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Review

Trends in the diagnosis and management of TTP: European perspective

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ABSTRACT

Thrombotic thrombocytopenic purpura diagnosis and therapy has transformed with improved understanding of the disorder and availability of therapies. Plasma exchange remains the cornerstone of treatment. Prompt therapy can improves morbidity and mortality. However, given the plasma volumes used, those offering protection against transfer of microbes are preferable. Reviewed is a brief history of TTP and current plasmas available, their use and safety profiles, concentrating on the current UK recommendations.

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Thrombotic thrombocytopoenic Purpura was first described in 1924 by Moschcowitz in a 16-year-old girl presenting with fever, haemolytic anaemia, paralysis, coma and died within 2 weeks of presentation. Histology at postmortem confirmed microthrombi [1].

TTP was therefore classically defined by the pentad of fever, thrombocytopoenia, microangiopathic haemolytic anaemia (MAHA), renal dysfunction and neurological symptoms, although the presentation may be variable. The pathological hallmark is platelet rich microthrombi in the small vessels of multiple organs.

Up until 1964, with the introduction of plasma, the mortality was greater than 90%, with up to 98% of cases demonstrating the classical pentad at presentation. From 1964 to 1980, mortality rates had reduced to 54%, with reductions in presentation of neurological, renal and fever symptoms. Within the current era, diagnosis relies on the presence of thrombocytopoenia and microangiopathic haemolytic anaemia (MAHA), but the mortality remains at 10–20%.

Diagnosis is confirmed by the presence of characteristic findings on blood film of red cell fragmentation, anaemia, thrombocytopoenia and polychromasia. The presenting clinical features may vary and indeed, from the South East England TTP registry, 80% of patients have neurological features, from headaches to coma, 22% had fever, a third had renal impairment, 35% abdominal symptoms and 42% cardiac involvement, either symptoms or more frequently, raised troponin t levels [2]. Cardiac involvement has been the most elusive to confirm in TTP patients as they often have no symptoms, minor ECG changes and normal echocardiograms. With the availability of troponin assays, and the demonstration that patients with the highest levels in conjunction with raised Anti-ADAMTS 13 antibodies, have a worse outcome with highest mortality rates and severe disease, often requiring support in intensive units [3]. Indeed, sudden demise in cases of acute TTP appear due to acute conduction defects affecting the SA and AV node due to microarteriolar thrombosis, which has been confirmed at post mortem.

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A deficiency in the enzyme required to cleave VWF, ADAMTS 13, is the basis to the pathogenesis of TTP. Rarely, the abnormality is a congenital deficiency of ADAMTS 13. In the majority of cases, low ADAMTS 13 levels are a result of IgG antibodies formed to ADAMTS 13, with other secondary, precipitating causes demonstrated in approximately 15% of cases. Cases with no precipitating event associated with antibodies to ADAMTS 13 appear to have the severest disease phenotype. They are more likely to present with neurological features and all the cases presenting with coma were acquired idiopathic Anti-ADAMTS 13 positive. Cases with antibody mediated disease take three times as long to attain remission (median 23 days) compared to patients without antibodies (median 7 days) and therefore the plasma requirement is considerably greater [4].

More recently, it has become clear that many of the cases previously diagnosed as 'TTP' are in fact atypical HUS. With the advent of complement association with these cases [5] and a better understanding of differentiating between the two disorders using ADAMTS 13 assays, a more systematic approach to diagnosis and therapy is available. It is the unchecked activation of the terminal complement pathway that results in renal injury, endothelial activation and microvascular thrombosis, red cell shearing, thrombocytopenia and an increased risk of infection. Therefore, in all cases of TTP, aHUS [6] or indeed any TMA in which the initial diagnosis is not clear, PEX should be instigated.

The mainstay of therapy is plasma exchange (PEX). The first randomised controlled trial in TTP compared plasma infusion with plasma exchange, which demonstrated the superior benefit on survival of plasma exchange [7]. PEX allows an increased delivery of plasma and some removal of antibody, but there is a morbidity and mortality associated with such large volumes of plasma. Namely, there is the acute risk of allergic reactions/anaphylaxis and TRALI, but also the longer term consequences of transmission of infectious agents, initially hepatitis B, C and HIV but more recently variant CJD, a prion protein, resistant to current inactivation procedures, or indeed other as yet undefined agents.

There are a number of plasma components available for use in the treatment of TMAs, specifically TTP. Firstly there is single unit, standard FFP and cryosupernatant, usually produced by national blood services. The three other main sources are single donor or pooled plasma that have undergone further processing that results in improved safety profiles, specifically against transmittable infectious agents especially enveloped viruses. These include methylene blue, solvent detergent and Psoralen S-59 and UVA light. Further methodologies, such as riboflavin, remain in development.

A comparison of the in vitro parameters of available plasma components available to treat TTP and other TMAs reveals similarity when comparing standard FFP, cryosupernatant, Octaplas, Uniplas and MB-FFP, with exceptions of reduced VWF in cryosupernatant and reduced Protein S in Octaplas, but still within the normal range. The comparable ADAMTS 13 activity (measured at that time by multimeric analysis) was maintained after overnight storage. Furthermore, the multimeric pattern of Octaplas and Uniplas is similar to cryosupernatant, with lack of high molecular weight multimers [8].

Within the UK and other European countries, the decision was taken to use single donor, methylene blue treated plasma for patients using high volumes of plasma or indeed in the UK, those born after 1 January 1996, who would not have been exposed previously to prions. Therefore, plasma in these instances is non UK sourced before importation for MB treatment [9].

A retrospective review of 54 patients, half receiving MB FFP and the remaining receiving standard FFP, confirmed increased number of PEX to remission, increased risk of relapse and increased mortality due to resistant disease in those cases receiving MB-FFP [10,11]. In a prospective, multicentre study, patients receiving MB FFP compared to standard FFP required more PEX to remission, increased volumes of plasma to remission and increased recurrence rates in the MB FFP group [12].

Thereafter, a formal randomised prospective trial was undertaken by the same group. Comparing 25 acute TTP cases with 38 MB-TTP cases, the number of PEX to remission was higher in the MB-TTP cohort (16 versus 9; $p = 0.004$) and an increased recurrence rate, with reduced remission rate in the MB-FFP group by day 8 [13]. Therefore, the use of MB FFP is not advocated for patients with TTP. The precise reason for the discrepancies in MB-FFP compared to other standard and virally inactivated plasmas is not clear. In vitro, the coagulation factor levels and ADAMTS 13 are relatively similar. The only difference detected is in thrombin generation [14] confirmed by other groups [15]. During the preparation of MB-treated plasma, a significant drop ($p < 0.05$) in the endogenous thrombin potential (ETP) was seen after photooptical treatment. Although this was partially corrected following MB removal with a MacoPharma Blueflex filter, the changes seen remained significant but this has relatively little effect on the strength of clot formation as assessed by thrombelastometry. However, it remains to be confirmed if these effects in vitro are related to the reduced efficacy of MB-FFP in vivo.

Other viral inactivated plasma products available include the Intercept system – Amotosalen (S59) and UVA light. This uses photochemical treatment, binding DNA and RNA, inactivating viruses, bacteria and leucocytes. It retains critical levels of coagulation proteins and ADAMTS 13 [16] and in a randomised phase III controlled trial, it has been shown to be equally efficacious and safe to standard FFP in acute TTP [17].

Octaplas undergoes double viral inactivation steps using solvent detergent technology with 1% TNBP and 1% Triton X-100. It is a pooled product, using 500–1600 donations. The advantage of Octaplas is it eliminates all lipid coated viruses, including west Nile virus [18]. Plasma pooling reduces antibody titres against blood cells and plasma proteins. There are improved standards of plasma protein potencies and removal of residual blood cells and cell fragments eliminates the risk of blood cell mediated reactions. For non lipid coated viruses, which cannot be specifically eliminated, there is screening of starting material i.e. DNA for parvovirus B19 and RNA for hepatitis A, neutralising antibodies in initial plasma pools, reduction in virus threshold by dilution and the hydrophobic chromatography step.

More recently, the availability in Europe of prion reduced plasma (Octaplas LG), which has an additional affinity ligand