THROMBOTIC THROMBOCYTOPENIC PURPURA – CURRENT CONCEPTS OF PATHOGENESIS AND THERAPY

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INTRODUCTION

During the past 10 years, there has been greatly renewed interest in the pathophysiology and treatment of thrombotic thrombocytopenic purpura (TTP) and related disorders such as the hemolytic uremic syndrome (HUS). Much of this interest has been prompted by a growing body of literature demonstrating that this once relentlessly fatal disorder can now be successfully treated in the majority of patients, with case survival rates in excess of 80%. The success of empiric therapy with plasma infusion and plasma exchange has led to several lines of investigation in the laboratory that have broadened our understanding of microvascular thrombosis and the delicate balance between vascular defense mechanisms and thrombogenic insults.

TTP is a relatively rare disorder with an estimated incidence of one per million population per year, or about one one hundredth that of acute leukemia. In 1924, Moschowitz reported what is generally agreed to be the first documented case of TTP (1). This occurred in a 16-year-old girl who had the abrupt onset of fever, anemia, renal dysfunction, central nervous system impairment, and cardiac failure. She expired after fourteen days and at autopsy widespread hyaline thrombi were found in terminal arterioles and capillaries. Moschowitz postulated that the thrombi were composed of agglutinated red cells, and that the disease was caused by a circulating toxin with agglutinating and hemolytic properties. In 1936, Baehr published a series of four similar cases examined at autopsy and noted that the thrombi were in fact composed of agglutinated platelets and small amounts of fibrin (2). He recognized that thrombocytopenia was responsible for the bleeding problems in these patients. By 1954, when the subject was reviewed by Singer, 55 cases of TTP had been reported and the clinical triad of thrombocytopenic purpura, severe hemolytic anemia, and fluctuating neurologic signs was well established (3). Monroe and Strauss (1953) were the first to recognize that the hemolysis resulted from mechanical trauma to the red blood cell (4), and Brain and co-workers (1962) termed the phenomena microangiopathic hemolytic anemia (5). By 1966, when Amorosi and Ultmann published their classic review in Medicine, 271 cases had been reported, and the triad of clinical findings had been expanded to include fever and renal disease (6).

The current discussion will focus on what is presently known about this disorder with regard to clinicopathologic features, pathophysiology, and treatment.

DEFINITION

The initial problem facing a student of TTP is how to precisely define this unusual disorder. Since its etiology is unknown, and indeed may be multifactorial, it is perhaps best described as a syndrome, characterized by the constellation of severe microangiopathic hemolytic anemia, consumptive thrombocytopenia without coagulopathy, and widespread microthromboses, resulting in fluctuating neurologic deficits, abnormal urinary sediment, and fever (7,8). HUS, in contrast, is

characterized by many of the same clinical and pathologic features found in TTP, but is less frequently associated with fever or significant neurologic deficits. Unlike TTP, acute renal failure is a hallmark of the disorder and may persist following recovery from the acute process. HUS is for the most part seen in children and the outcome is often good with adequate supportive treatment, as opposed to TTP which primarily occurs in adults and has a high fatality rate without treatment. For many years, TTP and HUS were thought to represent discrete entities, despite their similarities. More recently, however, it has been suggested that they simply occupy the opposite ends of a continuum with some overlap (9). Evidence in support of this assertion is the fact that both syndromes can occur in adults and children, many organs can be involved with HUS, and renal disease may be prominent in TTP (10-12). There are also 2 reports of TTP and HUS occurring in members of the same family, suggesting a common predisposition or pathogenic mechanism (13). Despite this, as noted by Kaplan in his recent review of this topic, the gestalt of a typical case of HUS is quite different from that of a typical case of TTP. Precise definition must await the development of further information about the pathogenesis of the various clinical subsets that comprise the syndromes (10). For this reason, I have chosen to limit discussion of HUS to the areas of current research that may be relevant to mechanisms of disease in TTP.

CLINICAL FEATURES

Since 1966, there have been several literature reviews of the clinical and pathologic features of TTP, where data has been obtained from 30 or more patients. These include: Amorosi and Ultmann, 246 cases, 1924-1964 (6); Ridolfi and Bell, 275 cases, 1964-1980 (8); Kennedy et al, 48 cases, 1969-1980 (14); Petitt, 38 cases, 1950-1979 (15); Rose and Eldor, 38 cases, 1977-1986 (16).

Incidence

TTP is a relatively rare disorder. Petitt (15) noted an incidence of one case per million population per year in the Minnesota area, while Ridolfi (8) estimated that one case per year was identified at John Hopkin's Hospital, where yearly admissions exceed 45,000 and there is frequent tertiary referral. Amorosi and Ultmann (6) cited a 3:2 female:male ratio in the 246 cases they reviewed prior to 1966. Ridolfi and Bell reported a female:male ratio of 5:2 (8). All investigators agree that the majority of cases occur between the second and fourth decades of life, but that there is a broad range with occasional cases reported in infancy and in patients over the age of 70 (Figure 1) (14).

Figure 1 (14).

Age distribution of TTP in 48 patients reviewed by Kennedy et al.

Presentation

The clinical features leading patients to seek medical attention are detailed in Table 1 (7).

Table 1. Presenting Manifestations in TTP

Type	Amorosi, Ultman (246 Cases)	Ridolfi, Bell (225 Cases)	Petitt (38 Cases)	Kennedy et al (48 Cases)
Neurologic	60%	52%	92%	71%
Hemorrhagic	44%	38%	NS	74%
Malaise, weakness, fatigue	25%	29%	NS	27%
Nausea, vomiting	24%	24%	NS	14%
Fever	20%	NS	87%	14%
Pallor	17%	NS	NS	6%
Abdominal pain	11%	14%	NS	20%
Jaundice	9%	2.5%	NS	10%
Arthralgia, myalgia	7%	6%	NS	NS

Abbreviation: NS, not stated.

Nonspecific symptoms such as fatigue, malaise, and weakness, or nausea and vomiting, or fever, were identified in the majority of patients at the time of presentation. The most frequently recorded chief complaints, however, were due to neurologic abnormalities (52-92%) and hemorrhagic phenomena (38-74%) (6,7,8). Kennedy (14) noted that the majority of patients sought medical attention within the first week of becoming symptomatic. Less than 20% of patients had symptoms for longer than two weeks prior to obtaining medical attention.

Neurological Manifestations

The various neurologic signs and symptoms reported during the course of TTP are presented in detail in Table 2 (8).

Table 2 (8).

Neurologic Manifestations in TTP (218 Patients)

	#	%
Headache	68	31
Confusion	82	37
Altered mental state	32	15
Paresis	73	33
Aphasia, dysphasia	73	33
Coma	45	20
Seizures	44	20
Paresthesias	31	14
Visual problems	31	14
Ataxia, vertigo	5	2.5
Syncope	2	

Those most frequently cited include altered mental status, headache, paresis and paresthesias, aphasia and seizures. The most prominent aspect of the neurologic picture is that these findings can be evanescent and recurrent. It is not uncommon to demonstrate a unilateral hemiparesis and then several hours later find that the patient is normal or that the hemiparesis now involves the opposite side. It is also noteworthy that recurrent seizures and progressive deepening of the comatose state frequently herald the terminal phase of the disease, and at autopsy are associated with gross hemorrhagic lesions in the brain (7). Rose and Eldor's recent review emphasized that permanent neurologic deficits are not infrequent. Five of 30 survivors had a residual hemiparesis, cauda equina syndrome, dysphasia, or optic atrophy (16).

Fever

Fever is included in the classic pentad of diagnostic findings and has been found in over 90% of patients at some time during their illness, although frequently not present at the time of initial examination (6,7,8,14,15).

Bleeding

Bleeding is also very common and was present in more than 80% of patients in the two largest series (Table 3) (6). The skin is the most frequent site of bleeding but retinal hemorrhages, gross hematuria, gastrointestinal and gynecologic bleeding also occur, although the amount of blood lost is usually trivial.

Table 3 (6).

Hemorrhagic Manifestations in 251 Patients with TTP

	Cases	%
Any hemorrhagic manifestation...	241	96
Petechiae, purpura, ecchymoses...	157	63
Retinal hemorrhages.....	47	19
Hematuria, gross.....	45	18
Epistaxis.....	29	12
Gingival hemorrhage.....	20	8
Melena.....	20	8
Menorrhagia.....	19	8
Hematemesis.....	16	6
Hemoptysis.....	4	2
Thrombocytopenia.....	216/224	96

Renal Manifestations

Renal involvement, manifest by significant proteinuria, hematuria, purpura, and casts or by azotemia was found in 88% of the cases reviewed by Amorosi (6). Ridolfi found that hematuria was the most frequent renal abnormality (76%) and in almost one-fifth of the cases was macroscopic. He identified proteinuria in 59% of patients and some degree of renal function impairment in 57% (8). This is similar to the 48% noted by Amorosi in his earlier series (6). Ridolfi also noted that approximately 11% of patients went to on to develop acute renal failure (Table 4) (8). Similar results were found by Eknoyan in his recent review of the literature from 1966 on (17). Of interest, Rose and Eldor found no residual renal disease in survivors (16).

TABLE 4. Renal Manifestations in TTP (196 Patients)

	#	%
Hematuria (any)	149	76
Gross	30	15
Proteinuria (any)	116	59
2-5 g/day	3	
>5 g/day	3	
SUN >30 mg/dl and/or creatinine >2.0 mg/dl	89	45
SUN >50 mg/dl and/or creatinine >5.0 mg/dl	24	12
Acute renal failure	23	11.5

Pulmonary Manifestations

Prior to 1978, the presence of pulmonary abnormalities had not been reported in association with TTP. In his study of 7 consecutive patients with TTP, Bone et al documented respiratory impairment in 6 (18). X-ray abnormalities consisted of diffuse alveolar and interstitial infiltrates in 4 and localized abnormalities in 2. 5 of 6 patients

became overtly hypoxemic and 4 of these patients ultimately died. An ARDS syndrome has since been reported by other investigators (19), although the frequency of primary pulmonary complications is still not clear since most reports have failed to document normal pulmonary capillary wedge pressures, resulting in confusion about the effects of volume overload from renal insufficiency or congestive heart failure.

Cardiac Manifestations

Problems related to cardiac function are not a major feature of the clinical course of most patients. In their review of 17 autopsied cases presenting to the Johns Hopkin's Hospital from 1950-1979, Ridolfi et al (20) found that symptoms and signs suggesting mild-moderate left or right sided congestive heart failure were present in 9 patients, and pulmonary infiltrates in 7. While extensive microvascular thromboses were documented in 13 of 17 autopsies, associated evidence of myocardial damage was minimal, suggesting once again that much of the symptomatology is related to volume overload in the setting of renal insufficiency, or alternatively high-output cardiac failure secondary to severe anemia. Of note, extensive thrombosis and hemorrhage were found in 7 of 10 conducting systems examined by serial histologic sectioning. 2 of these patients had developed evidence of bradyarrhythmias and the authors speculate that such abnormalities may contribute to the sudden demise of some of these patients.

Eye Changes

Ocular involvement occurs in about 8% of patients with TTP (21,22). Typical primary ocular manifestations include neovascular reaction in the disc and retina, optic atrophy, retinal, choroidal, and intraorbital hemorrhages, and retinal detachment. Other manifestations such as diplopia, homonymous hemianopsia, external ocular palsies or papilledema result from primary CNS involvement.

Other Organ Systems

Hepatosplenomegaly is present in approximately 20% of patients (6). Abdominal pain is seen in up to 15% and is probably due to bowel ischemia or pancreatitis which rarely is the presenting manifestation of the syndrome (7,8). Indeed, diabetes, presumably a result of pancreatic islet cell infarction, was reported in three cases reviewed by Amorosi and Ultmann (6).

CLINICAL COURSE

It has become apparent that at least two clinical courses of TTP can be demonstrated: acute and relapsing. Patients who survive an initial episode without evidence of recurrence are said to have had "acute" TTP. Those whose disease recurs following variable periods of complete remission are said to have "relapsing" TTP. Some have also designated a third type "chronic", referring to TTP which does not

definitively respond to therapy for months or even years, but does not result in the demise of the patient.

Rifolfi and Bell reported a relapse rate of 7.5% in their review of cases from 1964-1980 and noted that 50% of patients died following recurrence (comparable to the mortality rate they reported for acute TTP) (8). This is similar to the 5.5% relapse rate noted by Kennedy (14) and others, but far lower than the 37% recently reported by Rose and Eldor (16). The latter most likely reflects the improved survival for original episodes (Table 5) and may reflect the use of plasma therapy in 37 of 38 patients in Rose and Eldor's series. Rose and Eldor also noted that 50% of those with "relapsing" TTP had 2 or more recurrences and that the mortality from recurrent episodes was no different. Patients who died had an average survival of 22 days. The average duration of disease to remission in survivors was 32 days.

Table 5 (adapted from Kwaan (7)).

Mortality Rate in TTP

	Period of Review	No. of Survivors	Total No. of Patients	Mortality Rate
Amorosi and Ultmann	1925-1964	13	271	95%
Ridolphi and Bell	1964-1980	127	275	54%
Kennedy et al	1969-1980	18	48	62.5%
Petitt	1950-1979	18	38	53%
Rose and Eldor	1977-1985	30	38	21.1%

A scoring system was also devised to compare the severity of typical findings at presentation in survivors versus non-survivors (Table 6) (16). The average score of non-survivors was 6.5, significantly higher than the 5.1 of survivors. The single factor found to be predictive of a poor prognosis was severe renal failure (creatinine greater than 2.5 mg/dl), results similar to those previously reported by Kennedy et al (14).

Table 6 (16).

Severity Scoring of Patients with Thrombotic Thrombocytopenic Purpura

Level of Abnormality	System Affected: Neurologic Findings	System Affected: Renal Function Impairment	Platelet Count at Presentation ($\times 10^9$/liter)	Hemoglobin Level at Presentation (g/dl)
0	None	None	>100	>12
1	Confusion, lethargy, behavioral changes	30 mg/dl < BUN < 70 mg/dl and/or 1.5 mg/dl < creatinine < 2.5 mg/dl and/or proteinuria > 2 g/day and/or hematuria	20–100	9–12
2	Focal neurologic deficits, convulsions, stupor, coma	BUN ≥70 mg/dl and/or creatinine ≥2.5 mg/dl and/or dialysis	<20	<9

BUN = blood urea nitrogen.

PATHOLOGY

The histopathology of TTP is characterized by the hyaline thrombus, often partially rather than completely occluding the lumen of involved vessels. Originally thought by Moschowitz to represent agglutinated red blood cells, immunofluorescent studies reveal that it is in fact composed of fibrin and platelets, occasionally with small amounts of complement and immunoglobulins (7,23,24,25,26). Neame et al, using both light and electron microscopic techniques, described three states in the evolution of platelet thrombi in TTP. First, an intravascular deposit of loosely aggregated platelets, next a dense aggregate, sometimes rimmed with thin layers of fibrin at the perimeter, and last a variable mixture of platelets and fibrin tightly packed together. Proliferating endothelial cells are frequently seen covering the thrombus, and in the oldest lesions the endothelial hyperplasia can be so extensive that the thrombus appears subendothelial in origin (27,28). Current thinking is that the subendothelial lesions may originate from intraluminal thrombi, but represent a later stage in their evolution (7). Characteristic of the lesion is its occurrence in arterioles and capillaries but sparing the venules. The underlying vessel shows no cellular infiltration or other signs of inflammatory reaction consistent with a vasculitis (7,25,27,28,29). At autopsy, the most severely affected organs include the brain, heart, kidneys, pancreas, spleen, and adrenal gland. Lesser degrees of involvement are seen in the lung, GI tract, gallbladder, skeletal muscles, retina, pituitary gland, ovaries, uterus and testes (6,7,8).

In the face of these widespread microthromboses, involved organs tend to show relatively mild parenchymal changes with only occasional areas of necrosis and hemorrhage. Discrete infarcts are unusual and when they occur, do so principally in the brain, kidney and pancreas (6,7,8). Bernheim has postulated that the absence of tissue infarction may be due to sparing of venous channels, thus providing some collateral circulation (30).

LABORATORY FEATURES OF TTP

Hematologic

Microangiopathic hemolytic anemia is a sine qua non of TTP, and it is often severe. Approximately 90% of patients in all reported series have hemoglobin values less than 10 gm/dl and in at least one third of these it is under 6.5 gm/dl (6,7,8,14,15). TTP without anemia is unusual, although in 2-3% of cases the hemolytic process is compensated for fully. The anemia is invariably of the normochromic, normocytic variety and a peripheral blood smear is remarkable for numerous schistocytes. Indeed, the diagnosis of TTP is untenable if red cell fragmentation is not an impressive part of the picture (31). Polychromatophilia, basophilic stippling, and nucleated red cells are frequently present and the mean reticulocyte count in Amorosi's series was approximately 20% (6).

The hemolytic anemia is characteristically Coomb's negative and the occasional cases in the literature reported to be Coomb's positive were associated with other ongoing disease processes such as systemic lupus erythematosus (SLE) (8). While indirect bilirubin elevation, and depression of haptoglobin or hemopexin levels are reported in the majority of patients in which these are measured, the serum LDH level is generally thought to be the most useful indicator of the severity of hemolysis over time when used in conjunction with the hemoglobin level and reticulocyte count (7,31).

White blood cell counts are generally increased moderately with a slight left shift. Leukopenia has only been reported in a total of 10 cases, while leukemoid reactions may occur in up to 10% of patients (6,7,8).

Severe thrombocytopenia is characteristic of TTP. Platelet counts less than 20,000 mm^3 were seen in over half the patients in the series reported by Ridolfi and Bell, and Kennedy (8,14). Kwaan has emphasized that large day-to-day fluctuations in the platelet count are common, particularly when plasma therapy is instituted (7). The peripheral smear is frequently remarkable for the presence of giant platelets (8).

Coagulation Studies

The vast majority of patients with TTP will have either normal or mildly deranged coagulation studies. In Ridolfi and Bell's review, prothrombin times were normal in 88%, partial thromboplastin times were normal in 94%, and plasma fibrinogen was normal in 79%. In only seven cases was the plasma fibrinogen level less than 100 mg/dl. These rare cases are thought to reflect an unusually great activation of the coagulation process resulting in concomitant DIC (8). On the other hand, low titers of fibrin split products (FSP) are frequently seen in TTP and do not detract from the diagnosis (7,8,14,15,31). Ridolfi found that 25%, or 17/67 patients tested, were positive for fibrin-split products at titers greater than 1:32. The increase in concentration of

FSP most likely results from lysis of fibrin that has been deposited around platelet clumps (8).

DIFFERENTIAL DIAGNOSIS

When a previously healthy individual presents with the classic triad of thrombocytopenia, microangiopathic hemolytic anemia, and neurologic dysfunction, the diagnosis of TTP is generally straightforward. Nevertheless, there are several other disorders that can mimic some of its manifestations (Table 7) (31).

Table 7 (Adapted from Kacich and Linker (31)).

Differential Diagnosis of
Thrombotic Thrombocytopenic Purpura (TTP)

- Disseminated intravascular coagulation (DIC)
- Evans' syndrome
- Vasculitis
  - Systemic lupus erythematosus
  - Severe glomerulonephritis
  - Other
- Other causes of microangiopathic hemolytic anemia (MHA)
  - Vascular malformations
  - Prostetic valves
  - Metastatic adenocarcinoma
  - Malignant hypertension
- TTP-like syndromes
  - Hemolytic-uremic syndrome
  - Eclampsia

Disseminated intravascular coagulation can lead to the presentation of an ill and febrile patient with bleeding, and evidence of microangiopathy on peripheral smear. DIC, however, is not usually characterized by hemolysis of the severity seen in TTP (7,8,31). Moreover, patients with TTP generally do not exhibit abnormal tests of coagulation, and when they do alterations are mild (8,31,32). There is usually an apparent underlying disorder in patients with DIC such as carcinomatosis or sepsis. This is exceptional in patients with TTP (31). Evan's syndrome refers to the combination of immune hemolytic anemia and immune thrombocytopenia, which could be confused with TTP. The hemolytic anemia in Evan's syndrome, however, is Coomb's positive and a peripheral smear will show many spherocytes. Red cell fragmentation should not be present (7,8,31).

SLE is a multisystem disorder which may manifest anemia, thrombocytopenia, fever, neurologic abnormalities and renal disease. The hemolytic anemia is generally Coomb's positive and serologic studies indicative of an autoimmune process are diagnostically discriminating. In the presence of a lupus-related vasculitis, however, microangiopathic findings identical to those of TTP may be seen on a peripheral smear.

In these instances biopsy of involved vessels may be useful since the inflammatory lesion of vasculitis should appear very different from the bland thrombus of TTP (7,8,31). Biopsies of the gingiva or bone marrow demonstrate the characteristic findings of TTP in 30-50% of cases (7,33). Kwaan was able to obtain confirmatory tissue diagnosis in 5 of 12 patients with TTP by skin biopsy of petechial lesions (7). Others have not found this. Since a skin biopsy causes only minimal discomfort, however, and bleeding is readily controlled, this may be a preferable first step in confusing cases (7).

Other causes of microangiopathy are shown in Table 7 (31), but these are usually readily distinguished from TTP on the basis of a history and physical examination. There is also a category of TTP-like syndromes that includes hemolytic-uremic syndrome and eclampsia. As mentioned previously, HUS may represent a clinical syndrome within the same spectrum of disorders as TTP (34). When there is significant renal involvement without other systemic findings the diagnosis is clear. Overlap cases, however, particularly in the adult, may be impossible to distinguish. Eclampsia is another disorder which may be confused with TTP in the pregnant patient, and is an important diagnosis to make since treatment involves delivery of the fetus. In a recent review of thrombotic microangiopathy in the peripartum period, Weiner (35) summarized current evidence that eclampsia differs from TTP and HUS in that there is ongoing, subclinical consumption of coagulation factors. A low antithrombin III level is typically seen in these patients and may provide a useful diagnostic tool.

ASSOCIATION OF TTP WITH OTHER CONDITIONS

Although TTP most frequently presents in previously healthy individuals without evidence of preexisting disease, there are many reports in the literature of associations with infection, pregnancy, immunologic disorders, environmental factors, or even genetic predisposition (7,8,36,37,38,39).

TTP has been described in association with systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, and Sjogren's syndrome (36). As pointed out by Neame in his review of immunologic factors in TTP, all the aforementioned disorders can result in small vessel vasculitis which may produce a similar clinical picture despite very different underlying pathology (36). Ridolfi and Bell felt that convincing cases of SLE associated with TTP were rare. In their review of 275 cases of TTP from 1964 on, 5 cases of associated SLE were reported, but only 3 fulfilled diagnostic criteria for both diseases (8). Rothfield on the other hand reviewed 433 cases of SLE and found only 2 cases of TTP (40). Thus, SLE is probably only rarely associated with TTP (36,39,40).

Suggestions that TTP could have an infectious etiology are based on the frequent history of a viral type prodrome, the occasional occurrence in members of the same household and rarely, the isolation of an infectious agent or serological evidence of recent infection (Table 8) (36).

Table 8 (Adapted from Neame (36)) (41-55)

TTP or TTP-Like Disorder Associated with Infection of Postvaccination

Author(s)	Age/Sex	Associated Infection or Vaccination	Other Features
Nussbaum & Dameshek 1957	30 F	Probable meningo-coccemia	Rapid response to penicillin & sulfadiazine
Antes 1958	24 M	Influenza vaccination	Review of previous cases. TTP with small-pox vaccination (1), influenza immunization (1), tetanus antitoxin (1)
Frick & Hitzig 1960	15/24M	Triple antigen & TAB vaccination	Onset within 24 hrs. vaccination. Agamma-globulinemia and lympho-penia.
Reisfield 1962	32 F	Virus ? Infectious mononucleosis	Thrombotic lesions produced in rabbits.
Mettler 1968	22 F	Microtatobiote isolated	Microtatobiote reported in 2 patients. HUS and 1 patient TTP.
Brown et al 1973	23 F	Influenza vaccination	TTP 14 days post-vaccination
Berberich et al 1974	15 F 6 M	Coxsackie, B.	Increase in Coxsackie B. Neutralizing antibody titres.
Reynolds et al 1976	17 F	Mycoplasma	Complement fixing antibody to mycoplasma pneumoniae increased.
Myers et al 1980	27 M	Herpes simplex	16-fold increase in complement fixation titer.
Wasserstein et al 1981	50 M	Influenza A_2	Positive throat culture
Riggs et al 1982	45 M	Legionella	(+) lung biopsy DFA
Morton et al 1985	72 F	Campylobacter Jejeuni	(+) stool culture
Ramsey et al 1986	53 F	E. Coli 0157:H7	(+) stool culture
Turner et al 1986	25 M	Rickettsia rickettsii	20-fold increase in IHA titer (-) biopsy for TTP.

TTP has also been reported following the administration of various antibiotics, particularly sulfonamides and penicillin, and following vaccination (36,39). In most cases, the infection, drug, or vaccination antedates the development of TTP by days or even weeks, or the diagnosis of TTP is not well established. Despite this, the more recent literature contains a few case reports substantiating an etiologic link, although it is clear that no single infection or drug is responsible.

Toxins have also been suggested as possible etiologic agents. Stonesifer reported the occurrence of TTP subsequent to carbon monoxide intoxication, which is particularly intriguing since carbon monoxide is known to cause endothelial damage (56). There are also numerous reports of thrombotic microangiopathy as a consequence of treatment with chemotherapeutic agents, although these have primarily been cases of HUS (39,57).

A genetic predisposition to TTP is suggested by several case reports of TTP occurring within the same family at different times. Wallace et al described a family in which 4 siblings suffered from recurrent episodes of TTP (58). Paz et al documented the simultaneous occurrence of TTP in 2 sisters, living together (59). Fuchs et al also documented TTP in 2 sisters, both during pregnancy (60).

The latter case also suggests an association with pregnancy, which has been reported by others. Neame reviewed these case reports in 1980 and concluded that it is still unclear if there is a true association with pregnancy or the post-partum period since the disease itself is most common in young females of childbearing age, and a careful review of the literature suggests that some cases originally reported as TTP were in reality pre-eclampsia or eclampsia (36).

PATHOGENESIS

While a specific etiology for TTP has yet to be determined, there is general agreement that widespread microthrombus formation and endothelial injury are the hallmarks of this disease. It has proven difficult, however, from pathologic study of the vascular lesions to determine whether endothelial damage precedes the formation of platelet thrombi or results from it (7,23,26,28). Before discussing the major lines of investigation into the pathogenesis of TTP that have been pursued in recent years, it is appropriate to briefly review the various properties of the microvasculature that normally render it resistant to thrombosis.

Blood vessels are lined with a confluent monolayer of endothelial cells resting on an underlying extracellular matrix. Unstimulated platelets will not adhere to intact endothelium in vivo, and only minimally in vitro (61). Rather, platelet adhesion to vascular walls occurs at sites of exposed subendothelium. This nonthrombogenic property of the endothelium appears intrinsic to the endothelial cell membrane, and may be related to the negative charge of both the endothelial and platelet cell membranes (61). Several other factors also contribute to the antithrombotic effects of the vascular endothelium. Endothelial cells modify the activity of aggregating platelets to some extent by virtue of their capacity to take up and metabolize platelet release products including ADP, serotonin, and thrombin, facilitating both complexation to antithrombin III and clearance (9,61). A specific endothelial cell surface protein, thrombomodulin, acts as a cofactor for the conversion of Protein C to an active protease. Activated protein C exerts an anticoagulant effect by

inactivating Factors V and VIII, and stimulates fibrinolytic activity by forming stable 1:1 complexes with plasminogen activator inhibitor 1, the principal physiologic inhibitor of tissue plasminogen activator (t-PA). t-PA, the principal activator of the endogenous fibrinolytic system, is synthesized and secreted by vascular endothelial cells. This protease converts plasminogen adsorbed to the fibrin skeleton of a clot into plasmin, a serine protease that catalyzes the proteolytic degradation of fibrin (9,61). Finally, endothelial cells synthesize prostacyclin (PGI_2) which is both a vasodilator and a potent inhibitor of platelet aggregation. PGI_2 binds to a specific receptor on platelet membranes, stimulating adenylate cyclase. The resulting elevation in intraplatelet cAMP inhibits platelet shape change, secretion, aggregation, binding of vWF and fibrinogen to specific surface receptors (glycoprotein Ib or IIa/IIIb complex), and adhesion to the endothelial substratum. PGI_2 levels in the capillary bed are probably only high enough to mildly inhibit platelet function under normal conditions. However, when platelets undergo contact activation at sites of endothelial injury, thrombin, serotonin, and other platelet alpha-granule components may greatly stimulate local endothelial PGI_2 production, a defense mechanism in limiting the extent of thrombus formation (9,61,62).

Since the maintenance of microvascular patency depends on the balance between these vascular defense mechanisms and various thrombogenic insults, it is likely that microvascular thrombosis in TTP develops as a consequence of compromised defense mechanisms, overwhelming insults that overpower defense mechanisms, or both (9,37,62,63).

Inadequate Defense Mechanisms

1. Alterations in the coagulation system and fibrinolysis.

Despite widespread microthrombus formation in TTP, generally only minimal abnormalities in coagulation studies are observed. This is in striking contrast to the syndrome of disseminated intravascular coagulation (DIC), where consumption of fibrinogen and coagulation factors, and production of fibrin degradation products, far exceeds the degree of microthrombus formation (32,37). Harker and Slichter (64) have compared the turnover of platelets and fibrinogen in patients with TTP or HUS to that in patients with DIC. These authors noted a 4-fold increase in the destruction of platelets in TTP with normal fibrinogen turnover, while patients with DIC demonstrated destruction of both platelets and fibrinogen at nearly 5-fold greater than normal rates. Similarly, most investigators have observed normal levels of antithrombin III, alpha-2 macroglobulin, alpha-1 antitrypsin, C1 esterase inhibitor, and protein C in patients with TTP/HUS (37), although a recent report cited depressed Protein C levels in 3 of 6 TTP patients examined (65).

Kwaan (29,66) has hypothesized that the lack of fibrinogen consumption in TTP results from defective fibrinolysis at the site of microthrombus deposition. He measured fibrinolytic activity in tissues obtained from 14 TTP patients using a modified fibrin slide technique, and observed normal fibrinolytic activity in unaffected vessels, but

absent activity in all tissues at the sites of microthrombus formation. Similar studies on tissues from patients with DIC have shown increased fibrinolytic activity. The decrease in fibrinolytic activity observed in TTP tissues is similar to that seen in experimental models of thrombosis in which vascular wall damage is induced by electrical current or toxic chemicals, leading to the suggestion that primary endothelial injury may be responsible for these findings (9,37,66). Since platelets synthesize plasminogen activitor inhibitor 1, however, and release this protein from alpha-granules during activation, the observed decrease in plasminogen activator activity at sites of microthrombus formation may simply relfect the ongoing platelet aggregation at these sites (37).

Glas-Greenwalt et al (65) recently reported that tissue plasminogen activator (t-PA) activity was markedly diminished in the plasma of 2 patients with TTP, despite normal t-PA antigen levels, consistent with an increase in plasminogen activator inhibitor activity. This abnormality persisted during clinical remissions, suggesting an underlying predisposition to thrombosis. As previously noted by Lian (37), diminished t-PA activity will aggravate the clinical course of TTP by stabilizing thrombi, whatever the original stimulus for thrombus formation.

2) Decreased PGI_2 activity.

The eicosanoid prostacyclin (PGI_2), synthesized and secreted from vascular endothelial cells in response to a variety of stimuli as noted previously, is a potent inhibitor of platelet aggregation (61). In 1978, Remuzzi et al (67) reported that vein biopsy specimens taken from 2 adult patients with HUS and 1 patient with TTP had reduced ability to inhibit platelet aggregation. Plasma taken from the 2 adults with HUS during the acute phase of their illness showed diminished platelet disaggregating activity when incubated with exhausted rat aortic rings or cultured endothelial cells. Decreased serum levels of 6-keto PGF_1, the stable metabolite of PGI_2, were found, suggesting diminished endothelial synthesis. Treatment with fresh frozen plasma was reported to reverse the defects in prostacyclin production (68,69). Since that time, several additional reports of deficient PGI_2 production in patients with thrombotic microangiopathy (TTP and HUS) have appeared, although most of these have concerned children with HUS (Table 9) (9,67,70-80).

Table 9 (Adapted from Remuzzi (9)).

Plasma 6-keto $PGF_{1\alpha}$, Vascular Generation of PGI_2 and PGI_2-Stimulating Activity

Author		Syndrome	Patient Age/Sex	Plasma Levels of 6-keto-$PGF_{1\alpha}$	Vascular Generation of PGI_2	PGI_2-Stimulating Activity
Remuzzi	1978	HUS	54/F 56/F		Undetectable	Decreased
Hensby	1979	TTP	45/F	Undetectable	--	--
Webster	1980	HUS	31/F	Decreased	--	--
Machin	1980	TTP	27/F	Undetectable	--	Absent
Wiles	1981	HUS	19/F	--	--	Decreased
Jorgensen	1981	HUS	2/F	--	--	Absent
Chen	1981	TTP	39/M	--	--	Normal
Defreyn	1982	HUS	5/F	--	Undetectable	Decreased
Levin	1983	HUS	13 children	--	--	Decrease in sporadic forms; normal in epidemic forms
Stuart	1983	HUS	4 mo/M	--	Undetectable	Decreased
Walters	1985	HUS	35 children	--	--	Decreased in atypical forms
Stuart	1985	HUS	5 children	Increased (Epidemic form)	--	--
Turi	1986	HUS	10 children	--	--	Decreased or absent
Siegler	1986	HUS	22 children	--	--	Decreased in 6

In the few published studies available, decreased PGI_2 production has been an inconsistent finding, although an association with the sporadic or atypical form of the syndrome has been more regularly noted. Remuzzi (62) has reported that the deficiency of plasma PGI_2 activity found during the acute phase of HUS may persist after clinical remission, and there are three reports of similar defects occurring in unaffected family members of HUS patients (73,74,79).

Several authors have reported that plasma from patients with TTP/HUS contains a factor(s) which antagonizes the biological activity of PGI_2 (62,77). Chen et al (75) have reported normal PGI_2 metabolite levels in the plasma of a 39 year-old man with chronic relapsing TTP, but diminished effective PGI_2 activity. The rate of PGI_2 degradation n this patient was significantly greater than in normal controls, and similar observations in 2 additional patients have been reported by Wu (63). Studies on serum samples obtained from these patients demonstrated diminished binding of PGI_2. The restoration of normal binding capacity by the addition of normal serum produced a significant increase in the effective half-life of PGI_2 activity in in-vitro assays.

It remains unclear whether defects in either PGI_2 synthesis or stability contribute to the pathogenesis of TTP. Exhausted prostacyclin production may simply reflect repeated injury to vascular endothelium from as yet unidentified factors (37,62). Alternatively, beta-thromboglobulin, secreted from platelets during the release reaction, binds to the surface of endothelial cells and inhibits PGI_2 production. Thus the observed decrease in PGI_2 activity in TTP may be secondary to ongoing platelet aggregation (37).

Insults to the Microvasculature

1. Microbial Infection

While clear evidence regularly linking TTP to any infectious precipitant is lacking, an association between infection and HUS in children has been better established (9,10,11,12). The organisms most frequently found in association with typical cases of HUS (preceded by gastroenteritis) have been verotoxin-producing strains of E Coli or Shigella. Koster found that 19 of 240 patients followed prospectively with Shigellosis in Bangladesh went on to develop HUS (81). In 1985, Karmali reported that 30 of 40 pediatric patients with "idiopathic" HUS screened for evidence of infection by verotoxin-producing E Coli were positive (82). Verotoxin is so named because it is cytotoxic for green monkey kidney cells in tissue culture. It is known that laboratory animals that die following the ingestion of verotoxin have lesions in several tissues compatible with ischemic injury (83-84). Both Cavanagh (83) and Bridgewater (84) have proposed that verotoxin acts by damaging endothelial cells of small blood vessels. Butler (85), in contrast, has developed an animal model of HUS where renal cortical necrosis can be produced by injections of lipopolysaccharides from Shigella species.

Others have found an association between HUS and Strep pneumoniae infection. By 1984 a total of 8 children had been described who developed HUS following pneumococcal bacteremia (86). Neuraminidase derived from bacteria, especially S. pneumoniae, and possibly from some viruses (influenza), can cleave N-acetyl-neuraminic acid exposing the Thomsen-Friedenreich antigen normally hidden on erythrocytes, platelets, endothelial cells, lymphocytes, and glycosubstances in the brain. Exposure of this antigen could allow agglutination with anti-TF IgM antibodies, normally present in serum, leading to renal capillary damage and erythrocyte and platelet agglutination (10). Klein, and later Alon, found immunofluorescent-labeled peanut agglutinin deposition in renal tissue of pediatric patients with HUS following pneumococcal sepsis, consistent with exposure of the TF antigen (86). It remains to be determined, however, whether similar mechanisms are operative in patients with TTP.

2. Immune-Mediated

There have been 2 reports in which IgM and complement (C_3) were demonstrated by immunofluorescent microscopy in capillaries and arterioles of patients with TTP, leading some to suggest a primary immune-mediated injury and to speculate on the role of circulating immune complexes (87,88). Others, however, have found no evidence of immunoglobins or complement in involved vessels (Table 10) (25,29,47,89).

Table 10 (Adapted from Neame (36)).

Vascular Deposits of Complement and Immunoglobulin in TTP

Author(s)	Date	Site	Complement	Immunoglobulin IgM	IgG
Feldman et al	1966	Splenic & renal tissues	C3 absent	ND*	present
Mant et al	1972	Kidney, myocardium brain, spleen	C3 present	present	absent
Berberich et al	1977	Kidney biopsy	C3 absent	ND*	absent
Weisenburger et al	1978	Kidney, brain	C3 present	present	absent
Celada & Perrin	1978	Skin biopsy	C1q,C3 absent	"Immunoglobulins" negative	
Kwaan et al	1980	Spleen & Skin	ND*	"Immunoglobulins" negative	

* ND=not done

Furthermore, the search for circulating immune complexes has been largely unrewarding - only one positive result has been reported to date in acute idiopathic TTP (36,89-93), although reports of positive assays for immune complexes in patients with TTP-like disorders associated with infection or malignancy for example do exist (50,51,55,94). Wall et al (95), and Foster and Anderson (96) reported a complement-dependent cytotoxic factor for endothelial cells in the serum of 10 patients with TTP. Weisenburger et al (93) could not confirm their results in his 3 patients. More recently, Burns and Zucker-Franklin (97) demonstrated the presence of IgG antibodies directed against endothelial cells in the sera of 3 consecutive patients with TTP. This antibody was observed by immunofluorescent techniques to bind specifically to cultured human endothelial cells and its cytotoxic effect was demonstrated morphologically and by radioisotope permeability. The problem with all these reports is that anti-HLA antibodies would also be detected by the techniques used, an important confounding variable since these patients are multiply transfused and often previously pregnant (31). Other conflicting data is found in reports of healthy fetuses delivered from mothers with ongoing TTP (37). Wurzel has reported that autopsy specimens from a pregnant woman who died of TTP revealed thrombi in the maternal circulation of the placenta, but not in the fetal circulation, suggesting that the factor responsible for TTP, unlike an IgG antibody, is not capable of crossing the placenta (98).

3. Toxic

A syndrome resembling HUS and less commonly TTP has been described following treatment with several chemotherapeutic agents (57).

Mitomycin C has been reported most frequently with over 128 documented cases in the literature and an estimated incidence as high as 10% (57). There is considerable evidence that Mitomycin C itself gives rise to renal vascular endothelial cell injury resulting in thrombotic microangiopathy. The vast majority of patients have been in clinical remission when this develops and are often receiving the drug as adjunct therapy following surgical resection of a primary tumor. Moreover, Cattel (100) has recently developed an experimental model in the rat where lesions indistinguishable from those of HUS can be induced by perfusion of the renal artery with mitomycin. She noted that the earliest abnormalities were small areas of glomerular endothelial damage followed by platelet accumulation and thrombosis. It has also been demonstrated that mitomycin C can have a direct depressant effect on the in vitro production of prostacyclin by human umbilical cord endothelial cells (101).

HUS has also been reported in transplant recipients receiving cyclosporin A (39,57), and it has been shown that CsA exerts a direct, dose-dependent cytotoxic effect on cultured endothelial cells (102), as well as reducing renal synthesis of prostaglandins (103), and in experimental animals, decreasing prostaglandin "stimulating" activity leading to impaired prostacyclin production (104).

Insults to Platelets

1. Immune-Mediated

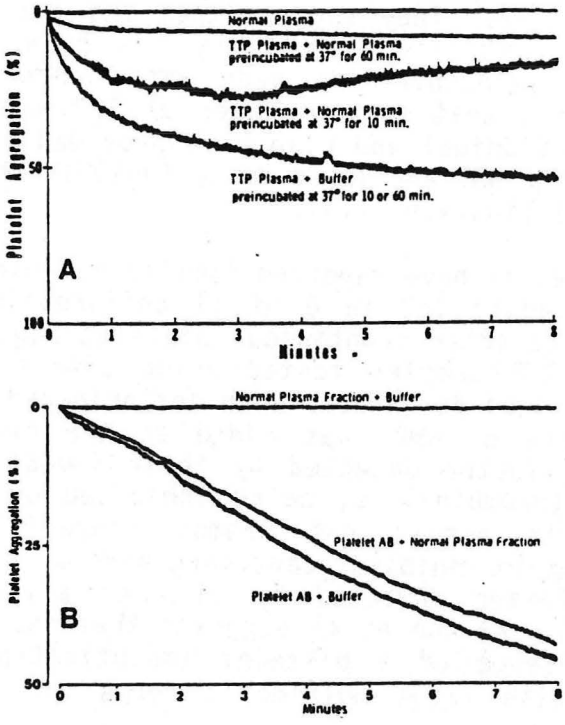
Morrison and McMillan (105) demonstrated the presence of an IgG immunoglobulin on the platelet surface in 2 patients with TTP using an Fab-anti-Fab assay, findings later confirmed by Kelton (106), and Sims and Boswell (107) in 20 additional patients using a different technique (quantitative consumption assay). Ansell (91), however, could not confirm their results. In all reported cases, elevated platelet-associated immunoglobulin levels returned to normal following successful treatment with plasma exchange. This data could indicate the presence of an IgG related anti-platelet antibody, or immune complexes adherent to platelets, but more likely represents non-specific absorption of IgG onto already damaged platelets (36,37).

2. Platelet Aggregating Factors

It is of interest that treatment of normal plasma with verotoxin or neuraminidase will produce spontaneous platelet agglutinating activity (108). Treatment of plasma from patients with von Willebrand's disease with neuraminidase, however, does not produce such activity, suggesting that neuraminidase is dependent on changing vWF (108). Purified vWF has been shown to be deasialated by neuraminidase resulting in asialo forms that are capable of spontaneously agglutinating platelets (109). (Normal vWF requires the addition of ristocetin or other small cationic substances to partially neutralize the negative surface charge on platelets, since normal vWFs are also negatively charged). Whether such abnormalities may play a role in infection - related HUS or even TTP remains unclear.

In 1979, Lian et al (110) first demonstrated that plasma samples from 3 patients during acute TTP could induce in vitro clumping of washed platelets from both normal donors and patients during remission. This observation has since been confirmed by Ansell et al (91), Brandt et al (111), Byrnes et al (112) and Bukowski et al (113). Since the platelet aggregating factor was not dialyzable it should have not been epinephrine, ADP, serotonin, or prostaglandins. ADP and serotonin were released during the aggregation, however, they were not felt to be essential since the aggregation was shown to occur in the presence of apyrase or creatine phosphate and phosphokinase . Thrombin and trypsin were excluded since the platelet aggregating factor was not adsorbed by $Al(OH)_3$ and was not inhibited by diisopropylflurophosphate, hirudin, or heparin in the presence of normal amounts of antithrombin III. It was not collagen because the platelet agglutination was not inhibited by ASA. While the presence of isoantibodies, secondary to repeated transfusions, could cause clumping of platelets, Lian demonstrated that the acute TTP plasma also caused agglutination of autologous platelets obtained after recovery. Furthermore, he demonstrated that the platelet aggregation could be inhibited by prior incubation of TTP plasma with normal plasma in a time dependent fashion, which was not true of plasma containing isoantibodies (Figure 2) (110).

Figure 2 (110).



(A) Time-dependent inhibition of TTP plasma-induced platelet aggregation. (B) Lack of inhibition of platelet aggregation after incubation of three parts of platelet isoantibody and one part of the 30% to 50% ammonium sulfate fraction of normal plasma or buffer at 37°C for one hour. Reprinted with permission.[110]

Lian went on to show that plasma samples from 20 of 30 TTP patients possessed platelet agglutinating activity that was inhibited by normal plasma but not heparin or hirudin (37). In contrast, platelet agglutination induced by plasma from patients with autoimmune thrombocytopenia, Evan's syndrome, DIC, or vasculitis was not influenced by normal plasma.

In 1985, Siddiqui and Lian reported the purification of a 37,000 dalton agglutinating factor (PAFp37) with characteristics of a glycoprotein from the plasma of a patient with typical manifestions of TTP (114). PAFp37 was found to be present in 2 of another 4 TTP plasmas possessing platelet agglutinating activity and was not demonstrated in normal controls, patients with ITP, or DIC.

In a subsequent paper they determined that normal adult IgG could inhibit the platelet aggregation induced by acute TTP plasma from 2 patients, and that this ability resided in the Fab fragment (115). IgG obtained initially from 5 infants and young children under the age of 4 years did not possess any inhibitory activity, however, as 1 child grew older his IgG was seen to inhibit aggregation in one and then the other TTP plasma. Moreover, IgG purified from the TTP plasma during active disease failed to inhibit aggregation caused by the same plasma, but following recovery the IgG effectively inhibited aggregation. The investigators suggested that these results are consistent with the presence of heterogenous platelet-agglutinating factors in at least some patients with TTP. They suggest that the IgG present in normal adult plasma may be partially responsible for the success of plasma therapy, and that the seroconversion seen with increasing age and after the disease suggests that certain cases of TTP may be caused by infection. Most recently Siddiqui and Lian have provided evidence that IgG forms a complex with PAF p37 and in so doing inhibits the ability of this factor to induce agglutination (116).

Monnens et al have reported similar platelet agglutinating activity inhibited by adult IgG in 6 of 11 children with epidemic HUS (117). Kelton et al detected spontaneous platelet agglutinating activity in 20 of 47 acute TTP samples tested using Lian's techniques (106). This increased to 41 of 48 however when defibrinated cryoprecipitate (rich in large multimers of wWF) was added to the preparation. The platelet agglutinating factor detected by these investigators also differed in that it was thrombin-like, being inhibited by edetic acid and heparin but not aspirin, but was not thrombin since it was not inhibited by the specific thrombin inhibitor dansylarginine at high concentrations. Also unlike the factor detected by Lian et al, it was not affected by monomeric IgG. Kelton et al suggests that these results are compatible with the presence of a platelet agglutinating factor which requires interaction with large multimeric forms of vWF to initiate platelet agglutination.

It is likely that platelet agglutinating factors derived from infection or other sources play a role in at least some cases of TTP. Whether the different properties ascribed to these factors reflects their true heterogeneity or merely different methodology, however,

remains to be determined. Further investigation will also be needed to establish the source of these agents and ultimately an animal model to demonstrate that they can actually produce the full syndrome of TTP.

Other Defects

1. Abnormal Platelets

An obvious question to be asked with respect to the pathogenesis of this disease is whether there may be intrinsic abnormalities of platelets resulting increased reactivity. Even this simple question has met with varied responses. Lian reported that the platelets obtained from two acute TTP patients during remission reacted normally with ADP, epinephrine, collagen, thrombin, and ristocetin (37). In contrast, there are several other reports that platelets actually aggregate subnormally in chronic relapsing TTP when the patient is in clinical remission (38,118,119). Whether these results represent differences in the times that samples were obtained, or differences in the pathogenesis of acute and chronic TTP remains unclear.

2. vWF Abnormalities

vWF is a heterogeneous multimeric plasma glycoprotein with 2 primary functions. The first is to facilitate platelet adhesion to the subendothelium under conditions of high shear stress by forming a bridge between platelet receptor Ib and the vessel wall. The second is to serve as a carrier for procoagulant factor VIII, an activity that is distributed among a series of plasma multimers with molecular weights ranging from 400,000 to over 20 million. vWF is synthesized in endothelial cells and megakaryocytes as a single large precursor subunit that is cleaved and assembled into multimers before the protein is secreted (38).

In 1982, Moake et al reported the presence of unusually large vWF multimers in the sera of 4 patients with chronic relapsing TTP during remission, which disappeared at the onset of clinical relapse (120). These multimers resembled the large multimers normally found in endothelial cells that are not, however, present in normal plasma. Two other investigators have since found similar results in 2 additional patients (121,122). Moake has concluded that the large vWF multimers are cleared during recurrent TTP episodes by their mediating platelet agglutination, and further that their original presence may be due to a lack of proteolytic enzyme normally present on endothelial cells responsible for reducing large multimers into smaller forms. He further cites recent studies on patients with Type IIb von Willebrand's disease, where platelet agglutination is due to the inappropriate binding of vWF to platelets resulting in cyclic thrombocytopenia, as evidence for the role of vWF in chronic TTP (123).

As mentioned previously, Kelton et al (106) provided some data to suggest that large vWF forms (although not "unusually large") might be important in initiating platelet agglutination during acute episodes of TTP as well. As Lian has stated, this makes an attractive hypothesis,

but the in vitro or in vivo direct evidence that large vWF multimers disappear during acute TTP episodes specifically through binding to platelets is still lacking. The decrease of vWF forms could also result from the attachment of vWF to exposed subendothelium of damaged vessels, decreased synthesis or release from injured endothelial cells, or accelerated proteolysis by a number of enzymes such as plasmin, trypsin, chymotrypsin, calcium-activated protease from platelets, or protease from activated white blood cells, all shown to cleave vWF to smaller forms in vitro (37). In this context, Lian and Siddiqui recently reported that the platelet aggregating activity of 5 samples of TTP plasma was not inhibited by prior incubation with nonspecific antibodies to vWF or a monoclonal antibody to platelet glycoprotein Ib (the usual binding site for vWF) (124).

Summary

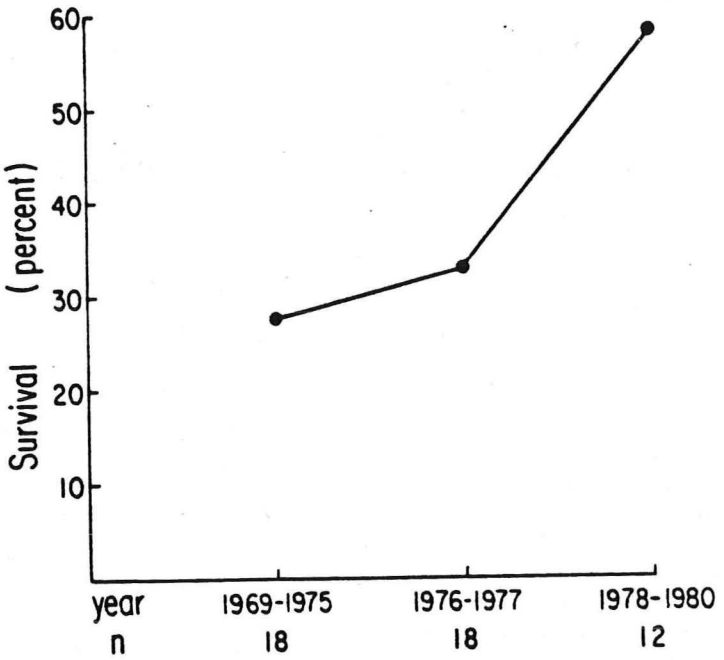
Despite many intriguing reports of platelet agglutinating factors, abnormal vWF, deficient prostacyclin production, and defective fibrinolysis in patients with acute and/or chronic relapsing TTP, the etiology of the syndrome remains obscure. Since much of the difficulty with research in this area has resulted from the limited availability of pathologic material, it is hoped that organization of a new Serum Repository for Thrombotic Microangiopathy by the National Heart, Lung, and Blood Institute will facilitate future studies in this area.

TREATMENT

Evaluation of therapeutic interventions in TTP is difficult for many reasons. The disease is rare and the clinical course highly variable. Even in large medical centers, experience with TTP is limited and the diagnosis frequently slow to be made, potentially influencing the effects of treatment. A plethora of therapeutic combinations have been utilized, virtually eliminating the potential for meaningful comparisons. There are no controlled trials of any specific intervention, and as many have suggested, apparent successes are more likely to be published than are failures (38).

Despite these problems, it is clear from review of the literature that the outlook for patients with TTP has changed dramatically over time. Figure 3 from Kennedy's study (14) is consistent with results reported by others (8,15,16).

Figure 3 (14).



Survival in 48 episodes of TTP in 47 evaluable patients. n = number of cases in each time interval.

Indeed, remission rates in excess of 80% are now consistently being reported (16,125,126,127). While some have attributed these results solely to the advent of specific therapy, particularly plasma infusion or exchange, the literature suggests that additional factors such as improved supportive care may play an important role. In evaluating the effectiveness of specific treatment it is therefore not appropriate to make a comparison with Amorosi's (6) 95% mortality rate, since many of the cases in his series antedate modern medical care. Rather, the 50-60% mortality reported by Ridolfi (8) and others from series where a minority of patients received any consistent form of therapy, including plasma manipulation, is more likely to reflect the true natural history of this disease.

Exchange Transfusion, Plasma Infusion, and Plasma Exchange

The role of whole-blood exchange transfusions, plasma infusion, and plasma exchange was recently reviewed by Shepard and Bukowski (126). The first report of the effectiveness of exchange transfusions in TTP was published by Rubinstein et al in 1959 (128). By 1980, Bukowski (129-130) had reported complete remission in 8 of 17 (47%) patients following treatment with exchange transfusions. Patients responding to therapy demonstrated marked improvement in both clinical and laboratory features of the disease within 48 hours. Pisciotta (131) subsequently published a similar study in 12 patients and reported a response in 8 (66%). He also reported that several patients with neurologic deficits seemed to improve during the exchange, and that the hematocrit and reticulocyte count 1 week after treatment were strong predictors of

survival. In both series, the majority of patients appeared to receive sequential or concurrent treatment with corticosteroids, splenectomy and/or anti-platelet drugs, and the number of exchanges required to effect a complete response was variable.

In 1977, Byrnes and Khurana (132) reported that plasma infusions alone could effectively treat some patients with TTP. They found during the course of plasma exchange therapy that replacement with albumin alone was not effective. However, when they simply infused fresh frozen plasma without plasma removal, the patients responded. In 1980, Byrnes (112) reported results from 19 patients and noted that 14 responded to plasma infusion as their sole treatment. While there are a handful of reports claiming similar results in additional patients (120-122, 133), the total number of patients treated with plasma infusion is very small. In addition, other investigators have reported the need to resort to alternate therapy when plasma infusion failed (91). Some have suggested that relapsing TTP may be especially reponsive to this form of treatment, but only anecdotal reports exist to substantiate this (120-122).

The success of whole-blood exchange transfusions led to the empiric use of plasma exchange with fresh-frozen plasma. In 1977, Bukowski et al (134) described 2 patients who recovered after intensive plasmapheresis, and similar reports followed (49,125,127,135,136). Table 11 (126) summarizes the results of plasma exchange therapy in TTP.

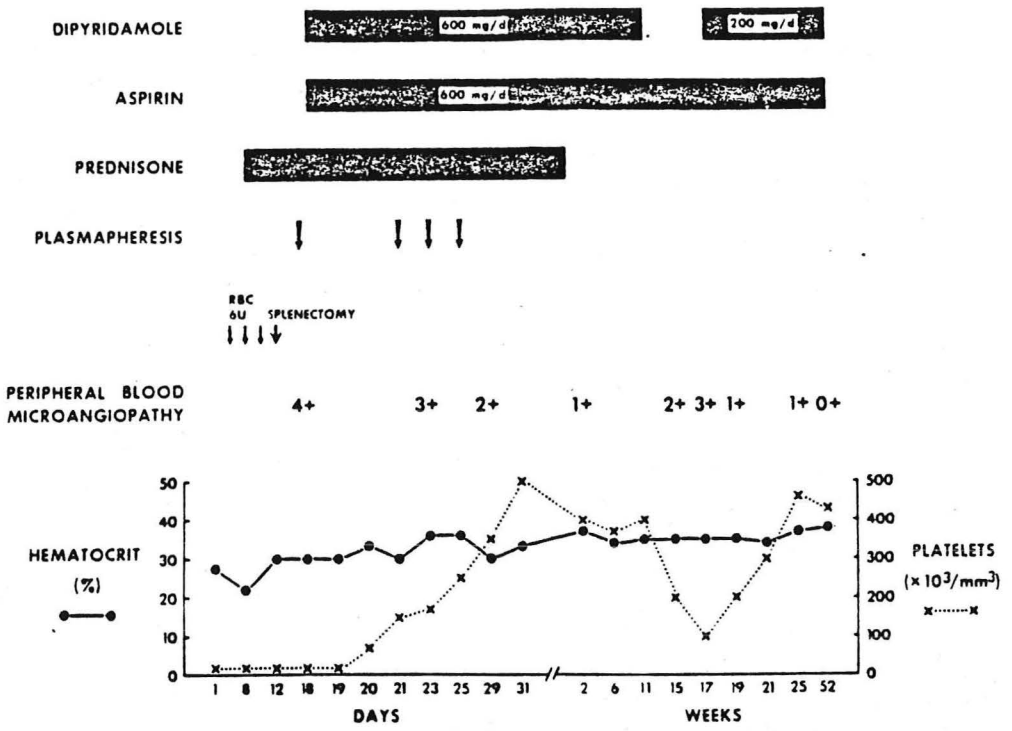
Table 11 (Adapted from Shepard and Bukowski (126)).

Results of Plasma Exchange Therapy in TTP

First Author	Patient Number	Responses(%)
Lichtin	24	20 (83)
Blitzer	17	14 (82)
Pisciotto	16	13 (81)
Bukowski	13	10 (77)
Myers	8	8 (100)
Taft	5	4 (80)
Total	63	52 (82)

It is noteworthy that 5 patients in the series by Bukowski (134) did not receive corticosteroids or antiplatelet drugs, and all were felt to have complete responses to plasma exchange alone. In the series reported by Pisciotto (136) and Myers (49), all but one patient received concurrent therapy with corticosteroids, aspirin and dipyridamole. Similarly, most patients in the recent series reported by Lichten (125) and Blitzer (127) received additional therapy as well. Once again, the number of exchanges required to effect a response was variable, and Figure 4 from Myer's report (49) illustrates just how difficult it is to determine which specific therapy caused a response.

Figure 4. (49).



(The authors interpret these results as consistent with an initial response to plasma exchange and anti-platelet drugs, a recurrence secondary to discontinuation of dipyridamole, and a second remission following reinstitution of this drug. Alternative explanations would seem equally plausible.)

Other literature also exists to support the role of plasma therapy. In these series, groups of patients were treated with plasma infusion and/or plasmapheresis with or without concurrent corticosteroids and anti-platelet drugs. Some report marked clinical improvement immediately following plasma manipulation, others do not. Ridolfi and Bell (8) noted that 47 of 67 patients (70%) managed with plasma therapy (exchange, pheresis or infusion) survived. Petitt (115) reported survival in 9 of 10 patients (90%) treated with plasma therapy, Rose and Eldor (16) 30 of 37 (81%).

What is clear from the literature is that over 80% of patients currently treated with plasma exchange therapy survive. Whether this represents the sole reason for improved survival remains to be determined. A randomized, controlled trial is currently underway in Canada to compare treatment with plasma infusion alone versus treatment with plasma exchange with plasma replacement, or plasma exchange with crystalloid solutions. It is hoped that the results of this trial will improve current therapy.

Other Treatment

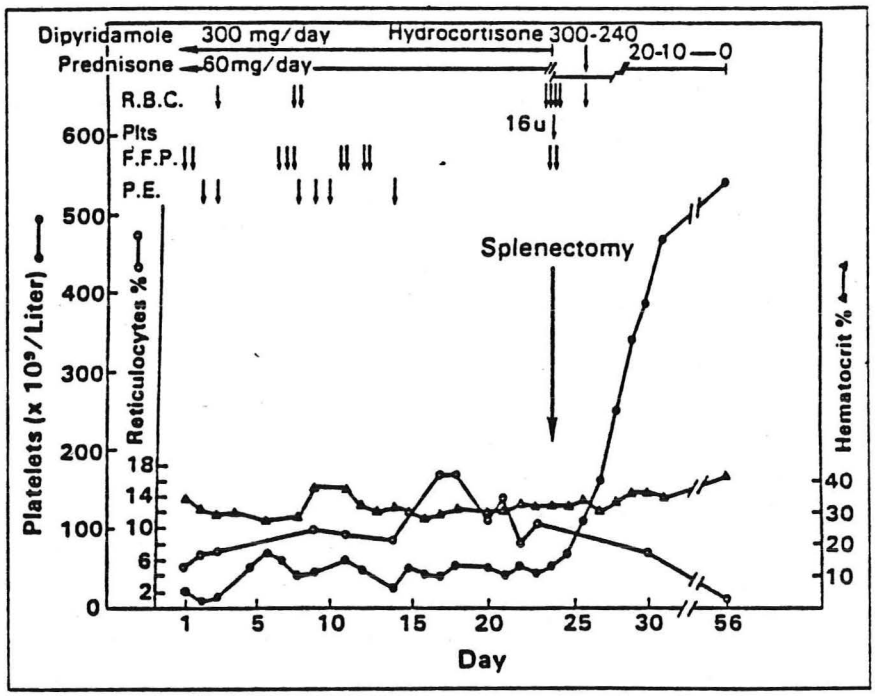
There are only anecdotal reports of clinical remission during treatment with steroids alone (137). Nevertheless, the vast majority of patients treated for TTP in the past two decades have received corticosteroids at some point, so it is difficult to assess if they have an adjunctive role in therapy. For this reason, many investigators recommend institution of high dose steroids at the time of diagnosis (38), although others do not (7). Similarly, corticosteroids, vincristine, and azathioprine have also been reported to induce permanent remission in a few anecdotal cases of relapsing TTP (138-139). The Canadian trial does not utilize corticosteroid therapy and may therefore provide additional information with regard to its "necessity" in acute TTP.

In a similar manner, the role of anti-platelet therapy remains unclear. Kennedy et al (14) reported a distinct survival advantage in patients treated with aspirin, dipyridamole, and sulfinpyrazone as part of their therapeutic regimen. When dextran was substituted for sulfinpyrazone in this three-drug regimen, the survival advantage disappeared. Rosove (139), however, noted serious bleeding complications only in his patients concurrently treated with aspirin and dipyridamole. Only one of 14 patients treated with anti-platelet drugs as part of their therapeutic regimen did not develop new neurologic signs or worsening thrombocytopenia while on therapy. He concluded that the risk of anti-platelet drugs outweighed any potential benefit. Bukowski (130) reviewed 91 cases from 1970-1980 in which platelet inhibitors were used. Aspirin, dipyridamole, dextran, and sulfinopyrazone were used in different combinations. Improvement occurred in 49, and there was no response in 42. Aspirin and dipyridamole were used together in 44 cases. There was no response in 20. The clinical status of 24 patients improved. Because other therapeutic modalites were also used in most patients, it is unclear what specific treatment benefitted them. As in the case of corticosteroid therapy, there are only anecdotal reports of clinical remission achieved on anti-platelet therapy alone, but their role in adjunctive therapy remains unclear (140). Unfortunately, all patients in the Canadian trial will receive aspirin and dipyridamole, thus precluding our ability to gather new data to answer this question.

Splenectomy was a standard form of therapy for many years. Cuttner (141) reported survival in 13 of 15 patients (87%) treated with splenectomy, corticosteroids and average molcular weight dextran. While she is generally credited with the only series supporting a role for splenectomy, it is interesting to review Ridolfi and Bell's (8) data. 19/29 (65%) of patients treated with steroids and splenectomy, 8/14 (54%) receiving this and anti-platelet drugs, and 10/12 (82%) treated with steroids, splenectomy, and average molecular weight dextran survived. This results in an overall survival of 70% in 55 patients treated with splenectomy, results equivalent to those reported in his series for any form of plasma manipulation. In contrast, Kennedy et al (14) found no survival advantage when splenectomy was included in therapy. Since most patients undergoing splenectomy also receive blood

products, including fresh frozen plasma, some have simply attributed any beneficial effect to this (38). More recently, there have been three small series reporting efficacy with splenectomy as second line therapy in patients not responding to, or relapsing despite, repeated plasmapheresis (121,142-144) (Figure 5) (143). These results need to be confirmed.

Figure 5 (143).



Treatment and course of the recurrent episode of thrombotic thrombocytopenic purpura as manifested by the platelet count, hematocrit, and reticulocyte count. Numbers of units of blood products transfused are indicated by arrows. F.F.P. = fresh frozen plasma; P.E. = plasma exchange; Plts = platelet transfusion; R.B.C. = packed red cells.

It appears that 2 forms of treatment are contraindicated - anticoagulation and the routine administration of platelets to patients who are not hemorrhaging. Petitt (15) noted that no patient receiving heparin or urokinase survived. Similarly, Kennedy (14) reported that 9 of 10 patients died after not responding to full dose heparinization. Harkness (145) and more recently Gordon (146), has presented evidence of clinical deterioration temporally associated with unnecessary platelet transfusions, not surprising given what we currently know about the pathophysiology of this disease.

Finally, a handful of patients have been treated with intravenous prostacyclin (62,70-71,147-148), or gammaglobulin (149-153), usually as second-line therapy. Prostacycin infusions have yielded conflicting results, but this does not appear to be a particularly promising form of therapy. Several reports have recently appeared citing anecdotal reponses to intravenous gamma globulin. It remains to be determined whether these results will be borne out in large numbers of patients. Certainly, neither of these approaches should currently be entertained as a first-line therapy outside a research protocol, given the success associated with plasma exchange.

In summary, thrombotic thrombocytopenic purpura is a syndrome probably with several etiologies. Current therapy with plasma exchange has resulted in successful treatment in over 80% of cases, although the reasons for this are still poorly understood. The prospective, randomized, controlled trial of various forms of plasma therapy, currently underway in Canada, will hopefully advance our knowledge in this area.

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