

Thrombotic thrombocytopenic purpura

What is thrombotic thrombocytopenic purpura?

Thrombotic thrombocytopenic purpura (TTP) is a rare form of thrombotic microangiopathy. It is characterised by:

- Microangiopathic haemolysis.
- Thrombocytopenia.
- Neurological abnormalities.
- Fever.
- Renal dysfunction.

The diagnosis of TTP should be treated as a medical emergency. Without treatment the mortality is 90% and around half of all deaths occur within 24 hours of presentation; however, this can be greatly reduced with prompt treatment with plasma exchange.^[1]

Pathogenesis

Congenital and acute acquired TTP are due to a deficiency of von Willebrand factor cleaving protein, also known as ADAMTS1.^[1]

How common is TTP? (Epidemiology)

The incidence is rising as there is greater recognition of the condition.

- TTP is rare, with a reported incidence of 6 per 1,000,000 per year in the UK.^[1]

- It is most common in adults, although it has been reported in neonates and nonagenarians. The peak occurs in the fourth decade of life.
- It is more common in females than in males; the ratio is 3:2.

What causes thrombotic thrombocytopenic purpura? (Aetiology)

Pregnancy and the postpartum state account for 10–25% of cases of TTP. The course of the syndrome is not altered by termination of pregnancy. It occurs in greater frequency in patients with HIV infection and may be the initial presenting syndrome. TTP may also be associated with autoimmune disease and cancer and may also be iatrogenic, related to drugs such as quinine and simvastatin. The most common form of TTP is idiopathic.

TTP symptoms

There may be a prodrome resembling a flu-like illness, including fever, fatigue and generalised malaise and arthralgias. A patient can present with:^[1]

- Thrombocytopenia (epistaxis, bruising, petechiae, gingival bleeding, haematuria, menorrhagia, gastrointestinal bleeding, retinal haemorrhage, haemoptysis).
- Confusion, headache, paresis, aphasia, dysarthria, visual problems, encephalopathy, coma.
- Fever, pallor, jaundice (haemolytic anaemia), fatigue, arthralgia, myalgia.
- Proteinuria, micro-haematuria, raised urea and creatinine.
- Chest pain, heart failure, arrhythmias, hypotension.
- Abdominal pain.
- Hemiparesis, hemiplegia or seizure – 35% of children with TTP present in this way.

Examination

This may be normal. However, you may find:

- Fever.
- Purpura - non-palpable small purpuric spots or petechiae occur with thrombocytopenia, ie platelet count $<50 \times 10^9/L$.



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- Jaundice - secondary to haemolysis.
- Severe hypertension.
- Neurological problems as above.
- Splenomegaly.

Investigations^[2]

- Blood smear shows fragmented erythrocytes, ie schistocytes. This is consistent with haemolysis. Schistocytes are a hallmark of the disease but there are no guidelines as to the number of schistocytes required to differentiate TTP from other thrombotic microangiopathies.
- Renal function tests; creatinine level is mildly elevated in about half of patients.
- Coagulation studies are non-diagnostic.
- LDH level is extremely elevated. This is released from ischaemic or necrotic tissue cells.
- Indirect bilirubin level is elevated.

- Reticulocyte count is elevated.
- Urinalysis shows proteinuria and microscopic haematuria.
- Pre-treatment measurement of ADAMTS13 activity levels and anti-ADAMTS13 antibodies may be done in secondary care.^[1]
- Serological tests for HIV, hepatitis B virus and hepatitis C virus, autoantibody screen and a pregnancy test (when appropriate) should be performed at presentation.^[1]

Differential diagnosis^[1]

- Autoimmune haemolysis/Evans' syndrome.
- [Disseminated intravascular coagulation](#).
- Pregnancy-associated - eg, [HELLP syndrome](#).
- Drugs - eg, quinine, simvastatin, interferon, calcineurin inhibitors.
- Malignant hypertension.
- Infections - typically, viral (cytomegalovirus, adenovirus, herpes simplex virus) or severe bacterial (meningococcus, pneumococcus), fungal.
- Autoimmune disease (lupus nephritis, acute scleroderma).
- Vasculitis.
- [Haemolytic uraemic syndrome](#) (diarrhoea positive/negative).
- Malignancy.
- Catastrophic [antiphospholipid syndrome](#).

TTP treatment and management

Intravenous (IV) plasma exchange

IV plasma exchange is also called plasmapheresis. It is the present gold standard of treatment for TTP. During the plasma exchange, the inhibitory antibodies are removed and the plasma is replenished with the deficient protease.

- Plasma exchange should be initiated as soon as possible, preferably within 4–8 hours.^[1]
- Infusion of fresh frozen plasma (FFP) 30 mL/kg can be used until the patient can be transferred to a facility where plasma exchange is available.
- Glucocorticoid steroid and antiplatelet agents are used. Steroids often are administered prior to plasma exchange. Steroids have no proven added benefit over plasmapheresis alone, but some patients respond to high-dose prednisone (200 mg/day) alone, without plasma therapy.
- Haemorrhage is a concern with antiplatelet therapy and its benefit has not been proven.^[3]
- Rituximab:
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 - In acute idiopathic TTP with neurological or cardiac pathology (associated with a high mortality) rituximab, a monoclonal anti-CD20 antibody, should be considered on admission, in combination with plasma exchange and steroids.^[1]
 - Patients with refractory or relapsing immune-mediated TTP should be offered rituximab.^[1]
 - Increased plasma exchange and/or rituximab therapy are the agents of choice in relapsing disease.^[1]
 - In patients with an acute episode of TTP, initial treatment with rituximab, plasma exchange and corticosteroids result in remission in over 90% of patients within 14 to 21 days. Rituximab may also decrease the frequency of subsequent relapses.^[4]

- Other treatments:^[1]
 - Red cell transfusion should be administered according to clinical need, especially if there is cardiac involvement.
 - Folate supplementation is required during active haemolysis.
 - Platelet transfusions are contra-indicated in TTP unless there is life-threatening haemorrhage.
 - Thromboprophylaxis with low molecular weight heparin (LMWH) is recommended once platelet count has reached $>50 \times 10^9/L$.
 - The use of antiplatelet agents in TTP is unproven but low-dose aspirin may be given during platelet recovery (platelet count $>50 \times 10^9/L$).

Surgery

Splenectomy is sometimes used but has limited proven benefit, and significant risks, with a mortality of 40% if carried out during acute TTP.^[1]

Other measures

Supportive care for end-organ damage may be required - eg, haemodialysis for acute kidney injury.

NB: platelet transfusions are contra-indicated due to the risk of causing further thrombotic events - the only exception might be in the case of life-threatening haemorrhage.^[1]

Prognosis

Improved treatment has improved mortality associated with acute episodes, from 90% to about 10-20%.^[1] About one third of survivors experience a relapse within the subsequent ten years.

Further reading

- [Thrombotic Thrombocytopenic Purpura, Congenital, TTP](#); Online Mendelian Inheritance in Man (OMIM)

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Last updated by: Dr Toni Hazell 15/12/2022	
Peer reviewed by: Dr Colin Tidy, MRCP 15/12/2022	Next review date: 14/12/2027

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