Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies

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The guideline group was selected to be representative of UK-based medical experts. MEDLINE and EMBASE were searched systematically for publications in English, using the keywords: thrombotic thrombocytopenia purpura (TTP), ADAMTS13, plasma exchange (PEX) and relevant key words related to the subsections of this guideline. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the BCSH. The guideline was then reviewed by a sounding board of British haematologists, the BCSH and the British Society for Haematology Committee and comments incorporated where appropriate. The ‘GRADE’ system was used to quote levels and grades of evidence, details of which can be found at http://www.bcshguidelines.com.

The objective of this guideline is to provide healthcare professionals with clear, up-to-date, and practical guidance on the management of TTP and related thrombotic microangiopathies, defined by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and small vessel thrombosis.

Pathogenesis

Thrombotic thrombocytopenic purpura (TTP) is rare, with a reported incidence of six cases per million per year in the UK (Scully et al, 2008). It is an important diagnosis to make because the untreated mortality is 90%, which can be reduced with the prompt delivery of plasma exchange (PEX). Early death still occurs: approximately half of the deaths in the regional UK registry occurred within 24 h of presentation, primarily in women (Scully et al, 2008).

In the last 15 years there has been a marked increase in the understanding of the pathogenesis of TTP. It is now recognized that congenital and acute acquired TTP are due to a deficiency of von Willebrand factor (VWF) cleaving protein, also known as ADAMTS1, (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 – von Willebrand factor cleaving protein) (Fujikawa et al, 2001; Levy et al, 2001). In the absence of ADAMTS13, ultra large multimers of VWF (ULVWF) released from endothelium are not cleaved appropriately, and cause spontaneous platelet aggregates in conditions of high shear, such as in the microvasculature of the brain, heart and kidneys.

Congenital TTP is due to an inherited deficiency of ADAMTS13, but acquired immune TTP is due to the reduction of ADAMTS13 by autoantibodies directed against ADAMTS13 (Furlan et al, 1998a; Tsai & Lian, 1998). Other clinical forms of thrombotic microangiopathy (TMA) occur in the absence of severe deficiency.

Diagnosis can be difficult, as there is clinical overlap with haemolytic uraemic syndrome (HUS), autoimmune disease and a spectrum of pregnancy-related problems.

Diagnosis of TTP

Thrombotic thrombocytopenic purpura was originally characterized by a pentad of thrombocytopenia, MAHA, fluctuating neurological signs, renal impairment and fever, often with insidious onset. However, TTP can present without the full pentad; up to 35% of patients do not have neurological signs at presentation and renal abnormalities and fever are not prominent features. The revised diagnostic criteria state that TTP must be considered in the presence of thrombocytopenia and MAHA alone (Galbusera et al, 2006). This can result in an increased referral of other TMAs (Table I). TTP remains a
Cardiac: Chest pain, heart failure, hypotension.
Renal: Impairment, proteinuria, microhaematuria.
Jaundice: Resulting from microangiopathic.
Non-specific: Pallor, jaundice, fatigue, arthralgia or fever.

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).
Malignancy.
Catastrophic antiphospholipid syndrome.

Table I. Differential diagnosis of thrombocytopenia and microangiopathic haemolytic anaemia.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Blood film</th>
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<tbody>
<tr>
<td>Autoimmune haemolysis/Evans syndrome</td>
<td>Low haptoglobin, reticulocyte counts</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>High reticulocyte counts, decreased haptoglobin</td>
</tr>
<tr>
<td>Pregnancy-associated e.g. HELLP (haemolysis, elevated liver enzymes and low platelets), eclampsia, haemolytic uraemic syndrome</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
</tr>
<tr>
<td>Drugs e.g. quinine, simvastatin, interferon, Calcineurin inhibitors</td>
<td>Low haptoglobin, reticulocyte counts</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
</tr>
<tr>
<td>Infections, typically viral (cytomegalovirus, adenovirus, herpes simplex virus) or severe bacterial (meningococcus, pneumococcus), fungal</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
</tr>
<tr>
<td>Autoimmune disease (lupus nephritis, acute scleroderma)</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
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<tr>
<td>Vasculitis</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome (diarrhoea positive/negative)</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
</tr>
<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td>Low haptoglobin, reticulocyte counts, conjugated bilirubin</td>
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</tbody>
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Table II. Presenting clinical features and signs in acute TTP.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Signs and symptoms</th>
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<tbody>
<tr>
<td>Epistaxis, bruising, petechiae, gingival bleeding, haematuria, menorrhagia, gastrointestinal bleeding, retinal haemorrhage and haemoptysis</td>
<td>Confusion, headache, paresis, aphasia, dysarthria, visual problems, encephalopathy, coma (10%)</td>
</tr>
<tr>
<td>Confusion, headache, paresis, aphasia, dysarthria, visual problems, encephalopathy, coma (10%)</td>
<td>Pallor, jaundice, fatigue, arthralgia or myalgia</td>
</tr>
<tr>
<td>Resulting from microangiopathic haemolytic anaemia</td>
<td>Proteinuria, microhaematuria</td>
</tr>
<tr>
<td>Chest pain, heart failure, hypotension</td>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>

ADAMTS13 assays

Blood must be taken prior to treatment to assess baseline ADAMTS13 activity. Severely reduced ADAMTS13 activity (≤5%) ± the presence of an inhibitor or IgG antibodies, confirms the diagnosis (Peyvandi et al, 2004; Coppo et al, 2006; Ferrari et al, 2007; Scully et al, 2007a). Decreased ADAMTS13 activity (<40% but >5%) has been reported in a wide variety of non-TTP conditions such as uraemia, inflammatory states, post-operatively and during pregnancy (Loof et al, 2001; Mannucci et al, 2001; Moore et al, 2001). The specificity of severe ADAMTS13 deficiency (<5%) in distinguishing acute TTP from HUS is 90% (Bianchi et al, 2002; Zheng et al, 2004).

ADAMTS13 assays currently available include assays of activity, antigen and neutralizing or non-neutralizing anti-ADAMTS13 autoantibodies. Functional assays measuring ADAMTS13 activity are based on the failure of the patient plasma to degrade VWF multimers or synthetic VWF peptides. Inhibitory autoantibodies can be titrated in vitro using classical mixing studies and non-neutralizing antibodies can be detected by Western blotting or enzyme-linked immuno-sorbent assays (Peyvandi et al, 2010).

Recommendation

1. The diagnosis of TTP should be treated as a medical emergency (1A).
2. The initial diagnosis of TTP should be made on clinical history, examination and routine laboratory parameters of the patient, including blood film review (1A).
3. In view of the high risk of preventable, early deaths in TTP, treatment with PEX should be initiated as soon as possible, preferably within 4–8 h, regardless of the time of day at presentation, if a patient presents with a MAHA and thrombocytopenia in the absence of any other identifiable clinical cause (1B).
4. Serological tests for HIV, hepatitis B virus and hepatitis C virus, autoantibody screen and when appropriate, a pregnancy test, should be performed at presentation (1A).
Pre-treatment samples should be obtained to measure ADAMTS13 activity levels and to detect anti-ADAMTS13 antibodies. Measurement of ADAMTS 13 antigen levels is also useful in congenital TTP cases (1B).

Subgroups of TTP

**Congenital TTP**

Congenital TTP is a rare disorder, with over 100 patients described worldwide, but this is likely to be an underestimate. It has a varied phenotype and can present at any age. As a general rule, those with more severe phenotypes present early:

1. Neonates typically have severe neonatal jaundice. Blood film examination may show schistocytes together with red cell anisocytosis. (Scully et al, 2006a).

2. More frequently, the diagnosis is made later in infancy or childhood (Schiff et al, 2004), typically with thrombocytopenia, MAHA, jaundice and elevated LDH, although some children may only have an isolated thrombocytopenia. Neurological symptoms, such as hemiparesis, hemiplegia or seizures, occur in 35% of cases (Loirat et al, 2006).

3. Patients may present in adulthood. In women, pregnancy is a common precipitant and is associated with a significant neonatal morbidity and mortality (Fujimura et al, 2009). Rarely 'late-onset phenotype' cases may not develop symptoms until their 50s and 60s with isolated cerebral events or renal disease ((Fujimura et al, 2011). Asymptomatic male cases have been reported, usually detected because they have affected siblings.

Patients with congenital TTP have persistently low levels of ADAMTS13, but they can be asymptomatic until a further precipitating event results in a frank TTP episode. Events include febrile episodes, infections, vaccinations, excess alcohol intake and pregnancy (Furlan et al, 1997, 1998b; Schneppenheim et al, 2003).

Congenital TTP has been missed in the past, because the diagnosis has not been considered, or diagnosed as idiopathic thrombocytopenic purpura or 'atypical' HUS (Veyradier et al, 2003), illustrating the importance of consideration of the diagnosis, review of the blood film and measurement of ADAMTS13.

The diagnosis of congenital TTP is dependent on detecting ADAMTS13 activity <5%, in the absence of antibodies to ADAMTS13. In the last few years molecular diagnosis has been used to confirm the diagnosis, and either a homozygous or compound heterozygous defect in ADAMTS13 is found. Testing of siblings and other first-degree relatives at risk should be considered.

**Recommendations**

1. Congenital TTP should be considered in neonates presenting with severe jaundice. Presentation may also occur in childhood or as an adult (1A).

2. The diagnosis of congenital TTP should be considered in children and adults with unexplained thrombocytopenia (1B).

3. The diagnosis of congenital TTP is confirmed by ADAMTS13 activity <5%, absence of antibody and confirmation of homozygous or compound heterozygous defects of the ADAMTS13 gene (1A).

**Acute idiopathic TTP**

Acute idiopathic TTP is the most common form of TTP. It is an autoimmune disease characterized by antibodies, usually IgG, directed against ADAMTS13. The incidence is
four to six cases per million of the population per year in the United States (Miller et al, 2004; Terrell et al, 2005) and six cases per million per year in the UK (Scully et al, 2008).

HIV-associated TTP

Thrombotic thrombocytopenia purpura may be the initial presenting feature of HIV disease or in those with low CD4 counts following non-compliance with antiviral treatment (Ucar et al, 1994; Gervasoni et al, 2002). Remission is dependent upon improving the immune status of the patient, for stopping highly active anti retroviral therapy (HAART) can result in acute TTP relapse (Miller et al, 2005), but continued use of HAART usually prevents further relapses. TTP in HIV-positive individuals may be associated with the presence of severe ADAMTS13 deficiency and anti-ADAMTS13 antibodies. Those with severe ADAMTS13 deficiency (<5%) have fewer acquired immunodeficiency syndrome-related complications and higher CD4+ T cell counts, compared to HIV-TTP with ADAMTS13 levels >5%, who have an increased mortality (Malak et al, 2008).

Pregnancy-associated TTP

Pregnancy can be the initiating event for approximately 5–25% of TTP cases (Ridolfi & Bell, 1981; Vesely et al, 2004; Scully et al, 2008), which are late onset adult congenital TTP or acute idiopathic TTP. Differentiating TTP from the more common pregnancy-related TMAs, such as pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and HUS is difficult, especially if TTP presents post-partum (Table IV). Thrombosis occurs in the placenta in untreated TTP pregnancies and results in fetal growth restriction, intrauterine fetal death and pre eclampsia. There is a continued risk of relapse during subsequent pregnancies. Women with normal levels of ADAMTS13 pre-pregnancy have a lower risk of relapse (Ducloy-Bouthors et al, 2003; Scully et al, 2006b).

Drug-associated TTP

Drugs appear to be responsible for <15% of all TTP cases (Vesely et al, 2003; Scully et al, 2008). Quinine can cause an antibody-mediated idiosyncratic disorder, typically in females. Thienopyridine-associated TTP is well recognized in association with ticlopidine with an incidence of one per 1600–5000 patients treated, but it has rarely been described with clopidogrel and there is uncertainty whether there is a true association (Zakarija et al, 2009). Simvastatin (Koduri, 1998; McCarthy et al, 1998; Vesely et al, 2003; Sundram et al, 2004; Scully et al, 2008), trimethoprim (Martin et al, 2007) and pegylated interferon used to treat hepatitis C (Deutsch et al, 2007; Serrano et al, 2007; Saile et al, 2008) have been anecdotally associated with antibody-positive TTP. There are anecdotal reports of acquired TTP associated with oestrogen-containing hormonal preparations such as the combined oral contraceptive pill (COCP) and hormone replacement therapy (Scully et al, 2008). Some chemotherapy agents, such as gemcitabine, bleomycin and mitomycin–C can cause HUS but not TTP.

Recommendation

1 Medications associated with precipitation of TTP include quinine and oestrogen-containing medications, which should be avoided to prevent relapse in patients with a previous episode of TTP (2C).
2 Women with previous TTP should be offered non-oestrogen containing contraception (1C).

Transplant-associated microangiopathy

Transplant-associated microangiopathy (TAM) is a MAHA and thrombocytopenia that occurs after bone marrow transplantation. It may reflect endothelial toxicity associated with chemotherapy, infections, immunosuppressives, such as ciclosporin A (CSA), and graft-versus-host disease (GVHD). TAM has important differences from de novo TTP, namely, absence of ADAMTS13 deficiency; rare neurological symptoms; a

Table IV. Typical features in pregnancy-associated microangiopathies.

<table>
<thead>
<tr>
<th>MAHA</th>
<th>Thrombocytopenia</th>
<th>Coagulopathy</th>
<th>HBP</th>
<th>Abdominal symptoms</th>
<th>Renal Impairment</th>
<th>Neurological symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>HELLP</td>
<td>+</td>
<td>++</td>
<td>±</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>TTP</td>
<td>++</td>
<td>+++</td>
<td>–</td>
<td>±</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>HUS</td>
<td>+</td>
<td>++</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>AFLP</td>
<td>±</td>
<td>+</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>SLE</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>APLS</td>
<td>+</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

PET, pre-eclampsia; HELLP, haemolysis, elevated liver enzymes and low platelets; TTP, thrombotic thrombocytopenia purpura; HUS, haemolytic-uraemic syndrome; AFLP, acute fatty liver of pregnancy; SLE, systemic lupus erythematosus; APLS, Antiphospholipid syndrome (catastrophic), MAHA, microangiopathic haemolytic anaemia; HBP, hypertension.
poor response to PEX and lack of evidence of systemic microthrombi formation (Ruutu et al, 2007).

**Malignancy-associated thrombotic microangiopathy**

Thrombotic microangiopathy occurs in association with a variety of malignancies, especially adenocarcinomas, (Kwaan & Gordon, 2001). Presentation may be either at an early stage of cancer or associated with disseminated disease. ADAMTS13 activity is not significantly reduced in these patients (Fontana et al, 2001).

**Pancreatitis-associated TTP**

Microangiopathic haemolytic anaemia has recently been reported in association with acute pancreatitis, sometimes a number of days after resolution of pancreatitis. ADAMTS13 activity was only moderately reduced and did not correlate with the severity of TTP or pancreatitis. All patients were successfully treated with PEX and corticosteroids (McDonald et al, 2009).

**Haemolytic uraemic syndrome**

Diarrhoeapositive (D+) HUS, associated typically with vaso-toxin-induced bloody diarrhoea, is treated with supportive care, which in some cases includes renal dialysis. Diarrhoea negative (D–) HUS, not typically associated with bloody diarrhoea, but may sometimes be associated with multisystem symptoms, similar to TTP, should be urgently treated with PEX (Kim et al, 2011). The primary differentiating factor between HUS and TTP is the presence of oliguric/anuric renal impairment/failure in HUS. Increasingly, the role of complement defects in D–, atypical HUS is being defined (Kavanagh & Goodship, 2010) and use of the complement inhibitor, eculizumab, appears successful in these cases (Al-Akash et al, 2011; Riedl et al, 2011), but may also have a role in severe D+HUS (Lapeyraque et al, 2011).

**Treatment of acute TTP**

A summary of the treatment protocol is shown in Fig 1.

**Plasma therapy**

Daily PEX, preferably with spin apheresis, is the mainstay of treatment and has reduced mortality rates, from over 90% to 10–20%. It allows removal of autoantibody, and repletes ADAMTS13. Delay in initiation of PEX leads to preventable early mortality (Pereira et al, 1995). Although PEX remains the treatment of choice, large volume plasma infusions are indicated if there is to be a delay in arranging PEX. PEX has been shown to be superior to plasma infusion at the end of the first treatment cycle and at 6 months (response rates 47% and 78% vs. 25% and 49%) (Rock et al, 1991). The duration of PEX and the number of procedures required to achieve remission is highly variable, but is longer in antibody-mediated TTP (Coppo et al, 2006).

An optimal regimen has not been determined. In the Canadian apheresis trial, 1.5× plasma volume (PV) exchange was performed on the first 3 d followed by 1.0 PV exchange thereafter (Rock et al, 1991). More intensive exchange, such as twice daily PEX, may be required in resistant cases especially if there is new symptomatology, such as neurological or cardiac events. The benefit of an intensified PEX regimen has been difficult to document as other treatments are often initiated or intensified simultaneously (Nguyen et al, 2008).

Daily exchanges should continue for a minimum of 2 d after complete remission, defined as normal platelet count (>150×10^9/l). Tapering (reducing frequency and/or volume of PEX) has not been shown to reduce relapse rates (Bandarenko & Brecher, 1998).

Cryosupernatant is at least as efficacious as standard fresh frozen plasma (FFP) (Rock et al, 1996; Brunskill et al, 2007). The UK Department of Health recommends the use of solvent/detergent-treated (S/D) plasma (O’Shaughnessy, 2006) in TTP patients to reduce the risk of transfusion-transmitted infection and adverse immune responses (Scully et al, 2007b). S/D plasma contains reduced levels of protein S, but an increased thrombotic rate has not been reported in 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 (Scully et al, 2007b).

ADAMTS13 activity is present in normal amounts in FFP, S/D plasma, methylene blue-treated FFP (MB-FFP) and psoralen-treated FFP (Yarranton et al, 2005).

In the UK, single donor MB-FFP is the recommended plasma for use in all indications in those born after 1st January 1996 to minimize the risk of prion transmission (O’Shaughnessy et al, 2004). However MB-FFP has been associated with increased numbers of PEX and longer hospital stay in TTP (de la Rubia et al, 2001; Rio-Garma et al, 2008). A prospective study using psoralen–FFP compared to standard FFP showed equal efficacy and safety (Mintz et al, 2006).

Plasma-related adverse events, such as allergic reactions, anaphylaxis and central venous catheter thrombosis, appeared to be more frequent prior to the use of S/D plasma (Scully et al, 2007b).

**Recommendation**

1 PEX should be started with 1.5 PV exchanges, using S/D plasma in all age groups and reassessed daily (1B).

2 The volume of exchange can be reduced to 1.0 PV when the clinical condition and laboratory test results are stabilizing (2C).

3 Intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases (2B).
**Suspected TTP**
- Suspect TTP if patient has MAHA and thrombocytopenia in absence of other identifiable cause
- Start treatment immediately if TTP is suspected and refer urgently for specialist advice and PEX
- See Tables I, II and IV

**Investigations**
- Take blood before starting PEX: FBC, blood film, reticulocytes, clotting, fibrinogen, U+E, Troponin I/Troponin T, LFTs, Amylase, TFFs, calcium, LDH, pregnancy test. DAT, blood group with antibody screen, ADAMTS13, Hepatitis A/B/C, HIV serology and autoantibody screen
- See Table III

**Further Investigations**
- Other investigations should be performed promptly but can be delayed until after starting PEX: urinalysis, stool culture (if diarrhoea), echocardiogram, CT brain (if neurological signs), and CT chest/abdomen/pelvis to check for underlying malignancy (if indicated)
- See Table III

**Blood Products**
- Request S/D FFP. If any delay in starting PEX then give FFP infusion (watch for fluid overload)
- Use standard FFP if S/D unavailable
- Transfuse packed red cells when necessary to correct anaemia
- Platelet transfusions are contraindicated unless bleeding is life-threatening

**URGENT treatment**
- Start PEX with S/D FFP as soon as possible
- 1–5 plasma volumes × 3, then 1 plasma volume/day with stabilization of condition

**Start immediately after PEX**
- Give steroids; either IV methylprednisolone (1 g/day for 3 days) or oral prednisolone (e.g. 1 mg/kg/day) with an oral proton pump inhibitor
- Give oral folic acid 5 mg OD

**Special cases**
- If HIV-positive, start HAART immediately
- If neurological or cardiac involvement, start rituximab
- See Section 3.7.2

**Prevent thrombosis**
- When platelet count >50 × 10^9/l, start low molecular weight heparin thromboprophylaxis and aspirin 75 mg OD

**Treatment Success?**
- Continue daily PEX for a minimum of 2 d after platelet count has been >150 × 10^9/l, then stop
- If progressive symptoms, refractory disease or early relapse, then refer to Section 4

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**Fig 1.** Summary of treatment protocol for acute TTP. TTP, thrombotic thrombocytopenia purpura; MAHA, microangiopathic haemolytic anaemia; PEX, plasma exchange; FBC, full blood count; U + E, urea and electrolytes test; LFTs, liver function tests; LDH, lactate dehydrogenase; DAT, direct antiglobulin test; HIV, human immunodeficiency virus; CT, computerized tomography; S/D FFP, solvent/detergent-treated fresh frozen plasma; IV, intravenously; OD, once daily; HAART, highly active anti retroviral therapy.

4 Daily PEX should continue for a minimum of 2 d after platelet count has been >150 × 10^9/l and then stopped (2B).  

**Congenital TTP**

Plasma-derived or recombinant concentrates of ADAMTS13 are not yet available. Therefore current treatment consists of plasma infusion/exchange or the use of a virally-inactivated intermediate purity factor VIII concentrate containing ADAMTS13, such as 8Y (BPL; BioProducts Laboratory, Elstree, Herts) (Allford *et al.*, 2000), which has a small infusion volume and can be given in the outpatient or home setting. 15–30 u/kg of 8Y has been used with reported success, although there is no guaranteed constant quantity of ADAMTS13 in such concentrates. Antibodies to ADAMTS 13 have not been detected following the use of 8Y. Despite that ADAMTS13 has a half-life of only 2–3 d (Furlan *et al.*, 1999; Suzuki *et al.*, 2000).
Treatment regimens for congenital TTP should be individualized according to the patient’s phenotype (1A).

Treatment of TTP in pregnancy

Diagnosis of pregnancy-associated TTP is especially difficult if it develops postnatally. In any mother with a TMA, and uncertainty as to the diagnosis (and recognizing that pre-eclampsia and HELLP can present in the postnatal period), PEX should be considered.

If TTP develops in the first trimester, regular PEX may allow continuation of pregnancy with delivery of a live infant (Ambrose et al, 1985; Rozdzinski et al, 1992; Mokrzycki et al, 1995; Scully et al, 2006b). Delivery is the definitive treatment of choice for pregnancy-associated TMA, although delivery does not guarantee remission of TTP.

Pre-treatment ADAMTS13 assays will distinguish congenital and acquired TTP from other pregnancy-associated TMAs. In pre-eclampsia and HELLP syndrome ADAMTS13 activity is reduced (median 31% range 12–43%) but antibodies to ADAMTS13 are not found.

Close liaison with an obstetrician with expertise in thrombosis and fetomaternal medicine is required. Serial fetal monitoring with uterine artery dopplers should be used to assess if there is adequate fetal growth and to assess placental blood flow.

Plasma infusions alone may be sufficient in mothers with congenital TTP. However, at delivery PEX may be required to ensure adequate levels of ADAMTS13. The ideal frequency of plasma replacement during pregnancy is unknown.

In acquired TTP, it is difficult to predict future relapse in pregnancy. A reduction in ADAMTS13 activity (<10%) at the start of pregnancy may require elective therapy to prevent microvascular thrombosis during pregnancy. Rituximab has been used in pregnancy in autoimmune disorders and lymphoma (Chakravarty et al, 2011).

Recommendation

1 If a TMA cannot be fully explained by a non-TTP pregnancy-related TMA, then the diagnosis of TTP must be considered and PEX should be started (2B).

2 Mothers with congenital TTP should attend a specialist centre and receive ADAMTS13 supplementation regularly throughout pregnancy and the post-partum period (1A).

3 Close liaison with an obstetrician with a special interest in feto-maternal medicine is required in mothers with TTP (1A).

4 In mothers with acquired TTP, ADAMTS13 activity should be monitored throughout pregnancy to help predict the need for adjuvant therapy and outcome (1B).

5 Pre-conceptual counselling is advised for subsequent pregnancies and women of child bearing age should be counselled about potential risks of pregnancy and COCP (2B).

HIV–related TTP

In those with severe ADAMTS13 deficiency, there is normalization in ADAMTS13 activity, as the CD4 count recovers and HIV viral load falls, after treatment with HAART and PEX. Occasionally, further therapy is required, for example with rituximab or steroids, which do not cause a significant increase in infectious complications (Hart et al, 2011).

Practically, HAART should be given immediately after PEX to allow for maximal time for absorption.

Recommendation

1 If a patient with TTP is found to have HIV infection then viral load should be measured and an HIV physician should be closely involved in management (1A).

2 TTP should be considered in an HIV-positive individual with a MAHA and thrombocytopenia (1A).

3 PEX in conjunction with HAART (triple or quadruple therapy) should be started as soon as the diagnosis of HIV-associated TTP is made (1B).

4 HAART should be given immediately after PEX therapy to maximize time for absorption (1A).

5 In resistant HIV-related TTP, rituximab could be considered (2B).

Bone marrow transplant–associated microangiopathy

Management is difficult, as stopping CSA or switching to another immunosuppressive, such as tacrolimus, may worsen GVHD. No benefit has been shown with PEX; indeed in a retrospective review it was associated with an increased mortality (George et al, 2004). There is anecdotal experience of successful use of defibrotide (Bayik et al, 1993; Pogliani et al, 2000).

Malignancy–associated thrombotic microangiopathy

Plasma exchange has no benefit (Werner et al, 2007). The treatment of the underlying cancer is the mainstay of therapy.
Recommendation

1 PEX is not indicated in the management of malignancy and bone marrow transplant-associated TMA (1A).
2 In cancer associated TMA, further treatment for the underlying cancer should be considered (1A).

Further treatments in acquired TTP

Corticosteroids. Steroids are widely used in combination with PEX in the initial treatment of acute immune TTP. Higher dose pulsed steroids have shown to be associated with an improved patient outcome and usually have minimal side effects (Balduini et al., 2010). However there is no randomized controlled trial addressing whether a combination of PEX and corticosteroids is superior to PEX alone.

Recommendation

Intravenous daily methylprednisolone (e.g. 1 g/d for three consecutive days – adult dose) or high dose oral prednisolone (e.g. 1 mg/kg/d) should be considered (1B).

Rituximab. Prospective studies have shown that rituximab is effective and safe in immune TTP, when patients failed to respond to daily PEX and methylprednisolone and in relapsed acute idiopathic TTP (Fakhouri et al., 2005; Scully et al., 2007a). Typically, 375 mg/m\(^2\) has been used weekly for 4 weeks. Patients receiving rituximab showed reductions in anti-ADAMTS13 IgG antibody levels and increased ADAMTS13 activity (Scully et al., 2007a). The risk of relapse appears to be reduced with rituximab use (Heidel et al., 2007; Scully et al., 2011).

Ideally PEX should be withheld for at least 4 h after completing a rituximab infusion (Hull & Eichbaum, 2006; Scully et al., 2007a). Giving rituximab more frequently than weekly e.g. every 3–4 d, may overcome removal during PEX (McDonald et al., 2010). There is no evidence of increased infection risk with rituximab in TTP patients. A recent Phase II UK study has shown benefit in using rituximab as a first line therapy at presentation of TTP (Scully et al., 2011).

Recommendation

1 In acute idiopathic TTP with neurological/cardiac pathology, which are associated with a high mortality, rituximab should be considered on admission, in conjunction with PEX and steroids (1B).
2 Patients with refractory or relapsing immune-mediated TTP should be offered rituximab (1B).

Ciclosporin A and tacrolimus. Ciclosporin A was used successfully in one patient with relapsing TTP (Pasquale et al., 1998), but further relapses occurred after cessation of therapy. In a clinical trial of PEX with either steroids or CSA (2–3 mg/kg twice daily), initial remission occurred in 89%, 14% subsequently relapsed while on CSA and there was a 33% relapse after stopping 6 months of CSA treatment.

None of the eight CSA-treated patients suffered a relapse in the first 30 d compared with 6/10 of the steroid-treated patients. Overall 16/18 patients achieved a remission with an increase in ADAMTS13 activity and decrease in antibodies to ADAMTS13 (Cataland et al., 2007a,b).

In patients with renal impairment, tacrolimus is an alternative therapy, but side effects may preclude medium and long-term use.

Recommendation

CSA may be considered as second line therapy in patients with acute or chronic relapsing acquired TTP (1C).

Other therapies. With the demonstrated utility and relative safety of rituximab, other drugs previously used for refractory and remitting cases, such as vincristine and cyclophosphamide, whose use is associated with severe side effects, and whose efficacy has been documented in small numbers of patients (Mazzei et al., 1998; Bohm et al., 2005), are not recommended except as part of a clinical trial.

Splenectomy. The mortality of open splenectomy in acute TTP was reported to be approximately 40% (Rutkow, 1978). In a retrospective case series of 33 patients splenectomized for acute refractory and relapsed disease, the 10-year relapse-free survival was 70% (Bohm et al., 2005; Kappers-Klunne et al., 2005).

Recommendation

Splenectomy may rarely be considered in the non-acute period of immune-mediated TTP but has limited proven benefit (2C).

Antiplatelet agents

The Italian Co-operative Group randomized 72 TTP patients to PEX and steroids with and without aspirin and dipyramidole (Bobbio-Pallavicini et al., 1997). There was no difference in response rate or excessive haemorrhage and a non-significant decreased rate of early death in the first 15 d in the antiplatelet-treated group (13.5% vs. 2.8%) (Bobbio-Pallavicini et al., 1997).

Recommendation

1 The clinical efficacy of antiplatelet agents in TTP is unproven but they are relatively safe (1B).
2 Low dose aspirin (75 mg OD) may be given during platelet recovery (platelet count >50 x 10^9/l) (2B).
**Supportive therapy**

Red cell transfusion and folic acid supplementation are required during active haemolysis. It has been shown that transfusion in the critically ill is safe using a transfusion trigger of 70 g/l. However this trigger was not applicable to those with cardiac disease (Hebert et al., 1999) and, as cardiac microvascular thrombosis is a feature of TTP, a higher haemoglobin level may be required in those with evidence of cardiac involvement and acute haemolysis.

Due to the risk of precipitating further thrombotic events, platelet transfusions are contra-indicated unless there is life-threatening haemorrhage.

The risk of venous thromboembolism has never been formally quantified in acute TTP but is likely to be increased due to immobility and acute illness. Therefore routine LMWH thromboprophylaxis should be given once the platelet count has recovered to >50 x 10^9/l (Yarranton et al., 2003). Hepatitis B vaccination should be considered in TTP, once a platelet threshold of 50 x 10^9/l has been achieved, but studies of efficacy are required in the face of continued PEX and/or immunosuppression with rituximab.

**Recommendation**

1 Red cell transfusion should be administered according to clinical need especially if there is cardiac involvement (1A).
2 Folate supplementation is required during active haemolysis (1A).
3 Platelet transfusions are contra-indicated in TTP unless there is life-threatening haemorrhage (1A).
4 Thromboprophylaxis with LMWH is recommended once platelet count has reached >50 x 10^9/l (1B).

**Refractory TTP**

There is a subgroup of patients who present with TTP who subsequently show a slow or incomplete response to PEX ± corticosteroids. Refractory disease was previously arbitrarily defined as persistent thrombocytopenia or LDH elevation after a total of seven daily PEX procedures. LDH is not however, a reliable marker of disease activity. We have therefore redefined refractory disease as progression of clinical symptoms or persistent thrombocytopenia despite PEX.

Intensification of PEX with the introduction of 12-hourly or double PV exchanges and the addition of further steroids have provided some benefit (Shumak et al., 1995; Bobbio-Palavicini et al., 1997; Bandarenko & Brecher, 1998; Kahwash & Lockwood, 2004; Nguyen et al., 2008). Rituximab is the current agent of choice in refractory disease (Scully et al., 2007a).

**Recommendation**

Increased frequency of PEX and addition of rituximab can be considered in refractory TTP (1B).

**Relapse**

Relapse is defined as an episode of acute TTP more than 30 d after remission, and occurs in 20–50% of cases (Shumak et al., 1995; Bandarenko & Brecher, 1998; Willis & Bandarenko, 2005). The Canadian Apheresis Group estimated that over a 10-year follow up, 36% of patients would relapse (Shumak et al., 1995).

Patients with ADAMTS13 activity <10% or an anti-ADAMTS13 antibody in remission had a 3-fold increase in relapse over 1 year (Peyvandi et al., 2008). In a further study, if ADAMTS13 was <5% in remission, relapse occurred in 38–5%, but if ADAMTS13 activity was >15%, only 5% relapsed (Ferrari et al., 2007).

The use of rituximab in an acute episode reduces and delays the incidence of relapse (Scully et al., 2011). Prior to discharge all patients should be counselled regarding the risk and the symptoms and signs of relapse. In patients who have had previous TTP episodes and where a reduction of ADAMTS 13 activity from detectable levels to <5% is demonstrated, elective rituximab therapy has been successfully used, with normalization of ADAMTS 13 activity (Scully et al., 2007a; Bresin et al., 2009). Patients require long-term follow up with ADAMTS 13 assay monitoring.

**Recommendation**

1 Increased PEX and/or rituximab therapy are the agents of choice in relapsing disease (1B).
2 Patients should be counselled about symptoms, signs and risk of relapse before discharge with verbal and written information (1A).

**Table V. Differential Diagnosis of haemolytic uraemic syndrome.**

<table>
<thead>
<tr>
<th>Infection (diarrhoea-positive)</th>
<th>Shiga &amp; verocytotoxin (Shiga-like toxin)-producing bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders of complement regulation (diarrhoea-negative)</td>
<td>Genetic disorders of complement regulation e.g. Factor H, I, MCP (CD46), factor B (CFB), C3 (C3), thrombomodulin</td>
</tr>
<tr>
<td>Acquired disorders of complement regulation e.g. anti-FH antibody</td>
<td><em>Steptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Other causes of secondary HUS</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
</tr>
<tr>
<td></td>
<td>Defective cobalamin metabolism</td>
</tr>
<tr>
<td></td>
<td>Drugs e.g. quinine, some chemotherapy e.g. gemcitabine, bleomycin)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Other autoimmune diseases e.g. SLE, APLS</td>
</tr>
</tbody>
</table>

HUS, haemolytic uraemic syndrome; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus; APLS, antiphospholipid syndrome.
In patients with a documented reduction of ADAMTS 13 activity to <5%, elective therapy with rituximab can be considered (1B).

Haemolytic uraemic syndrome

Haemolytic uraemic syndrome is characterized by MAHA, thrombocytopenia and acute renal failure. It maybe associated with extensive multi-organ involvement, e.g. neurological, hepatic complications, and cardiac problems and therefore diagnostic overlap with TTP can occur. It is important to differentiate between D + HUS, atypical HUS and TTP because the prognosis and management are different (Table V). The reader is referred to (Ariceta et al., 2009) and (Taylor et al., 2010) for further guidance in children and adults, respectively.

Conclusion

TTP and other TMAs remain diagnostically difficult. The current challenge is to ensure that haematologists, physicians, obstetricians and paediatricians are aware of the need to treat acute TTP as a medical emergency to prevent unnecessary early mortality. The development of new drugs and recombinant proteins, trialled in the developing networks should lead to better treatments in the future.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Guideline update

In 2003, the British Society for Haematology (BCSH) published the first evidence-based guidelines for the diagnosis and management of thrombotic microangiopathies (Allford et al., 2003). We have revised these based on new evidence available between 2003 and 2011.

Separate guidelines for atypical haemolytic-uraemic syndrome (HUS) (Taylor et al., 2010) and diarrhoea-positive HUS (Ariceta et al., 2009) are now available, so these sections have been reduced.

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Conflicts of interest

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urameic syndrome associated with heterogeneous factor H mutations. *Pediatric Nephrology* (Berlin, Germany), 26, 2073–2076.


