PEX has been used in case reports and small series(147-149). However, there is insufficient evidence to firmly recommend PEX in all cases. It should also be considered that an acute iTTP episode can manifest with signs of pancreatitis due to microangiopathy.

Transplant associated TMA

TMA is associated with both solid organ and stem cell transplantation and, whilst heterogenous in presentation and end-organ effects, the underlying pathology relates mainly to self-propagating endothelial injury and complement activation (150, 151). ADAMTS13 activity levels are not severely reduced and PEX is not indicated (28). Elucidation of the role of complement has seen a move towards treatment with terminal complement blocking agents.

Recommendations

- PEX is not recommended for cancer or transplant associated TMA (1C)
- Pancreatitis associated TMA is not associated with a severely reduced ADAMTS13 activity and the benefit of PEX is unclear (2C)

HUS

Clinical and haematological features in HUS may overlap with TTP. ADAMTS13 activity in HUS (of any cause) is rarely below 20IU/dL. Conversely, where patients present with unexplained TMA, thrombocytopaenia and ADAMTS13 activity above 20IU/dL, HUS should be considered (30).

Haemolytic Uraemic Syndrome (HUS) is a clinical syndrome characterised by the triad of microangiopathic haemolytic anaemia, thrombocytopaenia and acute kidney injury (AKI). This results from infection with Shiga toxin-producing Escherichia coli e.g. O157:H7, but also salmonella or shigella due to shared consumption of infected food, and there is usually a prodrome of diarrhoeal illness. HUS is the commonest cause of childhood AKI. Other organs, including the brain and gut, can also be affected. No prodromal illness (or absence of a Shiga toxin-producing organism) suggests a diagnosis of atypical, CM HUS, is rare, incidence of approximately

1/million(152) and sometimes familial disease in which genetic or acquired defects, usually of complement regulation, lead to uncontrolled endothelial cell damage and TMA. In the US, CM HUS has an incidence of approximately 1-2 per million population (153) and 60% of patients have an identifiable genetic variant or autoimmune cause. (154). There are a number of differential conditions associated with HUS (Table 5). Infusion of humanized anti-C5 monoclonal antibody (eculizumab or ravulizumab) (155, 156)) results in rapid inhibition of the terminal complement pathway and significant clinical efficacy of this treatment for CM HUS. In view of its efficacy and generally favourable safety profile, where available, C5 depletion therapy is often considered first line treatment for CM HUS and its use has been associated with significant improvement in renal outcomes. Rarely, atypical HUS that is not primarily attributable to a disorder of complement regulation has been reported (for example secondary to biallelic loss-of-function variants of the DGKE gene). In this situation evidence of responsiveness to complement inhibitor therapy is limited (157).

Prior to complement inhibitors, PEX was frequently used to treat CM HUS, with variable response rates (158). Although randomized controlled trials have not been reported, expert opinion-based guidelines suggest treatment is likely to benefit patients, with five daily 1.5x plasma volume (60-75 mL/kg) exchanges using either membrane filtration of centrifugal separation according to local availability, with subsequent tapering according to response (159).

Use of tetravalent and meningococcal B vaccinations should be given before complement inhibitor therapy is started and prophylactic antibiotics against encapsulated bacteria throughout therapy.

Recommendations:

1. In TMAs associated with renal impairment, ADAMTS13 activity should be checked to exclude TTP (1B)
2. CM HUS is a clinical diagnosis (that can sometimes be confirmed by detection of a pathogenic complement gene variant or relevant autoantibody) for which prompt complement inhibitor therapy should be initiated. (1A)

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Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (http://www.b-s-h.org.uk/guidelines).

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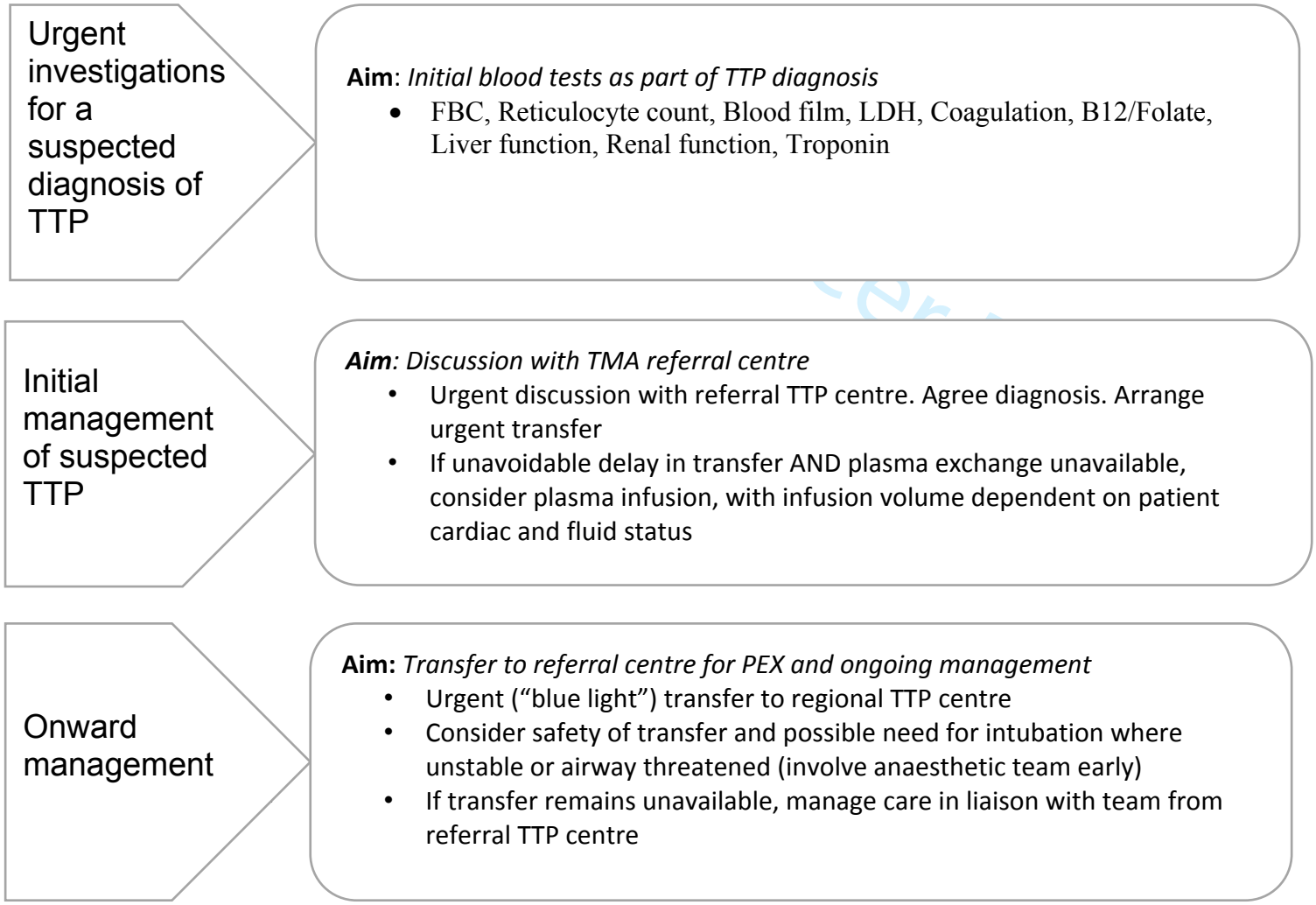
Appendix S1

The writing group was selected to be representative of UK-based experts. MEDLINE and EMBASE were searched for publications from 2012 onwards using the key words: Thrombotic thrombocytopenic purpura AND ADAMTS13, plasma exchange,

caplacizumab, rituximab, congenital, immune, prognostic, registry, HIV, scoring, factor concentrates, haemolytic uraemic syndrome

Figure 1a: Initial TTP management at a referring centre



1b Initial TTP management at a TTP/TMA centre

Initial management of suspected TTP

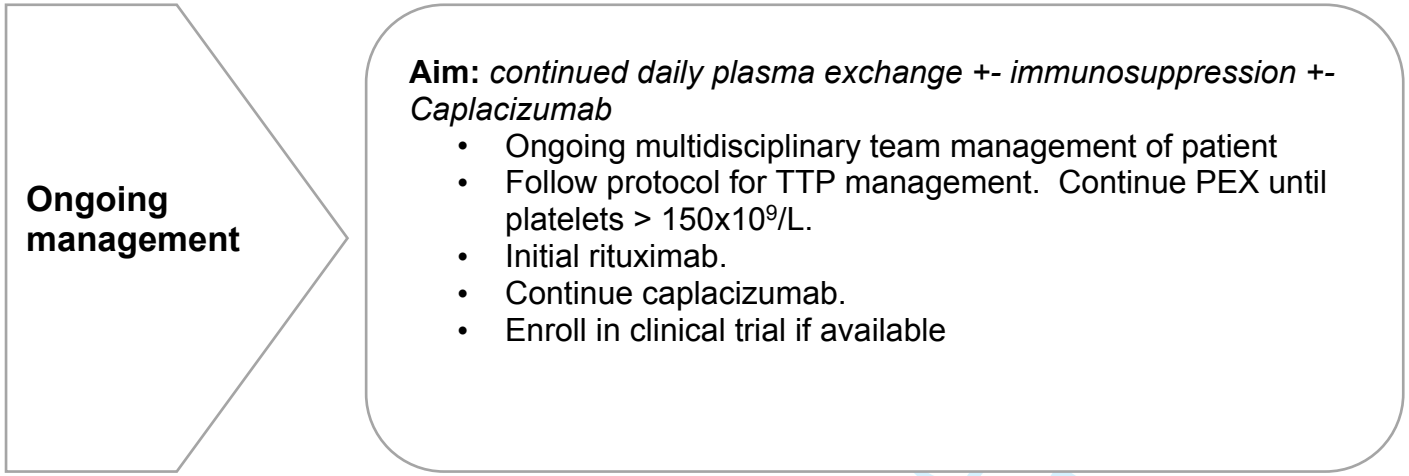
Aim: urgent plasma exchange in a safe clinical environment

- Admit patient under the experienced TTP team to agreed location for acute TTP management
- Defrost AB OctaplasLG during patient transfer to ensure PEX starts ASAP
- Arrange wide bore intravenous catheter (or peripheral access to avoid delay) to enable PEX
- Initiate 1.5 volume plasma exchange (PEX) as soon as possible (target 4-8 hrs).
- Avoid platelet transfusion
- Initiate steroids post PEX
- Initiate caplacizumab on confirmation of TTP

Urgent investigations to confirm suspected diagnosis of TTP

Aim: *Investigations required for a new TTP referral*

- As Table III
- *ADAMTS13* samples pre PEX



1c: TTP regional centres: England

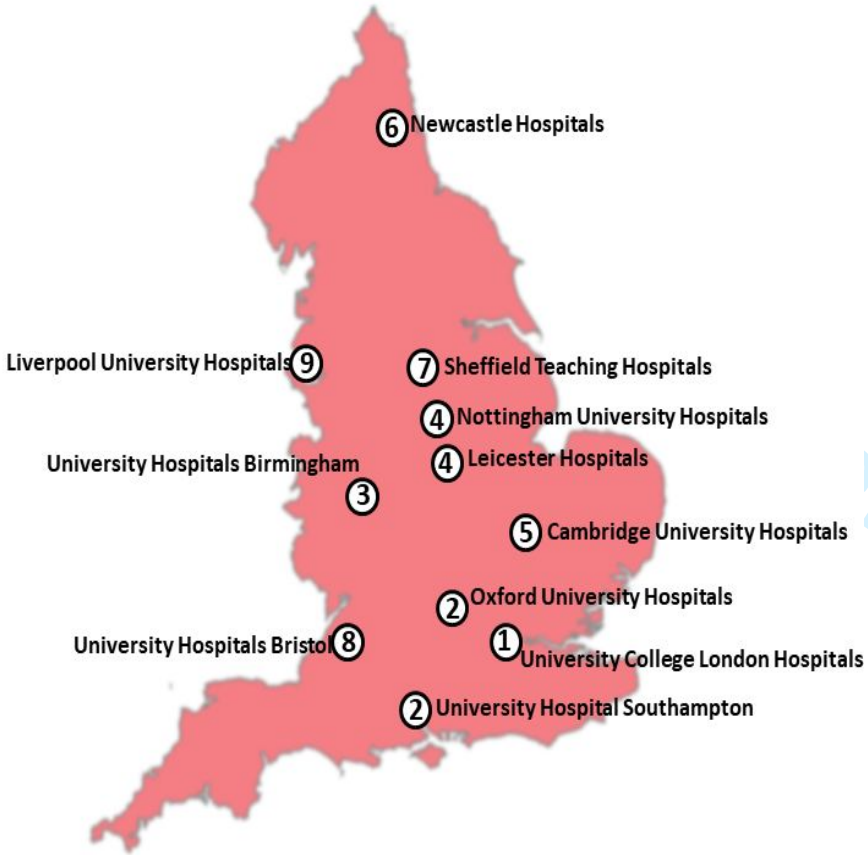


Table 1. Differential diagnosis of thrombocytopenia and microangiopathic haemolytic anaemia

Autoimmune haemolysis/Evans syndrome
Disseminated intravascular coagulation
Pregnancy-associated e.g. HELLP (haemolysis, elevated liver enzymes and low platelets), eclampsia, haemolytic uraemic syndrome
Drugs e.g. interferon, Calcineurin inhibitors
Malignant hypertension
Infections, typically viral (cytomegalovirus, adenovirus, herpes simplex virus) or severe bacterial (meningococcus, pneumococcus), fungal
Autoimmune disease (lupus nephritis, acute scleroderma) Vasculitis
Haemolytic uraemic syndrome (diarrhoea positive/negative)
Scleroderma
Malignancy
Pancreatitis
Malignant hyperthermia, heat shock
Severe aortic valve stenosis, paravalvular leaks
Catastrophic antiphospholipid syndrome

Table 2 Presenting clinical features and signs in acute TTP.

Thrombocytopenia	Epistaxis, bruising, petechiae, gingival bleeding, haematuria, menorrhagia, gastrointestinal bleeding, retinal haemorrhage and haemoptysis
Central neurological – often flitting and variable 70–80%	Confusion, headache, paresis, ***seizures***,aphasia, dysarthria, visual abnormalities, encephalopathy, coma (10%)
Fever (>37.5°C)	
Non-specific symptoms	Pallor, jaundice, Fatigue, arthralgia, myalgia
Jaundice	Unconjugated hyperbilirubinaemia, resulting from haemolysis
Renal Impairment	Proteinuria, microhaematuria

Cardiac	Chest pain, heart failure, hypotension, ***myocardial infarction, acute cardiac arrest***
Gastro-intestinal tract	Abdominal pain, ***pancreatitis, gut ischaemia***

Table 3 Testing and expected results for patients with a suspected diagnosis of TTP. Blood samples should be sent for investigation before first PEX

Essential investigations	**Rationale of investigation**
Full blood count and blood film	Anaemia, thrombocytopenia, fragments/schistocytes on blood film
Reticulocyte count	Raised
Haptoglobin	Reduced
Clotting screen including fibrinogen	Normal
Urea and electrolytes	Renal impairment
Troponin T/Troponin I	For cardiac involvement
Liver function tests	Usually normal, raised bilirubin related to haemolysis
Calcium	May reduce with PEX
Lactate dehydrogenase	Raised due to haemolysis
Urinalysis	For protein leak
Direct antiglobulin test	Negative
B12/folate/iron studies	To exclude haematinic deficiency
Blood group and antibody screen	To allow provision of blood products

Hepatitis A/B/C and human immunodeficiency virus testing	Pre-blood products and to exclude an underlying viral precipitant
Pregnancy test (in women of child-bearing age)	
Amylase	***Exclude Pancreatitis***
C3/4	***Complement reduction***
Urine protein: creatinine ratio	***With renal involement***
Glucose	***Exclude diabetes***
ADAMTS 13 assays	Do not wait for result before starting treatment in suspected TTP
Electrocardiogram/Echocardiogram	To document/monitor cardiac damage
CT/MRI brain	To determine neurological involvement*
Additional investigations	
Thyroid function tests	To exclude Graves Disease
Auto-antibody screen (ANA/RF/ LA/ACLA), including lupus anticoagulant	Exclude associated autoimmune disease
Stool culture	For pathogenic Escherichia coli (if diarrhoea)
CT Chest/abdomen/pelvis (if indicated) ± tumour markers	To look for underlying malignancy

Table 4: Prognostic factors in TTP

Parameter	Detail	Data/Finding	Reference
Age[100],[101]	>60 vs <40 vs <45 years	>60 independently associated with increased mortality (OR 10.6 [95% CI=2.0-32.0] vs age <40; adjOR 3.47, [95% CI=2.14-5.63] vs age <45)	Benhamou, *et al* 2012, Goel, *et al* 2016
Age[102]	Younger age	Younger age was also predictive of relapse	Jin, *et al* 2008
Ethnicity[103,104]	Caucasian v non-Caucasian	African-American patients at less risk of dying, compared to Caucasian counterparts on multivariate analysis (OR = 0.2, [95% CI = 0.03–0.74])	Cataland, *et al* 2009, Martino, *et al* 2016).
Presenting features[100,]	Arterial thrombosis	Arterial thrombosis (adjOR 6.73, 95% CI=1.11-40.91	Benhamou, *et al* 2012, Goel, *et al* 2016, Martino, *et al* 2016)

Presenting features[101]	Renal dysfunction/failure	Renal failure (adjOR 2.56, 95% CI=1.46-4.47)	Benhamou, *et al* 2012, Goel, *et al* 2016, Martino, *et al* 2016)
Presenting features[104]	Neurological involvement	Neurological involvement, both specific pathologies; ICH (adjOR 6.05, 95% CI=1.58-23.24) and ischaemic stroke (adjOR 2.42, 95% CI=1.17-5.01) (both these predict mortality on multivariate analysis); and symptoms, involvement headache, focal impairment, stupor and seizure (OR 2.6 [1.0, 6.9] p=0.05; OR = 3.43, [95% CI = 1.2–12.4] P < .05	Benhamou, *et al* 2012, Goel, *et al* 2016, Martino, *et al* 2016)
Blood tests[103]	ADAMTS13 activity	Three months after initial diagnosis ADAMTS13 activity may also predict risk of relapse	Jin, *et al* 2008)
Blood tests[26,106]	ADAMTS13 antibody	Anti-ADAMTS13 antibodies and mortality: higher anti-ADAMTS13 antibody titres in patients who died compared to those who survived (anti-ADAMTS13 antibody titre >2 Bethesda units), particularly when high titres were associated with a low ADAMTS13 antigen (ADAMTS13 antibody >77% and ADAMTS13 antigen <1.5%, and either of anti-ADAMTS13 antibody >77% or ADAMTS13 antigen,1.5% but not both, mortality was 27.3% and 10.2% respectively, P=0.02)	Alwan, *et al* 2017, Kremer Hovinga, *et al* 2010).
Blood tests	ADAMTS13 antigen	ADAMTS13 antigen <1.5% (lowest quartile) and antigen >10% (highest quartile) have been shown to be associated with mortality of 184% and 3.8% respectively (P=0.005) ADAMTS13 antigen at presentation may predict mortality and at time of clinical recovery, predict relapse (p=0.03; p=0.19 respectively)	Cataland, *et al* 2009)
Blood tests[153]	LDH	LDH 10x normal OR 3.0 [1.3, 11.6] p=0.014	(Benhamou, *et al* 2012)

		The speed of decline in LDH levels in response to treatment predicts mortality: A rapid reduction in LDH correlated with survival and failure to significantly reduce serum LDH by day 5, which persisted on Cox regression analysis (elevated LDH at day five [HR 2.93, P=0.04]), predicted mortality	(Patton, *et al* 1994)
Blood tests[153]	Platelet recovery rate	Platelet recovery rate overall was associated with improved survival on multivariate analysis (platelet recovery rate $5x10^9$/L per 24 hours OR 18.3 CI 95% [3.7-91.4] p<0.001) On univariate, the normalisation of the platelet count within 7 days was associated with clinical remission (P<0.001)	(Staley, *et al* 2019) .
Blood tests[153]	Total protein/albumin	Raised total serum protein or albumin on admission and reduced risk of in-hospital mortality (HR, 0.37 [p=0.032]; HR, 0.21, [p= 0.003] respectively)	(Staley, *et al* 2019)
Blood tests[105]	Troponin	A high troponin on multivariate analysis; • mortality (OR 2.39 [95% CI 1.02–5.63] p=0.046 OR 2.87; 95% confidence interval [CI] 1.13–7.22; P = 0.024) • refractoriness (OR 3.03; 95% CI 1.27–7.3; P = 0.01)	(Brazelton, *et al* 2017)

Table 5: Differential Diagnosis of HUS

Infection (Diarrhoea Positive)	-Shiga & *Verocytoxin* (Shiga-like toxin) producing bacteria
Disorders of Complement Regulation (Diarrhoea Negative)	-Genetic Disorders of Complement Regulation e.g. Factor H, I, MCP (CD 46), factor B (*CFB*), C3 (*C3*), DGKE mutations
	-Acquired disorders of complement regulation e.g. anti-FH antibody
Other Secondary causes of HUS	-*Steptococcus pneumoniae*
	-HIV
	-Malignancy
	-defective cobalamine metabolism
	-Drugs e.g. Quinine, some chemotherapy e.g. Gemcitabine, bleomycin)
	-Pregnancy
	-Other autoimmune diseases e.g. SLE, APLS

TABLE 1-APPENDIX - Drugs associated with DI TMA

Docetaxel
Doxorubicin
DCR-MYC
Gemcitabine
Oxaliplatin
Pentostatin
Vincristine

Carboplatin +
Etoposide + Melphalan
Cyclophosphamide
+ Thiotepa
Bortezomib
Carfilzomib
Ixazomib
Bevacizumab
Ramucirumab
Cetuximab
Imatinib
Ipilimumab
Pazopanib
Ponatinib
Palbociclib
Ruxolitinib
Sunitinib
Cyclosporine
Rapamycin
Tacrolimus
Adalimumab
Certolizumab pegol
Emicizumab + aPCC
Golimumab
OKT3
Ustekinumab
Moxetumomab pasudotox
Cocaine/ Ecstasy
Oxymorphone/Oxycodone
Polyethylene
oxide (PEO)
Interferon beta 1-a /1-b

Alemtuzumab
Fingolimod
Valproic acid Anticonvulsive
Tenofovir/Emtricitabine
Quinine/Hydroxychloroquine
Ciprofloxacin
Fluoroquinolone
Metronidazole
Penicillin