Guideline

GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF THE THROMBOTIC MICROANGIOPATHIC HAEMOLYTIC ANAEMIAS

Thrombotic thrombocytopenic purpura (TTP) was first described by Moschowitz (1924). The classic pentad of diagnostic features has been recognized for many years. However, several other syndromes are also characterized by similar features. These include haemolytic uraemic syndrome (HUS), eclampsia and the HELLP syndrome (haemolysis, elevated liver enzymes, low platelets). The concept has arisen that they might represent an overlapping spectrum of disease, although with varying pathophysiological features (see Table I). The recent characterization of a novel von Willebrand factor (VWF)-cleaving metalloprotease activity (Furlan et al, 1996; Tsai, 1996) and its deficiency or inhibition in some forms of microangiopathic haemolysis (Furlan et al, 1997, 1998; Tsai & Lian, 1998) has led to speculation that a pathogenic mechanism for individual patients can be defined more readily and appropriate treatment introduced more rapidly. However, there is still considerable confusion, a lack of properly conducted randomized clinical trials and poor co-ordination of clinical data. This is, in part, because these patients present to a range of specialists including haematologists, obstetricians, nephrologists and infectious disease physicians. These guidelines attempt to define the various clinical subtypes, specify the recognized diagnostic features and look critically at management options. It is acknowledged that there is a lack of evidence from well-conducted studies on which to support some of the recommendations made.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura (TTP) is rare. The reported incidence is 3.7 per million (Torok et al, 1995). However, its prompt recognition and treatment is vital, as delays in initiating treatment have been shown to adversely affect outcome (Pereira et al, 1995).

Diagnosis and clinical features

TTP is a clinical diagnosis. It is characterized by the classic pentad of thrombocytopenia, microangiopathic haemolytic anaemia, fluctuating neurological signs, renal impairment and fever, often with insidious onset. Neurological impairment has multiple manifestations including headache, bizarre behaviour, transient sensorimotor deficits (TIAs), seizure and coma. Presence of coma at presentation is a poor prognostic indicator (Pereira et al, 1995; Sarode et al, 1997). Additional complications may be seen: gastrointestinal ischaemia (manifest as abdominal pain) and serous retinal detachment are recognized associations. However, up to 35% of TTP patients do not have neurological symptoms or signs at presentation (Rock et al, 1991). As the triad of acute renal insufficiency, MAHA and thrombocytopenia defines HUS, diagnostic uncertainty may arise. Moreover, fever and renal impairment are present in only a minority of patients (Rock et al, 1991, 1998). In practice, therefore, a diagnosis of TTP may be made in the presence of a microangiopathic haemolytic anaemia and thrombocytopenia in the absence of any other identifiable cause.

Clinical subtypes

A number of different clinical variants of TTP have been documented. Clinical subtype may influence management and those recognized are listed in Table II.

Pathogenesis

The predominant histological abnormality found in TTP is the formation of platelet microvascular thrombi. The renal and cerebral circulations are primarily affected, thus accounting for the clinical features of the disease. Excessive platelet aggregation occurs when platelet-rich plasma (PRP) from patients with congenital TTP is exposed to shear stress (Moake et al, 1994). This is mediated by ultra-large VWF multimers (ULVWF) (Moake et al, 1994; Karpman et al, 1997). ULVWF are not a normal constituent of circulating plasma. Instead, VWF circulates as smaller multimeric forms resulting from proteolytic degradation of ULVWF. VWF fragments with mobility corresponding to 189, 176 and 140 kDa are consistently detected in normal plasma in addition to the predominant 225 kDa subunit (Zimmerman et al, 1986; Tsai et al, 1991). These originate as a consequence of cleavage of a single peptide bond between residues Tyr-842 and Met-843 of the mature subunit (Dent et al, 1991). Identical fragments may be generated in vivo by a novel metalloproteinase activity (Furlan et al, 1996; Tsai, 1996). The protease has recently been characterized as a new member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin type-I motif) family, ADAMTS13 (Fujikawa et al, 2001; Gerritsen et al, 2001; Levy et al, 2001). Deficiency of this VWF-cleaving protease (VWF-CP) activity has been associated with acquired and congenital TTP. While all cases of idiopathic TTP have, to date, been associated with severe protease deficiency, secondary TTP may occur in the context of normal protease...
activity (Veyradier et al. 2001). In a series of 111 patients with thrombotic microangiopathies of whom 66 manifested with TTP (25 idiopathic and 41 secondary) and 45 with HUS, protease deficiency had a sensitivity of 89% and specificity of 91% for TTP. Initial reports suggested that idiopathic TTP is secondary to an inhibitory auto-antibody of IgG subtype (Furlan et al. 1998; Tsai & Lian, 1998), but in the above series, a protease inhibitor was identified in only 14 patients (56%). While congenital TTP appears secondary to a constitutional deficiency (Furlan et al. 1997, 1998), presentation may be delayed until adulthood (Lamment et al. 2001). Cirrhosis (Mannucci et al. 2001), uraemia (Mannucci et al. 2001), acute inflammation (Mannucci et al. 2001), disseminated intravascular coagulation (DIC) (Loof et al. 2001) and malignancy (Oleksowicz et al. 1999) have now also been associated with reduced VWF-CP activity. Thus, although sensitive, reduced VWF-CP activity is not specific for TTP. Moreover, this model fails to explain the anatomical distribution of thrombi. The endothelium is a heterogeneous organ and is subject to regulation by multiple factors, including cytokines (Drake et al. 1993), microenvironment (Aird al. 1997) and shear stress (White & Fujikawa, 1986). Alterations in any one of these parameters could influence either VWF-CP activity per se or the susceptibility of VWF to proteolysis.

**Laboratory features and investigation**

TTP is often characterized by severe thrombocytopenia, which may be useful in its differentiation from HUS. However, in one series, although the mean platelet count was lower in TTP than HUS (18 × 10^9/l vs 36 × 10^9/l), there was a wide range and considerable overlap (Vesely et al. 2000). Severe thrombocytopenia at diagnosis (platelet count < 20 × 10^9/l) has been suggested to be a poor prognostic indicator, conferring increased mortality (Rock et al. 1998), although this is not a uniform observation (Sarode et al. 1997). Thrombocytopenia is typically accompanied by overt microangiopathic haemolysis. Thus, examination of the blood film usually shows striking red cell fragmentation and polychromasia. However, schistocytes may be absent from the peripheral blood film in the first 24–48 h following clinical presentation. Routine coagulation profiles are usually normal (Monteagudo et al. 1991; Sagripanti et al. 1996; Rock et al. 1998), although slight increases in D-dimer, fibrin degradation products and thrombin–anti-thrombin complex (TAT) may be seen (Monteagudo et al. 1991; Sagripanti et al. 1996; Wada et al. 1998). Secondary DIC may, however, arise from prolonged tissue ischaemia and is an ominous prognostic indicator. Evidence of endothelial perturbation is demonstrated by increased plasma levels of plasminogen activator inhibitor (PAI-1) (Anthony et al. 1998) and thrombomodulin. The latter has also been identified as a poor prognostic factor (Wada et al. 1998). Plasma VWF levels are often elevated acutely (Rock et al. 1998). Abnormalities of VWF multimers are also common and were identified in 86% of patients either at the onset of or during an acute episode of TTP (Moake & McPherson, 1989). These ranged from the presence of ULVWF multimers in 31% to a relative decrease in the largest plasma VWF forms in 36%. Acute changes in VWF multimeric distribution do not appear to correlate with clinical outcome. However, the finding of ULVWF multimers

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**Table I.** Characteristic spectrum of pathophysiological features seen in microangiopathic haemolytic anaemia.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>TTP</th>
<th>HUS</th>
<th>Pre-eclampsia/ eclampsia</th>
<th>HELLP</th>
<th>DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS symptoms/signs</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>+/-</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Fever</td>
<td>+/-</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Liver impairment</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-/+</td>
<td>+/-</td>
<td>+++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Haemolysis</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>–</td>
<td>–</td>
<td>+/–</td>
<td>+/-</td>
<td>+++</td>
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</tbody>
</table>

**Table II.** Clinical subtypes of TTP.

<table>
<thead>
<tr>
<th>Congenital TTP</th>
<th>Acquired TTP</th>
<th>Secondary TTP</th>
<th>Intermittent TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS symptoms/signs</td>
<td>No identifiable precipitant</td>
<td>Drugs</td>
<td>Recurrent episodes at unpredictable intervals</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>No subsequent relapse</td>
<td>oral contraceptive pill</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>ticlopidine</td>
<td></td>
</tr>
<tr>
<td>Liver impairment</td>
<td></td>
<td>cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>mitomycin C</td>
<td></td>
</tr>
<tr>
<td>Haemolysis</td>
<td></td>
<td>Post bone marrow transplantation</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+/+</td>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>–</td>
<td>Malignancy</td>
<td></td>
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<td></td>
<td></td>
<td>Pregnancy</td>
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<td></td>
<td></td>
<td>Infection</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>HIV</td>
<td>E. coli 0157:H7</td>
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</table>
during periods of remission has been associated with intermittent TTP (Moake & McPherson, 1989). Renal function is normal in the majority of patients: only 18% of patients presenting to the Canadian Apheresis Group had evidence of renal impairment (Shumak et al, 1995). Liver function tests often show not only hyperbilirubinemia but also a raised transaminase level. This is thought to represent hepatic ischaemia. Evans’ syndrome may be excluded by a negative direct anti-globulin test. Recommended diagnostic laboratory investigations to be performed at presentation are given in Table III.

In those TTP patients in whom significant renal impairment is a feature, it may be impossible to confidently exclude HUS. Where there is doubt, a presumptive diagnosis of TTP should be made and plasmapheresis initiated. Occasionally renal biopsy performed after recovery of the platelet count may allow accurate retrospective diagnosis. In TTP, arteriolar and capillary thrombosis is prominent. Thrombi are largely composed of platelets and stain strongly for VWF. Only weak staining for fibrin and fibrinogen is seen in contrast to those thrombi formed in DIC (Asada et al, 1985). Aneurysmal dilatation of arterioles may lead to the formation of glomeruloid structures with relative sparing of the glomeruli (Katoh & Shigematsu, 1999). These features should be contrasted with those seen in HUS when the primary histological changes are glomerular and arteriolar fibrin thrombi and subendothelial widening of the glomerular capillary wall on electron microscopy (Remuzzi & Ruggenenti, 1995).

If a diagnosis of TTP is made, consideration must be given to the presence of precipitants. These are drugs, autoimmune disease, malignancy and infection, particularly *Escherichia coli* 0157:H7 and human immunodeficiency virus (HIV). Although *E. coli* 0157:H7 is more closely linked with HUS, there have been cases with typical TTP features (Morrison et al, 1986; Kovacs et al, 1990). Of note VWF-CP deficiency was detected in one of 29 children with epidemic HUS, 25 of whom were positive for verotoxin (Hunt et al, 2001). In some series, up to 14% of TTP episodes have been associated with HIV infection (Ucar et al, 1994), although mortality data from the United States for 1988–1991 gives a figure of only 4·4% (Torok et al, 1995). Risk appears greatest at CD4 counts of less than 250 × 10⁹/l (de Man et al, 1997). Serological testing for HIV should, therefore, be performed at diagnosis in all patients. As treatment (see below) results in multiple donor exposure, hepatitis B and C serology is also recommended in all patients at presentation.

**Recommendation.** While there is no available diagnostic test for TTP, TTP may be diagnosed and treatment initiated if a patient presents with a microangiopathic haemolytic anaemia and thrombocytopenia in the absence of any other identifiable clinical cause. Routine investigations at presentation should include the following: full blood count, film, clotting screen, lactate dehydrogenase (LDH), direct anti-globulin test, urea and electrolytes, liver function tests, and urine dipstick for protein. An underlying precipitant should be considered. It is recommended that HIV and hepatitis serology tests are performed at diagnosis (Grade C, level IV).

**Management of acute idiopathic TTP**

**Plasma exchange**

The mainstay of treatment of acute TTP is daily plasma exchange. Prior to its institution, mortality rates were in excess of 90% and have now fallen to 10–30%. Plasma exchange is superior to plasma infusion. A prospective randomized study performed by the Canadian Apheresis Group assigned a total of 102 patients to receive either plasma exchange or infusion with fresh-frozen plasma (FFP) on 7 of the first 9 d after entry to the trial. Plasma exchange resulted in significantly superior response rates at both the end of the first treatment cycle and at 6 months (response rates 47% and 78% vs 25% and 49% respectively). Mortality was also reduced at 22% vs 37% (Rock et al, 1991). Plasma exchange should be instituted within 24 h of presentation as delay in treatment initiation may increase treatment failure (Pereira et al, 1995). Moreover, it would seem appropriate to commence plasma exchange as soon as practicable if renal impairment, cardiac failure or coma is present. Reduced level of consciousness has been identified as a poor prognostic factor with an overall survival of 54% (Sarode et al, 1997). The duration of plasma exchange therapy required to achieve remission is highly variable. The average number of procedures required for remission in the above study was 15·8 (range 3–36). As the premature omission of a single plasma exchange may be associated with exacerbation, patients should be treated in centres able to provide a daily plasmapheresis service.

Although undoubtedly efficacious, the optimal plasma exchange regimen has not been determined. In the Canadian apheresis trial, 1·5 × plasma volume exchange was performed on the first 3 d followed by 1·0 plasma volume exchange thereafter. Whether this intensity is superior to single plasma volume replacement from presentation is unclear. Currently, many centres initiate single-volume plasma exchange at presentation, reserving more intensive exchange for resistant cases. Similarly, the optimal duration of plasma exchange is unknown. It is empirically recommended that daily exchanges should continue for a minimum of 2 d after complete remission is obtained, defined as normal neurological status, platelet count and LDH with a rising haemoglobin. This is in agreement with the American Association of Blood Banks (AABB), which recommends daily plasma exchange until the platelet count is above

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**Table III.** Recommended diagnostic laboratory investigations at presentation of TTP.

<table>
<thead>
<tr>
<th>Investigation</th>
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<tbody>
<tr>
<td>Full blood count and blood film</td>
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<tr>
<td>Reticulocyte count</td>
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<tr>
<td>Clotting screen including fibrinogen and D-dimers</td>
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<tr>
<td>Urea and electrolytes</td>
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<tr>
<td>Liver function tests</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>Urinalysis</td>
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<tr>
<td>Direct antiglobulin test</td>
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150 × 10^9/l for 2 to 3 d (AABB Extracorporeal Therapy Committee, 1992). Although it is accepted practice to taper the frequency of exchange procedures rather than stopping abruptly in an effort to minimize the risk of early relapse: this is not based on randomized clinical trials.

The optimal replacement fluid administered also remains contentious. Possibly of note, cryosupernatant lacks the largest VWF multimers that are present in FFP and cryoprecipitate. Cryosupernatant is at least as efficacious as FFP. When used in previously untreated patients, the response rate was 75% after seven exchanges. Survival was 95% at 1 month, which compared favourably with historical control subjects treated with FFP (Rock et al, 1996). In contrast, a prospective randomized trial performed by the North American TTP Group failed to identify a significant difference in outcome between plasmapheresis with FFP or cryosupernatant from diagnosis. It should be noted, however, that only 27 patients were included in this trial (Zeigler et al, 2001). Larger trials are required to address this issue and a randomized controlled trial comparing plasma exchange with FFP versus cryosupernatant is currently being performed in Canada.

Side-effects secondary to plasmapheresis are common. In one study, 9.7% of procedures were complicated by adverse reactions with anaphylactoid reactions occurring in 0.25% (Mokrzycki & Kaplan, 1994). Solvent/detergent-treated (S/D) plasma not only reduces viral risk but may be beneficial in reducing allergic reactions. This is because the process of plasma pooling results in extreme dilution of those antibodies responsible for immune-mediated reactions. S/D plasma has a similar favourable multimer profile to cryosupernatant and has been used as replacement fluid from presentation (Evans et al, 1999). However, numbers treated are small and there is no published comparative data with FFP or cryosupernatant. Further clinical experience is required to ascertain the role of S/D plasma in the primary treatment of TTP.

Although plasma exchange remains the treatment of choice, plasma infusion (30 ml/kg/d) may still be indicated if there is to be an unavoidable delay in plasma exchange. It must be undertaken with care, however, as cardiac function may be compromised and cardiac failure can be precipitated.

Recommendation. Single-volume daily plasma exchange should be commenced at presentation (Grade A, level Ib) and ideally within 24 h of presentation (Grade C, level IV). Plasma exchange using cryosupernatant may be more efficacious than that using FFP (Grade B, level III). Daily plasma exchange should continue for a minimum of 2 d after complete remission is obtained (Grade C, level IV).

Adjunctive treatment

Corticosteroids. Steroids have been widely used in the treatment of TTP although there is scanty evidence documenting their efficacy. However, patients with TTP lacking central nervous system abnormalities other than headache have been shown to respond to steroid treatment alone, although of 54 such patients 44% required plasma exchange because of deterioration or failure to improve (Bell et al, 1991). Steroids have also been combined with plasma exchange in initial treatment of TTP. The addition of intravenous methylprednisolone 2 mg/kg/d to daily plasma exchange resulted in a complete remission rate of 76% (Perotti et al, 1996). As yet, no trial has addressed whether such a combination approach is superior to plasma exchange alone. Not surprisingly, there is no consensus regarding dose or mode of administration. Despite the lack of evidence, the addition of steroids to plasma exchange as standard therapy is attractive. Recent findings suggest that a functional deficiency of a novel VWF-CP activity secondary to a circulating inhibitory antibody of IgG subtype is of prime importance in the pathogenesis of TTP (Furlan et al, 1998; Tsai & Lian, 1998). It would, therefore, appear reasonable to institute steroids in all patients.

Recommendation. All patients should receive adjunct corticosteroid therapy (Grade B, level III). To achieve potent immunosuppression while minimizing long-term steroid side-effects, pulse methylprednisolone 1 g i.v. for 3 d is recommended (Grade C, level IV).

Anti-platelet agents. The use of anti-platelet agents in TTP remains controversial. Ticlopidine and its analogue clopidogrel inhibit ADP–platelet interactions and interfere with shear-induced aggregation and might, therefore, be predicted to be of use in TTP. Certainly ticlopidine appeared to reduce the risk of subsequent relapse from 21.4% to 6.25% when used as maintenance therapy for 12 months after remission of TTP was achieved (Bobbio-Pallavicini et al, 1997). However, at publication, follow-up in this trial was incomplete. Subsequently ticlopidine (Bennet et al, 1998) and clopidogrel (Bennet et al, 2000) have been associated with TTP. The estimated incidence of ticlopidine-associated TTP is 1 per 1600–5000 patients treated while that following clopidogrel is 1.5–5.8 per million treated. As the latter is similar to the reported incidence of idiopathic TTP an association remains controversial. Nevertheless in both cases, antibody inhibitors to VWF-CP have been identified (Bennet et al, 2000; Tsai et al, 2000). In keeping with this, plasmapheresis is effective treatment with reported survival rates of 76–91% and is superior to plasma infusion (Bennet et al, 1998, 2000). For these reasons, ticlopidine and clopidogrel should be avoided in patients with a previous history of TTP.

Aspirin and dipyridamole have both been used in the initial treatment of TTP. A 78% response rate at 6 months was achieved when aspirin and dipyridamole were administered in conjunction with plasma exchange (Rock et al, 1991). In a prospective randomized trial designed to address the effect of the addition of aspirin and dipyridamole to standard treatment (plasma exchange and steroids), a similar overall response was obtained in both groups. There was, however, a trend to reduced mortality at 15 d in those treated with anti-platelet agents. No excess haemorrhage was seen in the treatment group (Bobbio-Pallavicini et al, 1997), in contrast to the findings of a small retrospective study in which serious bleeding complications occurred in five of 14 patients receiving anti-platelet medication (Rosove et al, 1982). It should be noted, however, that large doses were administered in these last patients.
for FFP. Like cryosupernatant, S\textsuperscript{2} (Molinari et al., 1993) has been used. Unfortunately randomized clinical trials have not been performed because of the rarity and heterogeneity of this condition.

**Recommendation.** Low-dose aspirin (75 mg o.d.) should be commenced on platelet recovery (platelet count > 50 x 10\textsuperscript{9}/l) (Grade C, level IV).

**Supportive therapy.** Red cell transfusion is an essential component of treatment. However, there is no single reliable parameter to guide the need for red cell transfusion. Identical survival rates resulted when a transfusion was given based on a haemoglobin threshold of 7 g/dl rather than 10 g/dl in euvaenoa (Harrison et al., 1993) or S\textsuperscript{2}, 1993) and S/D plasma (Harrison et al., 1996) for FFP. Like cryosupernatant, S/D plasma lacks the largest plasma VWF multimers and this may be of importance. If, therefore, there is a suboptimal response to plasma exchange after 7 d or rapid clinical deterioration despite daily plasma exchange, an alternative replacement fluid should be substituted. While methylene blue (MB)-treated fresh-frozen plasma has been used in the management of TTP (Martinez et al., 2000), clinical experience is extremely limited at present and, unlike S/D plasma, VWF multimeric structure is not modified. Whether MB cryosupernatant has a role in the management of TTP will require further clinical experience.

Intensification of plasma exchange has also been used in cases of refractory TTP with the introduction of either 12 h or double-volume plasma volume exchanges. At present, this approach is empirical.

**Recommendation.** In the presence of refractory disease an alternative plasma product lacking high-molecular-weight VWF multimeric forms, cryosupernatant or S/D plasma should be used for plasma exchange (Grade C, level IV). Intensification of plasma exchange procedures should also be considered in life-threatening cases (Grade C, level IV).

**Vincristine.** Although vincristine is often used in the treatment of refractory TTP, published literature supporting its efficacy comprises only case reports or small retrospective studies. Nevertheless, these suggest that the administration of vincristine in refractory TTP may be temporally associated with platelet recovery (Welborn et al., 1990; O'Conner et al., 1992; Bobbio-Pallavicini et al., 1994). A role for the early administration of vincristine (within 3 d of presentation) has also been advocated following a small retrospective study (Mazzz et al., 1998). However, such practice would carry a risk of inducing neuropathy without proof of clinical benefit. Until this finding can be corroborated by larger controlled trials, vincristine should be reserved for refractory cases. A number of dosage regimens have been employed with no clear advantage for any single one. A schedule of 1 mg repeated every 3 to 4 d for a total of four doses is popular as it may limit toxicity while retaining efficacy. Higher dose regimens have, however, been used apparently successfully. The mechanism of action of vincristine remains unclear.

**Recommendation.** Vincristine 1 mg repeated every 3 to 4 d for a total of four doses is recommended in refractory TTP (Grade C, level IV).

**Cyclophosphamide.** Cyclophosphamide has also been advocated for the treatment of TTP, particularly those in patients who experience recurrent relapses (severe intermittent TTP) (Bird et al., 1990; Udvardy & Rak, 1990; Strutz et al., 1998). Both daily dosing and pulsed therapy have been used successfully, although reported numbers are extremely low. Cyclophosphamide is known to be a potent immunosuppressant and this is thought to underlie its efficacy.

**Cyclosporine.** Although cyclosporine is associated with an increased risk of post-bone marrow transplant microangiopathy, there are reports of its successful application to the treatment of refractory (Hand et al., 1998), severe intermittent (Pasquale et al., 1998) and post-autologous bone marrow transplantation (BMT) TTP (Van Ojik et al., 1996).
This is consistent with the current autoimmune model of TTP and cyclosporine’s immunosuppressive action. While spontaneous resolution cannot be excluded in these patients, clinical and haematological response uniformly occurred 7 to 14 days after initiating treatment. Cyclosporine may, therefore, prove to be a useful therapeutic modality in these difficult patients. However, much remains unanswered. The optimal duration of treatment is unknown, with relapses documented after cessation of therapy (Hand et al. 1998; Pasquale et al. 1998). The optimal target therapeutic range is also unknown: trough serum levels of 200–300 μg/l have been used. The potential toxicity of this drug must also be considered.

Recommendation. Intensive immunosuppression using either cyclophosphamide or cyclosporine is indicated in severe refractory or recurrent TTP (Grade C, level IV).

Treatment of malignancy-associated and post-bone marrow transplant-associated TTP

The advent of VWF-CP assays is now beginning to confirm the clinical suspicion that TTP currently represents a heterogeneous group of conditions. It has long been recognized that plasma exchange is rarely effective in the treatment of BMT-associated TTP, suggesting that an alternative pathological process might be involved. This theory is supported by the recent finding that VWF-CP activity was normal in seven and only moderately reduced in one of eight patients with BMT-associated TTP (van der Plas et al. 1999). Effective treatment for this group of patients is, however, lacking. Resolution of autologous BMT-associated TTP has been reported following initiation of cyclosporine (Van Oijk et al. 1997), although paradoxically cyclosporine therapy is a recognized risk factor, along with total body irradiation, for allogeneic BMT-associated TTP. In the latter setting, cyclosporine should be stopped. Whether protein-A column immunoadsorption might be useful in such patients is unclear. Certainly this technique has been successfully employed in the treatment of malignancy-associated TTP in which plasma exchange is often found to be ineffective. In one small retrospective series, it was found to be of benefit in seven of 10 patients who had been unresponsive to plasma exchange (Gaddis et al. 1997).

Recommendation. Malignancy and BMT-associated TTP are often refractory to plasma exchange. Protein-A column immunoadsorption may be considered (Grade C, level IV).

Management of relapse

Although remission is now attained in over 80% patients, subsequent relapse remains problematic. Data from the Canadian Apheresis Group estimate that over a 10-year follow-up period up to 36% of TTP patients relapse. Relapse has occurred up to 8 years after the index event (Shumak et al. 1995). All patients should be aware of the possibility of relapse and advised to report early if symptoms suggestive of relapse develop. At present, it is impossible to identify those patients at greatest risk, although the presence of ULVWF during periods of remission is associated with intermittent disease (Moake & McPherson, 1989). There is no consensus whether there is any effective intervention that might reduce this risk. Splenectomy has been advocated as a means of reducing the relapse rate. One small retrospective study including six patients showed encouraging results with relapse rates falling from 2.3 ± 2.0 to 0.1 ± 0.1 events per year when the operation was performed during haematological remission (Crowther et al. 1996). However, acute exacerbations of TTP have occurred post-operatively and this approach should not be undertaken lightly. Anti-platelet medication has also been proposed as a possible alternative. There was a trend to reduced relapse rate in those patients receiving ticlopidine for 12 months after attaining remission (Bobbio-Pallavicini et al. 1997). As ticlopidine has itself now been associated with TTP (Bennet et al. 1998), this is no longer advocated, although some centres empirically commence patients on aspirin 75 mg/d. There are no published data supporting such an approach.

Recommendation. Relapse is common. Urgent self-referral is advised if a patient develops symptoms suggestive of relapse. Splenectomy may reduce the risk of relapse (Grade B, level III).

Congenital TTP

Clinical presentation

Congenital TTP is extremely rare with fewer than 50 patients reported in the literature. It classically presents during infancy or early childhood with recurrent episodes of haemolysis and thrombocytopenia at predictable intervals (usually every 21–28 days) (Chintagumpala et al. 1992; Moake et al. 1994). In contrast, milder variants have been described in which patients may present at a later age with intermittent episodes of TTP (Karpman et al. 1996; Barbot et al. 2000). Such episodes are characterized by the classic clinical pentad of microangiopathic haemolytic anaemia, thrombocytopenia, fluctuating neurological signs, renal dysfunction and fever, and often appear to be precipitated by febrile illnesses (Upshaw 1978; Karpman et al. 1996). Both presentations are typified by the presence of circulating ULVWF multimers during remission periods consistent with defective post-secretory VWF processing (Moake & McPherson, 1989; Chintagumpala et al. 1992). Indeed, congenital TTP has recently been associated with an absolute deficiency of a novel VWF-CP (less than 5% normal activity) (Furlan et al. 1997, 1998; Allford et al. 2000). This protease has recently been identified as ADAMTS13, and DNA analysis has identified mutations within the ADAMTS13 gene located on chromosome 9q34 in those congenital TTP pedigrees studied (Levy et al. 2001). This is consistent with the recognized clinical finding that plasma infusion is effective treatment for this condition and an exchange procedure is not required.

Management

Successful long-term maintenance can be achieved in severe congenital TTP through prophylactic infusion with FFP (Moake et al. 1985; Barbot et al. 2000), cryosupernatant (Moake et al. 1985) or S/D plasma (Moake et al. 1994). Treatment is usually required every 3 to 4 weeks (Chintagumpala et al. 1992). Plasma infusion may, however, be reserved for symptomatic episodes in milder cases (Karpman et al. 1997).
et al. 1996; Allford et al. 2000). Viral inactivation and the consequent lower risk of transfusion-transmitted infection obviously makes S/D plasma an attractive treatment option. It should be remembered, however, that non-lipid viruses are not inactivated by this procedure and that the product is derived from large donor pools. Hepatitis vaccination should be offered to all patients.

**Recommendation.** Prophylactic plasma infusions should be administered every 3 to 4 weeks in severe congenital TTP (Grade B, level IIIb). Plasma infusion may be reserved for symptomatic episodes in milder variants (Grade C, level IV). A virally inactivated product should be given if available (Grade C, level IV). B, level IIb). Plasma infusion may be reserved for symptomatic infections (Grade C, level IV). A virally inactivated product should be given if available (Grade C, level IV). Hepatitis B vaccination is recommended for all patients (Grade B, level III).

### HAEMOLYTIC URAEMIC SYNDROME

The haemolytic uraemic syndrome is characterized by a microangiopathic haemolytic anaemia, thrombocytopenia and renal failure (Gasser et al. 1955). The disease may also be associated with more extensive multiorgan disease, including enterocolitis, neurological complications, liver dysfunction, pancreatic and cardiac problems. In such patients, particularly when neurological problems are present, there is clinical overlap with TTP (Seigler, 1994) (see Table I). Where possible, it is important to distinguish between the two conditions in order to plan the most appropriate clinical management.

**Clinical features and pathogenesis**

The epidemic form (D+) is associated with a prodromal illness often with bloody diarrhoea in contrast to the rare sporadic or atypical cases (D-) (Milford et al. 1990). HUS is seen increasingly following outbreaks of infection with verotoxin (VT)-producing organisms (Table IV). It represents a growing public health problem (Dundas & Todd, 1999). *E. coli* 0157:H7 is the most commonly notified VT-producing organism in the United Kingdom. Clinical manifestations may vary from an asymptomatic infection through to bloody diarrhoea, haemorrhagic colitis and HUS. Verotoxin enterococcal (VTEC)-associated HUS was seen in up to 20% of patients in recent outbreaks, mainly affecting children and the elderly (Dundas et al. 2001).

VT-producing organisms are characterized by their ability to produce one or more verocytotoxins (or Shiga toxin S1 or S2) (Tesh & O’Brien, 1991) and it is these toxins that are implicated in the pathogenesis of HUS. After ingestion of contaminated food or water, the organisms bind to gut wall receptors and remain within the gut lumen (Nataro & Kaper, 1998). Toxin transfer has been proposed to target organs with specific globotriosyl ceramide (Gb) receptors, in particular glomerular microvascular endothelial cells (Zoja et al. 1992), via neutrophils (Te Loo et al. 2000). Binding occurs through the B subunits (Lingwood et al., 1987) of the toxin with subsequent internalization of the A subunit. The free A chain cleaves adenine from ribosomal RNA at a point where aminocyl transfer RNA is assembled causing disruption of peptide assembly and inhibition of protein synthesis (Obrig et al., 1987). *In vitro* VT binding can also induce apoptosis of some endothelial cell lines and primary cultures via a caspase-dependent mechanism (Lucas et al. 2000).

**Laboratory features and investigations**

Poor prognostic features at presentation include a high neutrophil count (Walters et al. 1989). Severe thrombocytopenia is uncommon but prolonged thrombocytopenia for more than 10 d is associated with long-term renal sequelae. Persistent proteinuria after 1 year may be associated with increased risk of progressive renal dysfunction (Moghal et al., 1998). Extended follow-up is therefore required in all patients. Haemolysis and red cell fragmentation are usually present at presentation, although this rarely develops later in the disease even after improvement in the platelet count. Coagulation studies are usually normal with only mildly raised D-dimer levels in contrast to disseminated intravascular coagulation (Rose & Chant, 1998). The VWF levels are usually markedly raised during the acute illness while multimeric analysis may or may not show ultra-large multimers (Rose et al., 1984). Factor VIII levels do not correlate with clinical outcome (Milford et al., 1991), but high PAI-1 levels correlate with time for platelet recovery and are associated with poor disease outcome (Chant et al., 1994). In contrast to TTP, a deficiency of VWF-CP was not identified in 28 out of 29 children with D+ HUS (25 VTEC positive) (Hunt et al., 2001). Early stool culture is essential for diagnosis of VTEC-associated HUS (Karch et al., 1995). Serological diagnosis is unhelpful in the acute phase, for while IgG enzyme-linked immunosorbent assays are reported to be 95% sensitive and 94% specific, current IgM assays are unreliable (Reymond et al. 1996).

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**Table IV. Clinical subtypes of HUS.**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemic form (D+)</td>
<td>Mostly with prodromal illness of bloody diarrhoea (90% VTEC identified)</td>
</tr>
<tr>
<td>Sporadic form (D-)</td>
<td>2–7% VTEC identified</td>
</tr>
<tr>
<td>Other VTEC infections</td>
<td>Human immunodeficiency virus (Ray et al. 1999)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (Cabrera et al. 1998)</td>
<td></td>
</tr>
<tr>
<td>Aeromonas hydrophilia (Fang et al. 1999)</td>
<td></td>
</tr>
<tr>
<td>Campylobacter upsalensis (Bourke et al. 1998)</td>
<td></td>
</tr>
<tr>
<td>Capnocytophaga canimorsus (Tobe et al. 1999)</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus (Waiser et al. 1999)</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary causes**

1. Post solid organ/bone marrow transplantation
2. Drugs
   - Pentostatin (Antunes et al. 1999)
   - Cyclosporine (Kohli et al. 1998)/Tacrolimus (Schmidt et al. 1999)
   - Mitomycin C (Schiebe et al. 1998)/Estramustine (Tassinari et al., 1999)/Gemcitabine (Fung et al. 1999)
   - Interferon-β (Ubara et al. 1998)/Interferon-α in CML
   - Heroin (Peces et al. 1998)
   - Quinine (Hagley et al. 1992)
3. Systemic lupus erythematosus (SLE)
4. Malignancy
5. Pregnancy
6. Familial deficiency or defect in complement factor H

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Management of D* HUS

There are few randomized studies evaluating the therapeutic options in HUS. The prognosis for patients with D* HUS has improved as a result of careful supportive management (Kaplan et al. 1998). Advice from a renal specialist should, therefore, be sought at the onset of any episode. Careful rehydration while avoiding over hydration, which may precipitate pulmonary oedema, is essential, as is careful management of hyponatraemia. Hypertension may be successfully treated with angiotensin-converting enzyme (ACE) inhibitors (Hoorntje et al. 1981; Monnens et al. 1981). Extra renal problems are now the main cause of mortality as control of blood pressure and appropriate use of dialysis have reduced the renal mortality and morbidity (Robson et al. 1991a). Bilateral nephrectomy may still be advocated in severe HUS unresponsible to any other treatment (Remuzzi et al. 1996; Ruggenenti & Remuzzi, 1996). Blood transfusions should be given according to clinical evaluation and platelet transfusions avoided as in the management of TTP. Extended follow-up is required as there is evidence for the development of both hypertension and renal impairment in the long term.

Based on retrospective data from two large outbreaks of E. coli 0157:H7, anti-motility agents are contraindicated in E. coli 0157:H7 infection (Cimolai et al. 1994). Treatment with anti-motility agents for more than 24 h are associated with the development of HUS and increased central nervous system problems (Cimolai et al. 1992). In the recent Scottish outbreak in Lanarkshire, adults with low gastric acid (previous gastrectomy or taking proton pump inhibitors) were at significantly increased risk of HUS and death. A recent prospective cohort study has confirmed the risk of HUS after antibiotic treatment is increased in children and antibiotics should, therefore, be avoided (Wong et al. 2000). Several antimicrobial agents increase the release of toxin from E. coli 0157:H7 in vitro (Grif et al. 1998), furthermore some are potent inducers of the Shiga toxin 2 gene (Zimmerhacki, 2000).

Recommendation. Optimal management of D* HUS requires meticulous fluid and electrolyte balance and blood pressure control (Grade C, level IV). Renal dialysis should be administered as required (Grade C, level IV). Anti-motility drugs and antibiotic treatment adversely affect outcome and should be avoided (Grade B, level III).

Fresh-frozen plasma and therapeutic plasma exchange. In two prospective studies of FFP in D* HUS, no benefit in terms of the clinical course or outcome was identified (Loirat et al. 1988; Rizzoni et al. 1988). Potential risks of FFP include fluid overload, particularly in the young and elderly, hyperproteininaemia, hypertension, viral transmission and renal injury. Therefore, FFP has no proven benefit and is potentially harmful. There is no controlled prospective study in the use of therapeutic plasma exchange for D* HUS. The outcomes of children treated with plasmapheresis have been reported but there is no evidence to support its current use (Gianvitti et al. 1993). D* HUS in adults usually occurs in elderly patients associated with increased neurological complications and a high mortality. Eleven out of 12 patients with D* HUS in a Canadian Nursing Home outbreak not treated with plasma exchange died (Carter et al. 1987). Plasma exchange was used in 16 out of 22 patients in the Lanarkshire E. coli 0157:H7 outbreak with an overall mortality of 45% (Dundas et al. 1999). No conclusion as to the benefit of plasma exchange can be drawn from this report, in which 62% of the plasma exchange patients developed non-fatal pulmonary oedema.

Recommendation. At present there is no conclusive evidence that either FFP (Grade B, level IIA) or therapeutic plasma exchange improves outcome (Grade C, level IV).

Adjunctive treatment. Currently there is no evidence to support the use of anti-platelet agents (O’Regan et al. 1980), anticoagulation (Proesmans & Eeckels, 1974) or fibrinolytic agents (Loirat et al. 1984). While intravenous immunoglobulin has been shown to neutralize VT1 but not VT2 toxin, this has not been shown to be of benefit in D* HUS (Robson et al. 1991b). Antioxidants, in particular vitamin E, have not been shown to improve patient outcomes. Methylprednisolone is not recommended as a randomized double blind trial failed to show any benefit in terms of blood transfusion requirements, reduction in seizures or need for renal dialysis (Perez et al. 1998).

Recommendation. Adjunctive treatment is not recommended in the management of HUS (Grade C, level IV).

Future developments. For children who develop HUS after VTEC colitis, the time between onset of diarrhoea and renal injury usually varies from 5 to 9 d. Synsorb-Pk, a synthetic trisaccharide covalently coupled to a chromosorb which binds both VT1 and VT2, is able to absorb VT in polymixin extracts of VT-producing E. coli and also to neutralize VT when mixed in vitro with VT-positive stools from children with haemorrhagic colitis or HUS following gastrointestinal transit (Armstrong et al. 1995). Randomized prospective trials of its administration in the prodromal period of VTEC infection are ongoing. Further strategies currently under evaluation include immunization with a modified Shiga toxin (Bast et al. 1997) and galeenate mesilate, a serine protease reported to inhibit cytokine production by monocytes (Kusunoki et al. 1998).

In conclusion the management of D* HUS is based on meticulous attention to fluid and electrolyte balance combined with renal dialysis where necessary. The benefit of additional treatments has not been proven and the principle of management is first to do no harm. Agents to modify the cytokine response seen in HUS or to inhibit platelet function of endothelial cell apoptosis should only be considered in the context of a randomized prospective trial.

Management of D HUS

The optimal management of sporadic HUS is even less clear. This group represents a heterogeneous collection of patients with a substantially higher mortality and chronic morbidity than D* HUS. Several familial cases have been linked with a deficiency or defect of complement factor H (Noris et al. 1998). Factor H controls the activity of the alternative complement pathway C3/C5 convertase by competing with Factor B for C3b binding. Reduced or abnormal factor H may fail to prevent excessive C3 activation, membrane deposition and endothelial cell injury. Reduced levels of C3
have been reported in 73% of patients with familial HUS compared with 16% of control subjects \((P = 0.001)\) and is, therefore, recommended as a screening test for these patients (Noris et al. 1998). Historically patients have been treated with therapeutic plasma exchange, however, relapse rates remain high and it is of unproven benefit in prevention of progression to chronic renal failure (Ouali et al. 1998; Rougier et al. 1998; Warwick et al. 1998, 1999). The replacement of factor H using plasma is a logical but unproven approach. It is recommended that these patients should be treated at a tertiary renal unit, with experience in managing such patients.

**DIAGNOSIS AND THERAPY OF THROMBOTIC MICROANGIOPATHY IN PREGNANCY**

The differential diagnosis of pregnancy-associated thrombotic microangiopathy (TMA) is presented in Table V and discussed below. Accurate diagnosis of TTP and HUS in pregnancy is complicated by the ability of pre-eclampsia to produce TMAs with a variety of clinical pictures similar to TTP and HUS. Each feature of the clinical pentad of TTP can occur in a woman with pre-eclampsia. Pre-eclampsia can also produce a unique TMA involving the liver: HELLP syndrome (haemolysis, elevated liver function tests, low platelets). Fever occurs rarely in HELLP and may be a useful distinguishing feature. Reviewing the literature, there are many patients described as TTP that are probably due to pre-eclampsia/HELLP, having resolved quickly post delivery on ineffective treatment and, vice versa, revision of a diagnosis of pre-eclampsia has to be made when a TMA fails to resolve post partum.

Despite recent advances, there are no pathognomonic assays. The differentiation of these varying types of TMA in pregnancy remains based on history, physical examination and routine laboratory studies. As the management of TMA in pregnancy involves different approaches depending on the underlying diagnosis, the obstetrician and haematologist must distinguish the varying syndromes, to minimize maternal and fetal mortality (Weiner, 1987), and ensure the prompt delivery of efficacious, appropriate and cost-effective management. It is hoped that with the emergence of the understanding that TTP is related to a deficiency of VWF-cleaving protease, the clinical use of VWF-CP assays will bring clarity in diagnosis and management of TMA in pregnancy. This may, however, be obfuscated by the knowledge that levels of VWF-CP are reduced in the third trimester (Mannucci et al, 2001).

**Differential diagnosis of TMAs in pregnancy**

A summary of the differentiating presenting features and management of TMA in pregnancy is presented in Table VI.

**Pre-eclampsia**

Pre-eclampsia affects up to 4% of pregnancies; it most commonly occurs in multiparous women or multiparous women with new partners. The criteria for diagnosis are new onset hypertension and proteinuria developing in the second half of pregnancy. Both hypertension and proteinuria characteristically regress after delivery. Most

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**Table V. Differential diagnosis of TMA in pregnancy.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Classic TTP</th>
<th>Post-partum HUS</th>
<th>HELLP</th>
<th>Pre-eclampsia/eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>Usually &lt; 24 weeks</td>
<td>Post partum</td>
<td>Usually &gt; 34 weeks</td>
<td>Usually &gt; 34 weeks gestation</td>
</tr>
<tr>
<td>Histopathology of lesions</td>
<td>Widespread platelet thrombi</td>
<td>Thrombi in renal glomeruli only</td>
<td>Hepatocyte necrosis &amp; fibrin deposition in periporal sinusoids</td>
<td>Glomerular endothelial hypertrophy and occlusion of placental vessels</td>
</tr>
<tr>
<td>Haemolysis</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>–</td>
<td>–</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>CNS symptoms</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Liver disease</td>
<td>+/-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Renal disease</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Rare</td>
<td>+/-</td>
<td>+/-</td>
<td>+/+</td>
</tr>
<tr>
<td>Effect on fetus</td>
<td>Placental infarct can lead to IUGR and mortality</td>
<td>None, if maternal disease is controlled</td>
<td>Associated with placental ischaemia and increased neonatal mortality</td>
<td>IUGR, occasional mortality</td>
</tr>
<tr>
<td>Effect of delivery on disease</td>
<td>None</td>
<td>None</td>
<td>Recovery, but may worsen transiently</td>
<td>Recovery, but may worsen transiently</td>
</tr>
<tr>
<td>Management</td>
<td>Early plasma exchange is imperative</td>
<td>Supportive ± plasma exchange</td>
<td>Supportive, consider plasma exchange if persists</td>
<td>Supportive ± plasma exchange</td>
</tr>
</tbody>
</table>

---

women also present with peripheral oedema. Pre-eclampsia is thought to involve and arise from a maternal systemic inflammatory response (Redman et al. 1999). Maternal endothelial activation is one part of this inflammatory response and, although it occurs in all pregnancies, it is pronounced in pre-eclampsia. A variety of putative circulating pre-eclampsia factors of placental origin have been proposed. These include lipid peroxidation (Hubel, 1999), vascular endothelial growth factor (VEGF) (Hayman et al., 1999), neurokinin B (Page et al., 2000), activin A (Muttukrishna et al., 1997) or apoptotic debris from the syncytiotrophoblast (Redman & Sargent, 2000). One manifestation of endothelial cell activation (ECA) is that the endothelial surface can change from an antithrombotic to prothrombotic phenotype (Hunt & Jurd, 1998). Evidence for this occurring in pre-eclampsia is supported by increased levels of PAI-1. Other prothrombotic changes include reductions in protein C and antithrombin. Coagulation activation is demonstrated by increased thrombin–anti-thrombin complexes (TAT) and D-dimers. Platelet activation also occurs and thrombocytopenia is common. However, profound DIC is a rare complication in the absence of placental abortion. The fall in anti-thrombin levels seen in pre-eclampsia is not found in TTP (Sagripanti et al., 1996) and may, therefore, be of diagnostic value.

HELLP

HELLP is diagnosed in the presence of haemolysis, elevated liver enzymes and thrombocytopenia. At present there is no standardized definition for any of these criteria. HELLP occurs in up to 10% of women with severe pre-eclampsia. Severe thrombocytopenia and abnormal liver function can also present in the absence of significant hypertension or proteinuria. Exacerbations may occur post partum (Martin et al., 1990) and there is a risk of recurrence of approximately 3% in subsequent pregnancies (Sibai et al., 1995). Occasionally HELLP can present post partum, usually within 48 h of delivery, although it has been reported to occur as late as 6 days post partum (Schwartz & Brenner, 1985). Common presenting symptoms include nausea, malaise, epigastric or right upper quadrant abdominal pain and oedema (Sibai & Ramadan, 1993). In one large series, HELLP was frequently complicated by DIC (21%), abortion (16%), acute renal failure (8%) and pulmonary oedema (6%) (Sibai et al., 1993). Although mild increases in transaminases are present, profound renal failure or hepatic failure is uncommon in the absence of abortion and DIC, findings that help to distinguish HELLP from HUS and acute fatty liver of pregnancy respectively.

TTP

Although in some series, 10–25% of TTP episodes have been reported to be precipitated by pregnancy (Rose & Eldor, 1987), TTP in pregnancy is rare. As discussed previously, some of the former patients are likely to have been misdiagnosed. Debate continues as to whether TTP is precipitated by pregnancy, or whether the coincidence of pregnancy and TTP reflects the fact it is most common in women in their third and fourth decade. The prevalence of relapse during subsequent pregnancy suggests that pregnancy may be a precipitating factor (Rose & Eldor, 1987). Weiner (1987) reported that more than half the patients presenting in pregnancy occur at or before 24 weeks gestation. The diagnosis becomes difficult when TTP presents in the third trimester or post partum but the distinction of TTP from all other causes of TMA in pregnancy is vital because the disease is usually fatal in the absence of treatment and delivery has no effect on maternal outcome.

Post-partum HUS

In 1968, a post-partum HUS was described (Robson et al., 1968; Wagoner et al., 1968), distinct from antepartum renal failure or renal failure occurring within 48 h post partum associated with poor renal perfusion due to obstetric emergencies. It typically presents subacutely with oliguric renal failure and TMA after an otherwise uncomplicated gestation and delivery. Primiparous women are most commonly affected. In one series, the mean time of onset was 26 d after delivery with all cases occurring within the first 10 weeks (Weiner, 1987). Rarely, patients have been described during gestation as a result of VT-producing Escherichia coli (Martinez-Roman et al., 1996). The presentation is that of acute renal failure with a microangiopathic haemolytic anaemia. It has also been associated with HELLP syndrome more than ‘pure’ pre-eclampsia or chronic hypertension (Kahra et al., 1998).

Anti-phospholipid syndrome (APS) and systemic lupus erythematosus (SLE)

Many patients with TMA in pregnancy described in the literature are associated with SLE and APS (Kincaid-Smith et al., 1988; Huang et al., 1998). A renal flare of SLE may mimic HUS and/or pre-eclampsia. Correct diagnosis of such patients may be aided by a history of arthralgia or cutaneous manifestations. The propensity for anti-phospholipid antibodies to predispose to pre-eclampsia is now recognized in the new International Classification Criteria for Anti-phospholipid Syndrome (Wilson et al., 1999): severe pre-eclampsia in association with anti-phospholipid antibodies is a new defining criterion. Furthermore, anti-phospholipid antibodies have also been reported to be associated with the development of TTP and HUS in pregnancy (Kniaiz et al., 1992).

Acute fatty liver of pregnancy

This is a rare but potentially fatal cause of liver failure in the third trimester. The clinical picture is dominated by liver failure. Thrombocytopenia is usually mild. Haemolysis is not usually a feature, although pre-eclampsia may be present in half of the patients (Riely, 1987).

DIC in pregnancy

DIC must not be forgotten in the differential diagnosis of fever, microangiopathic haemolysis, thrombocytopenia and renal insufficiency (Mabie et al., 1997; Wheeler & Bernard, 1999).
Guideline

Recommendation. A thorough history and examination are required to differentiate the varying TMAs that can present in pregnancy. Routine investigations at presentation should include the following: full blood count, film, clotting screen, LDH, direct anti-globulin test, plasma haptoglobin, urea and electrolytes, liver function tests, and urine dipstick for protein. Anti-nuclear antibody, lupus anticoagulant and anti-cardiolipin antibody assays should be considered, depending on the history. Normal levels of anti-thrombin activity are helpful in discriminating TTP from pre-eclampsia (Grade C, level IV).

Management

Pre-eclampsia

Despite extensive research into the causes and pathogenesis of this condition, delivery of the fetus and placenta is still the only effective treatment. The timing of delivery has been the subject of debate. There is a consensus that the presence of multiorgan dysfunction, fetal distress or a gestational age greater than 34 weeks warrants immediate delivery. However, delivery at earlier gestations is associated with high perinatal mortality and morbidity resulting from prematurity (Sibai et al. 1984; Chua & Redman, 1992). It may be possible to delay delivery when severe pre-eclampsia develops remote in term in an attempt to deliver a more mature neonate. A number of randomized controlled clinical trials have demonstrated that perinatal outcome may be improved without significantly compromising maternal outcome when this approach is adopted (Odendaal et al. 1990; Sibai et al. 1994). Meticulous clinical monitoring is required and any sign of maternal or fetal deterioration necessitates urgent delivery. If eclampsia develops, magnesium sulphate is the treatment of choice for seizure prophylaxis (The Eclampsia Trial Collaborative Group, 1995).

HELLP

The neonatal mortality associated with HELLP is 10–20% and has been attributed to placental ischaemia leading to abruption, extreme prematurity and intrauterine asphyxia. Owing to modern management, the maternal death rate is less than 1%. Most authorities agree that expedited delivery is indicated for neonatal distress, abruption, maternal DIC or signs of progressive organ damage.

Corticosteroids given before or after delivery have been claimed to accelerate recovery of platelet count and haemolysis (Magann et al. 1994a,b; Martin et al. 1997), but no clear clinical benefit to mother or fetus has been found (Bell et al. 1991; Ruggenetti & Remuzzi, 1998). Retrospective observational studies suggest that FFP plasma exchange may help recovery in patients with persistent disease 72 h or more after delivery if there is persisting severe thrombocytopenia or haemolysis, or when there has been progressive hepatic, renal, pulmonary or CNS damage (Martin et al. 1990). However, plasma therapy is ineffective during pregnancy and may increase fetal and maternal risk when used to delay delivery (Weiner, 1987; Martin et al. 1990, 1994a, b). Haemostatic replacement therapy with FFP and platelets may be required for mothers with overt coagulopathy and bleeding.

Guidelines for the management of HELLP syndrome and pre-eclampsia-related TMA. Delivery is the treatment of choice and is usually followed by complete recovery within 24–48 h (Grade C, level IV). Persistent disease post partum may be an indication for plasmapheresis (Grade C, level IV).

TTP

Typically, maternal outcome is similar to that of the non-pregnant population assuming treatment is given (Hayward et al. 1994). Untreated TTP is not only associated with a poor outcome for the mother, but also the fetus as a result of the development of placental infarcts, leading to intrauterine growth restriction and death (Wurzel, 1979). However, successful treatment can result in the delivery of a normal-sized infant. Because TTP often develops before 24 weeks, when the fetus is unlikely to survive if delivered, and termination of pregnancy does not alter the clinical course of the disease, delivery or termination is not advocated. Fortunately pregnancy does not impair the response to plasmapheresis. No case of fetal thrombocytopenia has been described in maternal TTP. Pregnancy may precipitate relapse in women with a history of TTP (Hayward et al. 1994). There is anecdotal evidence to suggest the use of anti-platelet agents or steroids may prevent relapse (Ezra et al. 1996). Successful pregnancies have even occurred in women requiring maintenance plasma infusions preconception for the prevention of relapse. Increased plasma requirement may be noted during gestation (Lian et al. 1984; Koyama et al. 1990).

Guidelines for the management of TTP in pregnancy. Treat with plasma exchange as non-pregnant patients (Grade C, level IV). Delivery is recommended only for those women who do not respond to plasma exchange (Grade C, level IV).

Post-partum HUS

Post-partum HUS has a poor prognosis. Chronic renal failure is common and a 55% mortality rate was found in earlier reports. Likewise Sibai et al. (1993) reported a high maternal mortality rate of 13% and perinatal mortality rate of 34% in 32 patients with HELLP syndrome associated with renal failure (Sibai & Ramadan, 1993). Responses to plasmapheresis or plasma infusion have been reported but no form of management has been subjected to controlled studies (Weiner, 1987; Hayward et al. 1994; Martinez-Roman et al. 1996). The role of anti-platelet drugs, corticosteroids, heparin or splenectomy is even less well documented. Recurrence is rare, but the risk in women with familial HUS is uncertain (Berns et al. 1992).

Guidelines for the management of post-partum HUS. Supportive care with dialysis and transfusion is required (Grade C, level IV). The benefits of plasma exchange are uncertain (Grade C, level IV).

CLINICAL AUDIT

Routine audit of the clinical diagnosis and management of acute TTP and related conditions is difficult to conduct because of their infrequent presentation in most units. Larger haematological departments offering daily plasma exchange
facilities should consider an annual review of disease outcome, time to diagnosis and initiation of specific therapy, time taken to clinical response, relapse rate, and long-term morbidity and mortality. Smaller departments should consider regional referral patterns, particularly delay in obtaining initiation of regular plasma exchange, and consider conducting an audit on a regional basis with long-term outcome and relapse rates (including mortality) after a course of plasma exchange has been completed. Such an approach should highlight any deficiency in service provision.

CONCLUSION

Despite recent advances, further clarification of the pathophysiology of the microangiopathic haemolytic anaemias is required to aid correct diagnosis, management and identification of those patients at risk of progressive disease or recurrent episodes. Objective clinical data is lacking and prospective controlled clinical trials of treatment are urgently required to improve clinical outcome in these conditions.

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 nor the publishers can accept any legal responsibility or liability for any errors or omissions that may have been made.

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REFERENCES


Guideline


**Keywords**: microangiopathic haemolytic anaemia, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, gestational thrombotic miroangiopathic anaemia, management guidelines.

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**APPENDIX**

**Grades of recommendation**

| A (Evidence levels Ia, Ib) | Requires at least one randomized trial as part of the body of literature of overall good quality and consistency in addressing the specific recommendation. |
| B (Evidence levels IIA, IIB, III) | Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation. |
| C (Evidence level IV) | Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities; this indicates absence of directly applicable studies of good quality. |

**Levels of evidence**

| Ia | Meta-analysis of randomized controlled trials |
| Ib | At least one randomized controlled trial |
| IIA | At least one well-designed controlled trial without randomization |
| IIB | At least one other type of well-designed quasi-experimental study |
| III | Well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies |
| IV | Expert committee reports or opinions and/or clinical experience of respected authorities |