THE NORTHERN HOSPITAL

THROMBOTIC THROMBOCYTOPENIC PURPURA

The Emperor Caracalla, bust in marble, Roman, Severan period, AD 212-217, Metropolitan Museum of Art, New York.

Two sons, Caracalla and Geta, where the fruit of this marriage, and the destined heirs of the empire. The fond hopes of the father, and of the Roman world, were soon disappointed by these vain youths, who displayed the indolent security of hereditary princes; and a presumption that fortune would supply the place of merit and application. Without any emulation of virtue or talents, they discovered, almost from their infancy, a fixed and implacable antipathy for each other...

The declining health and last illness of Severus inflamed the wild ambition and black passions of Caracalla's soul. Impatient of any delay or division of empire, he attempted, more than once, to shorten the remainder of his father's days, and endeavoured, but without success, to excite a mutiny among the troops. The old emperor had often censured the misguided lenity of Marcus, who by a single act of justice, might have saved the Romans from the tyranny of his worthless son. Placed in the same situation, he experienced how easily the rigour of a judge dissolves away in the tenderness of a parent. He deliberated, he threatened, but he could not punish; and this last and only instance of mercy was more fatal to the empire than a long series of cruelty. The disorder of his mind irritated the pains of his body, he wished impatiently for death, and hastened the instant of it by his impatience. He expired (A.D 211, February 4th) at York in the sixty-fifth year of his life, and in the eighteenth of a glorious and successful reign. In his last moments he recommended concord to his sons, and his sons to the army. The salutary advice never reached the heart, or even the understanding, of the impetuous youths; but the more obedient troops, mindful of their oath of allegiance, and of the authority of their deceased master, resisted the solicitations of Caracalla, and proclaimed both brothers emperors of Rome...The emperors met only in public, in the presence of their afflicted mother; and each surrounded by a numerous train of armed followers. Even on these occasions of ceremony, the dissimulation of courts could ill disguise the rancour of their hearts.

This latent civil war already distracted the whole government. When a scheme was suggested that seemed of mutual benefit to the hostile brothers. It was proposed, that since it was impossible to reconcile their minds, they should separate their interest, and divide the empire between them...it was agreed that Caracalla, as the elder brother, should remain in possession of Europe and western Africa; and that he should relinquish the sovereignty of Asia and Egypt to Geta, who might fix his residence at Alexandria or Antioch...The tears of the empress Julia interrupted the negotiation, the idea of which had filled every Roman breast with surprise and indignation. The mighty mass of conquest was so intimately united by the hand of time and policy, that it required the most forcible violence to rend it asunder. The Romans had reason to dread that the disjointed members would soon be reduced by a civil war under the dominion of one master, but if the separation was permanent, the division of the provinces must terminate in the dissolution of an empire whose unity had hitherto remained inviolate.

Had the treaty been carried into execution, the sovereign of Europe might soon have been the conqueror of Asia; but Caracalla obtained an easier though a more guilty victory. He artfully listened to his mother's entreaties and consented (A.D 212, 27th February) to meet his brother in her apartment, on terms of peace and reconciliation. In the midst of their conversation, some centurions, who had contrived to conceal themselves, rushed with drawn swords upon the unfortunate Geta. His distracted mother stove to protect him in her arms; but, in the unavailing struggle, she was wounded in the hand, and covered with the blood of her younger son, while she saw the elder animating and assisting the fury of the assassins...Geta had been the favourite of the soldiers; but complaint was useless, revenge was dangerous, and they still revered the son of Severus. Their discontent died away in idle murmurs, and Caracalla soon convinced them of the

justice of his cause, by distributing in one lavish donative the accumulated treasures of his father's reign...

The crime went not unpunished. Neither business, nor pleasure, nor flattery, could defend Caracalla from the stings of a guilty conscience; and he confessed, in the anguish of a tortured mind, that his disordered fancy often beheld the angry forms of his father and his brother rising to life; to threaten and upbraid him. The consciousness of his crime should have induced him to convince mankind, by the virtues of his reign, that the bloody deed had been the involuntary effect of fatal necessity. But the repentance of Caracalla only prompted him to remove from the world whatever could remind him of his guilt, or recall the memory of his murdered brother.

Edward Gibbon, "The History of the Decline and Fall of the Roman Empire", volume 1 1776.

As the great Emperor Septimius Severus lay dying he could defer no longer the critical decision of to whom the empire should be bequeathed. He had two sons, Caracalla and Geta, both of whom he loved very much. He could not separate the two. Caracalla was by rights the most legitimate as the eldest son, however he was an impulsive and violent man, whereas the younger Geta was gentler more popular with the troops. In the end he made the fatal decision to commend the empire to both of his sons. The decision was fatal because the two sons detested each other, virtually from the time of their birth. Is was obvious to most close to the emperor that the two would be a fatal combination, neither would accept the other in a partnership of rule over the Roman world. As soon as Septimius died the army, loyal to his memory, proclaimed both his sons as joint emperors. Each maintained an immense personal body guard and lived in different sections of the city. The tension between them became unbearable and the senate in a desperate attempt to ward off seemingly inevitable bloody civil war, proposed that the empire be divided between to the two of them even though this idea was abhorrent to the majority of most Romans of the mid-third century. Their mother desperate to bring her two sons together in a peaceful arrangement tearfully begged them both to meet her on neutral ground in her apartments to try and negotiate some workable arrangement. Geta was willing to talk - Caracalla had no such intention. He arranged to have some of his own men hidden within his mother's palace, and when two brothers met face to face in the presence of their mother he gave the signal for his hidden men to kill Geta. Ancient sources tell of heart rending scenes of the mother desperately trying to fend off the assassins, but alas to no avail, and amidst her horrified screams echoing down the corridors of the palace, her youngest son, Geta, dies in her arms of his wounds. Caracalla would prove a cruel and vicious emperor who would in turn be assassinated himself by his own troops six years later.

Gibbon placed the blame of this disaster squarely on the shoulders of Septimius Severus. He wrote that even though Severus was very well aware of the disastrous decision of the great Marcus Aurelius to allow his unstable son Commodus to succeed him, he turned a blind eye to the vices of his own son, Caracalla, when faced with exactly the same decision of succession. By naming both his sons to succeed him, he created a lethal combination which would destroy his own family and have violent repercussions for the wider Roman world in general when Caracalla took severe reprisals on all who had shown even the slightest support for his murdered brother. The tragic story of the brothers Caracalla and Geta, must serve as a reminder of "lethal combinations". Some combinations were simply never meant to be! In the field of Haematology we must be ever alert to one lethal combination in particular - that of profound thrombocytopenia and microangiopathic haemolytic anaemia - a combination that portends the presence of TTP.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Introduction

Thrombotic thrombocytopenic purpura (TTP) is an acute clinical multi-system syndrome, which follows a rapidly progressive course and has a mortality rate of 90% without treatment and so is important to recognize.

In adults there is some confusion with the condition Hemolytic Uremic Syndrome (HUS).

Traditionally those patients who had predominantly neurological features with minimal or no renal involvement were labelled TTP. Those with predominant renal failure with little or no neurological features were labelled as having HUS.

This distinction in adult patients however seems unnecessary, many patients present with significant neurological abnormalities in addition to renal impairment. These patients can only really be described by the comprehensive term TTP-HUS, (though in adults it is most commonly termed simply TTP). Further as the pathology and treatment is the same in adults the distinction seems unnecessary. HUS which is caused by an episode of bloody diarrhoea after infection with an entero-hemorrhagic strains of E. Coli, may represent a different disease process in **children.**

Recognition of thrombotic thrombocytopenic purpura is difficult because of lack of specific diagnostic criteria as well as the non-specific nature of the clinical presentation.

The only consistent abnormalities are:

- **Microangiopathic hemolytic anaemia, characterized by red-cell fragmentation**

And

- **Thrombocytopenia**

These features can also occur in other conditions, so if there is no other obvious reason for these abnormalities then the diagnosis of TTP must be considered, and the case discussed urgently with the specialist Haematology Unit.

Pathophysiology

The exact pathophysiology of the disease is uncertain and probably involves a number of different causes, probably of auto-immune etiology.

The TTP syndrome is characterized by microangiopathic hemolysis and platelet aggregation/hyaline thrombi whose formation is unrelated to coagulation system activity. Platelet microthrombi predominate; they form in the microcirculation (ie, arterioles, capillaries) throughout the body causing partial occlusion of vessels. Organ ischemia, thrombocytopenia, and erythrocyte fragmentation (ie, schistocytes) occur. The brain and kidney are especially involved.

Theories include:

1. ADAMTS-13 deficiency.

- This is an enzyme deficiency which may be congenital or acquired. The enzyme is involved in the activation of von Willebrand factor (VWF)

  ULVWF → VWF

  Excess ULVWF results in excessive platelet aggregation. Patients with TTP have significantly reduced levels of ADAMTS-13

- HUS does not appear to have this deficiency.

2. Endothelial injury due directly to drug or toxin or indirectly by neutrophil or platelet activation.

   - Drugs, may include quinine.

   - Toxin can include shiga toxin, produced by entero-hemorrhagic strains of E. Coli.

   - Other conditions that have an association include pregnancy, malignancies and HIV.

3. Rare genetic predispositions.

Diagnostic Criteria

Note that TTP is a clinical diagnosis with no pathognomonic laboratory test findings.

The "classic" description of TTP has been the clinical "pentad" of:

1. Fever
2. Thrombocytopenia
3. Neurological dysfunction.
4. Renal impairment / failure.
5. Microangiopathic haemolytic anemia.

(The diagnosis was further supported by the histologic presence of platelet micro-thrombi)

Today, however the availability of a curative treatment for this condition with high mortality has created an urgency for diagnosis and therefore the stringency of diagnostic criteria has decreased.

It is now more appropriate to think in terms of a clinical "dyad" of:

1. **Microangiopathic haemolytic anemia, (not explained by another cause)**
2. **Thrombocytopenia, (not explained by another cause)**

This should be enough to initiate urgent treatment.

Clinical Features

The onset is usually abrupt and the disease runs for days to weeks, occasionally for months.

The diversity of presenting clinical features is related to the presence of microvascular thrombi in many different organs.

Clinical features are non-specific and may include:

1. Fever, (*however this is uncommon, and significant fevers should prompt consideration of sepsis*).
2. Anemia
3. Purpura, due to the thrombocytopenia, (clinically severe bleeding is uncommon however)
4. Neurological dysfunction. This is usually within the CNS:
    - Altered conscious state, drowsiness.
    - Confusion.
    - Seizures
    - Coma

    These neurological signs and symptoms may fluctuate.
5. Renal impairment / failure:
    - May be associated with anuria
6. Abdominal symptoms:
    - Nausea
    - Vomiting
    - Diarrhoea
    - Abdominal pain

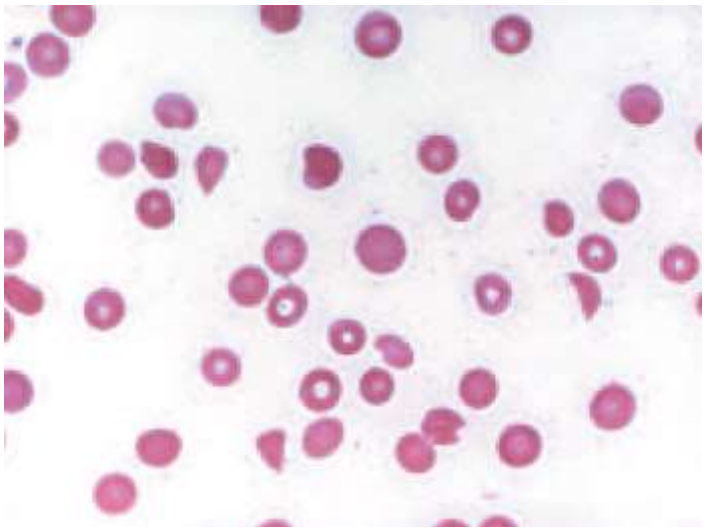
Investigations

1. FBE
    - Anemia, can be mild to severe.

- Thrombocytopenia
    - ♥ Can be mild to severe
    - ♥ And especially in the absence of leucopoenia.
- **Blood film examination, this is critical to making the diagnosis:**

  There is evidence of a micro-angiopathic haemolytic anemia. This is defined as a non-immune hemolysis, (there is a negative direct anti-globulin test) with evidence of RBC fragmentation, (schistocytes) seen on the peripheral blood film.

  In the appropriate clinical setting and in the absence of other known causes of thrombotic micro-angiopathy a schistocyte count of greater than 1.0 % is strongly suggestive of TTP.



Blood film from a 40 year old woman with TTP, showing fragmented red cells (schistocytes), polychromatophilic red cells (reticulocytes), and a lack of platelets, consistent with the presence of microangiopathic hemolysis. [1]

2. Assessment of haemolytic process:
    - Negative direct anti-globulin test, (ie negative coomb's test)
    - Typical biochemistry suggesting hemolysis with:
        - ♥ Elevated LDH levels
        - ♥ LFTs, show elevated indirect (non-conjugated) bilirubin
3. U&Es
    - May show renal impairment / failure, but may also be normal.

4. Coagulation profile:

    - In uncomplicated TTP the PT and aPTT are normal.

      Note there is a distinction between DIC and TTP. DIC is associated with the activation of the coagulation cascade, leading to the intravascular deposition of fibrin and platelet thrombi as well as the consumption of all the components of this cascade and a microangiopathic haemolytic anemia. As a result patients with DIC typically have not only thrombocytopenia, they also have low fibrinogen levels and prolongation of the PT and aPPT times.

      In comparison, TTP-HUS represents isolated platelet consumption due to endothelial injury or a primary increase in platelet activation. Fibrinogen levels and clotting times are normal.

5. ADAMTS 13 activity:

    - Measurement of ADAMTS 13 activity is **not** necessary for decisions about diagnosis and initial management

    - A severe deficiency indicates an increased risk of relapse and so is useful for future prognostic purposes.

The main differential diagnoses will be:

- Sepsis
- Disseminated cancer
- Malignant hypertension
- Severe preeclampsia

Management

There should be early consultation with a hematologist and ICU because of the diagnostic and management complexity of TTP.

1. Immediate attention to any ABC issues.

2. Plasmapheresis:

    Once the diagnosis is suspected the treatment is urgent plasmapheresis, (or plasma exchange, ie removal of the patient's plasma and replacement with transfused plasma)

    - Without this treatment, mortality is up to 90%.

    - Plasma infusion is thought to provide the missing ADAMTS-13 protease enzyme, and plasma exchange may remove the acquired autoantibody directed against

ADAMTS-13. Exchange may also remove the ULVWF multimers causing the excessive platelet activation.

- Note that plasma infusion alone is less effective than plasma **exchange.**

- Plasma exchange is initially performed daily or twice daily until platelet counts normalise and hemolysis ceases. On average 7-16 daily exchanges will be needed, however this is highly variable and a much larger number may be required.

- Post diarrheal HUS in children is an exception as it usually resolves spontaneously. Plasma exchange may be considered, however in patients with persistent or severe disease.

3. Infusion of FFP (30 mL/kg) may be used as a temporizing measure if there is going to be a significant delay before the patient can be transferred to a facility where plasma exchange is available.

4. Platelet transfusions

    - The role of these is uncertain, but they are generally avoided as they may lead to new or worsening renal and neurological symptoms due to consumption and further microvascular thrombi of the infused platelets.

5. Renal dialysis may be needed, especially if the patient becomes anuric.

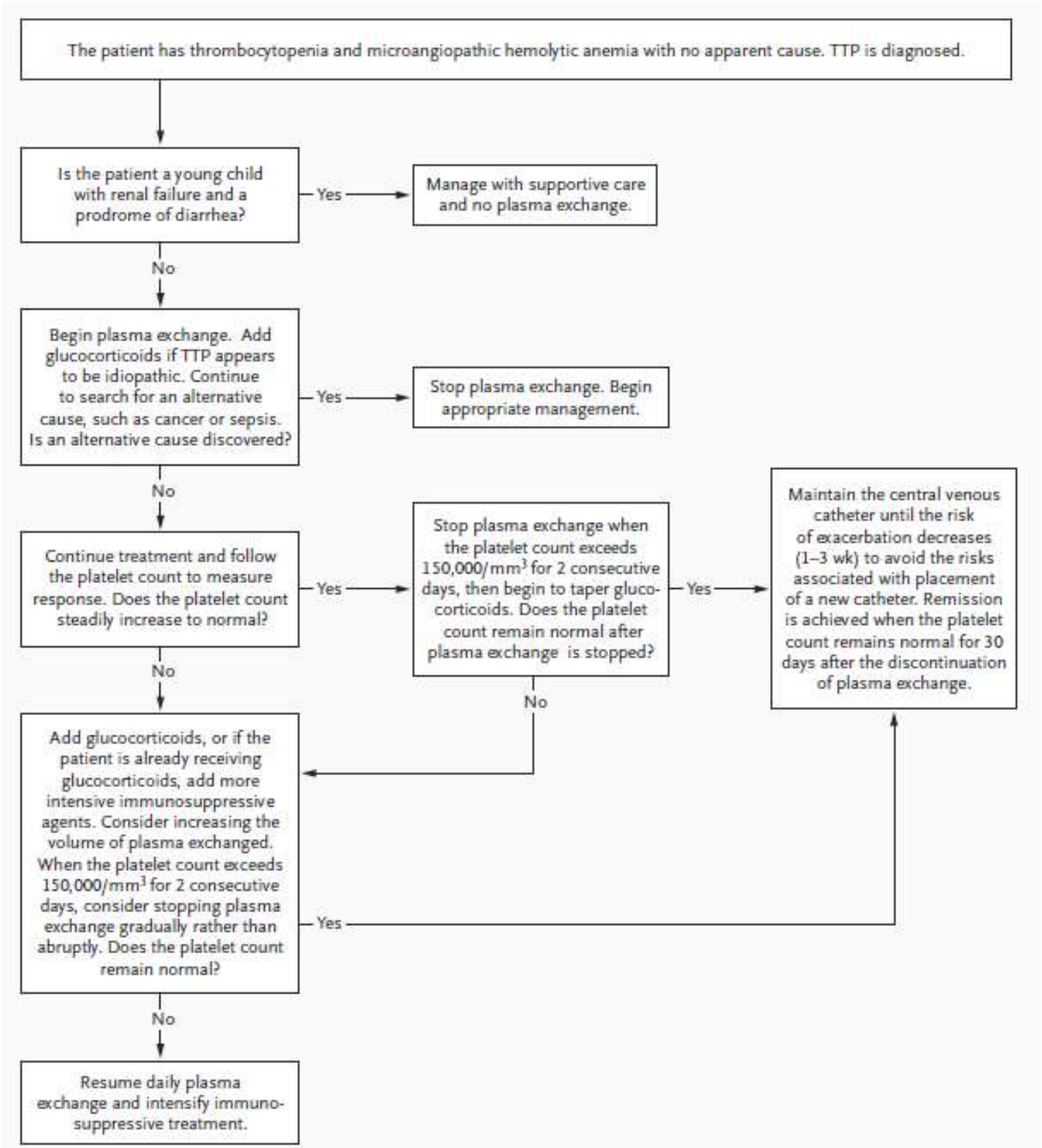
6. Steroids / immunosuppressants may have a role in severe or resistant cases.

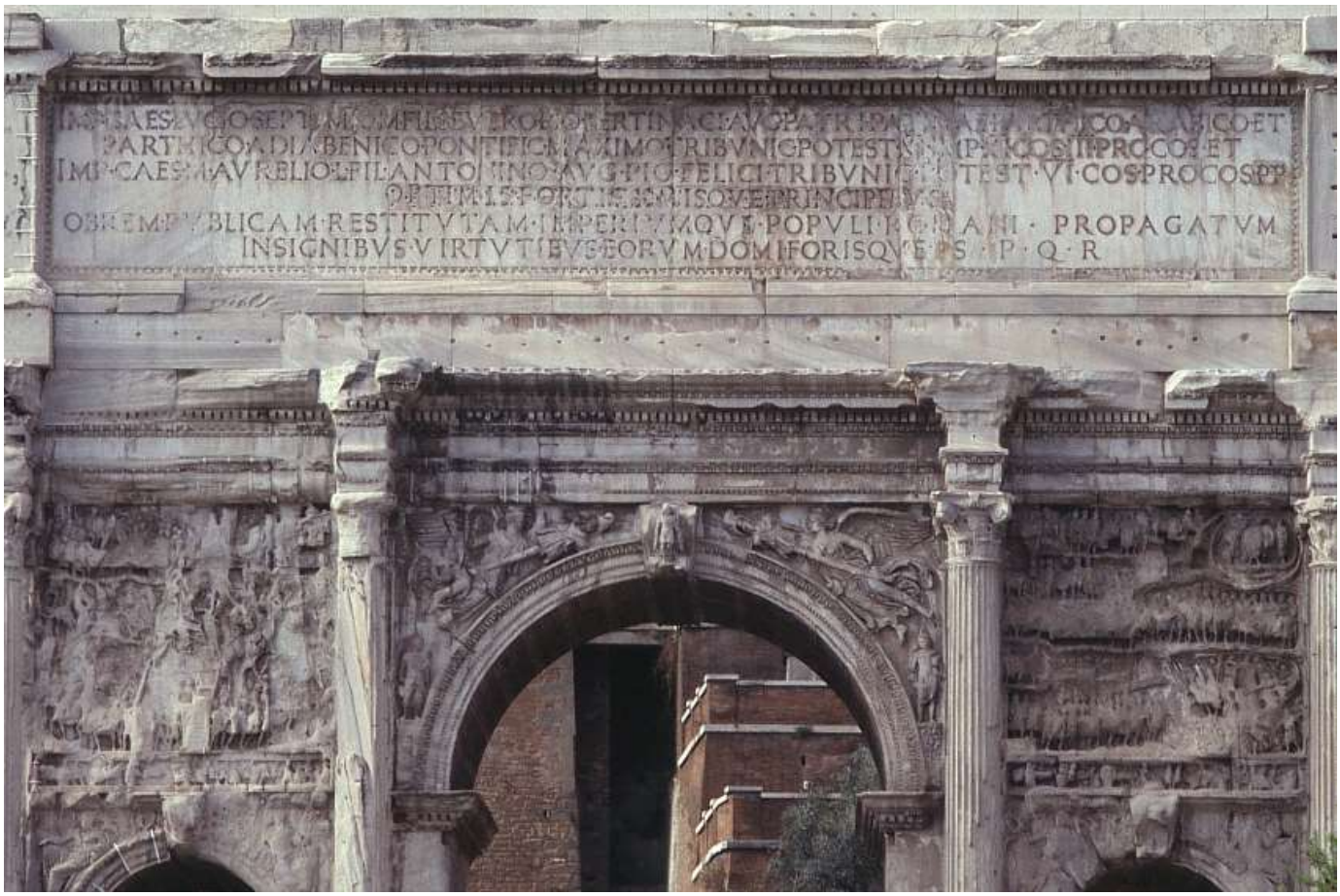
Relapse

Relapses are rare in patients with thrombotic thrombocytopenic purpura, except in those with a **severe** deficiency of ADAMTS 13 activity; half of such patients may have a relapse, most within a year. Long-term follow-up data suggest a diminished frequency of relapses over time, though a relapse can occur years after the initial episode.

Appendix 1

Management pathway for TTP: [1]





The Arch of Septimius Severus, Severan period, AD 212-217, Capitol, Rome

Archaeologists after careful examination of the Latin inscription carved into the ancient Arch of Septimius Severus now conclude that the fourth line of the inscription had been erased and re-worded soon after the arch was built. It is believed that the original inscription made reference to the two sons of Septimius Severus - Caracalla and Geta. All mention of Geta was removed from the inscription by his elder brother Caracalla. The reworked inscription today stands silent witness across the millennia, to those in the know, of an ancient and horrifying case of fratricide.

References

1. George J.N Thrombotic Thrombocytopenic Purpura. NEJM, 354; 18, May 4, 2006.

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