

Thrombotic Storm Revisited: Preliminary Diagnostic Criteria Suggested by the Thrombotic Storm Study Group

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ABSTRACT

Physicians periodically encounter patients with an extraordinarily accelerated course of hypercoagulability who develop thromboses in multiple organ systems over days to weeks. Such patients may harbor underlying hypercoagulable clinical conditions, but their clinical course sets them apart from most patients with similar risk factors. Underlying triggers of “thrombotic storm” include pregnancy, inflammation, trauma, surgery, and infection. Aggressive anticoagulant therapy may control thrombotic storm, yet thrombotic storm may resume with even brief interruptions of anticoagulant therapy. The authors of this communication formed the Thrombotic Storm Study Group in order to identify clinical characteristics of such patients, thus constructing preliminary criteria to better define, identify, and study the course of patients deemed to have thrombotic storm. The characteristics culled from these 10 patients are: younger age (oldest was 38 years old at time of presentation); at least 2 arterial or venous (or both) thromboembolic events, typically in unusual sites with or without microangiopathy; unexplained recurrence; and frequently preceded by a trigger. The following characteristics were not used in defining thrombotic storm: underlying malignancies; use of acute myocardial infarction as a defining arterial event in the setting of established coronary artery disease; use of cocaine; thrombotic complications expected with various intravascular devices; known paroxysmal nocturnal hemoglobinuria or myeloproliferative disorders; severe trauma; and premorbid conditions.

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A decade ago, Kitchens¹ described “thrombotic storm” as a pattern of serial acute to subacute thrombotic events that escalated over a period from a few days to a few weeks, involving progressive thromboses at multiple sites to include many so-called “unusual sites.” Despite its virulence, thrombotic storm may respond to aggressive uninterrupted parenteral anticoagulant therapy. Relapse may be sudden if anticoagulant therapy is interrupted or “held” for as brief a period as a few hours.

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The long-term prognosis, once the storm resolves, is generally excellent based on subset analysis.² Whereas many of these patients’ laboratory studies revealed any of several objective indicators of hypercoagulability, the phenotypic behavior of their syndrome is out of proportion and more progressive than more commonly observed patients. We hypothesize that these patients might harbor novel risk factors. By developing clinical characteristics in order to accrue selected patients, we will enhance chances to discover novel factors. These characteristics are preliminary and not meant to define thrombotic storm strictly or biologically at this time, and no doubt our list of characteristics will be amended as observations dictate.

Kitchens¹ elected to not define this syndrome by any specific tests or pattern of hypercoagulable or thrombophilic markers but rather recognized it by its stereotypic clinical behavior. Other clinicians have described small series rem-

iniscient of thrombotic storm patients under what has variously been termed “catastrophic occlusion syndrome,”³ “devastating non-inflammatory vasculopathy”⁴ and, notably, “catastrophic antiphospholipid syndrome” (CAPS).⁵⁻⁷ Other syndromes that often described patients with features resembling thrombotic storm or described a subpopulation of patients who might degenerate into thrombotic storm, include patients with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome,⁸⁻¹⁰ preeclampsia,^{11,12} combinations of HELLP and preeclampsia with or without features of thrombotic thrombocytopenic purpura or antiphospholipid syndrome,¹³⁻¹⁷ thrombotic thrombocytopenic purpura and other thrombotic microangiopathies,¹⁸⁻²⁰ systemic inflammatory response syndrome,²¹⁻²³ and most recently, spontaneous heparin-induced thrombocytopenia (HIT).²⁴ Various conditions (pregnancy, surgery, or inflammation) might trigger previous underlying hypercoagulable or thrombophilic conditions in concert to produce this clinical picture.²⁵ Thrombotic storm, regardless of its etiology, is recognized by what one sees at the bedsides of these critically ill patients.

CASE REPORTS

The first 3 patients each sustained an episode of thrombotic storm more than 20 years ago and have been described previously.^{1,26} Updates are presented here. The subsequent 7 patients have not been published previously and represent the array of clinical manifestations associated with thrombotic storm. Relevant clinical and laboratory characteristics are summarized in [Table 1](#).

Case 1 – Paroxysmal Nocturnal Hemoglobinuria Appearing 10 Years after Thrombotic Storm

Of the 6 cases initially described by Kitchens,¹ long-term follow-up is available for 1 patient. This woman developed thrombotic storm with features convincingly substantiating the diagnosis of HELLP syndrome and then rapidly became preeclamptic in the hours following cesarean delivery, with papilledema from cerebral venous thrombosis and hepatic vein thrombosis, for which she was given thrombolytic therapy with excellent results. She did well for 10 years and then developed hemolysis and now has been diagnosed as paroxysmal nocturnal hemoglobinuria despite no prior evidence to support that diagnosis. She has not experienced

further thrombosis, as she remains on chronic oral anticoagulant and eculizumab therapy.

Case 2 – Long-term Follow-up of a Patient with Venous Thromboembolism, Warfarin-induced Skin Necrosis, Superior Sagittal Vein Thrombosis, and a Positive Lupus Anticoagulant Test

This patient²⁶ had been on oral contraceptives for about 15 years without experiencing thrombosis. She developed pulmonary emboli early in gestation and underwent a therapeutic abortion. Two weeks later she developed a spontaneous left axillary vein thrombosis and was begun on warfarin therapy; 4 days into that therapy she developed warfarin-induced skin necrosis. She had evidence for lupus anticoagulant, yet enzyme-linked immunosorbent assays for antiphospholipid antibodies were negative. She was found to be completely lacking free protein S; at the same time, her protein C activity was

normal. While on a dose of 5000 units of heparin administered subcutaneously twice a day with compliance, she developed frontal headaches, papilledema, and superior sagittal sinus thrombosis. She was treated with prednisone and heparin. Two months later she continued to have laboratory evidence for lupus anticoagulant, but analysis for free protein S was then normal. We had not seen her for 20 years, during which time she had noticed that following surgical drainage of an infected Bartholin cyst, her “toes turned black” temporarily, for which she sought no medical attention.

Case 3 – Recurrent Purpura Fulminans in a Patient with Prior Thrombotic Storm

This patient was 20 years old at the time she was seen 20 years ago,²⁶ being admitted 12 days postpartum with seizures and a left hemiparesis from cerebral venous thrombosis with right frontoparietal infarction. Warfarin administration was started, yet she promptly developed typical signs of warfarin-induced skin necrosis. Debridement of necrotic material was successfully done under full heparin therapy without “holding heparin.” She was found to have lupus anticoagulant and no detectable amounts of free protein S after warfarin had been discontinued, yet enzyme-linked immunosorbent assays for antiphospholipid antibodies were negative. She remained on therapeutic heparin for 8 months and during that time underwent emergent cholecystectomy

CLINICAL SIGNIFICANCE

- Some patients develop a peculiar, aggressive, acute hypercoagulable syndrome called thrombotic storm, defined by its linked pattern of events.
- Age <55 years, thrombotic events in unusual sites, unexplained recurrence, and possible triggering events are preliminary supportive criteria for the diagnosis.
- Diagnosis of thrombotic storm is currently based on physician suspicion and recognition of the preliminary criteria.
- Therapeutic intervention remains controversial but includes continuous anticoagulation.

Table 1 Summary Table of Patients Presenting with Thrombotic Storm

Patient	Age (Years)	Sex	Prior TE	Possible Trigger	aPL or APS	Inherited Thrombophilia	Thrombotic Events	Treatment*	Outcome
1†	38	F	No	Pregnant	No	No	HELLP, BC, PVT, IVC thrombosis	CD, LT, OAC	Chronic OAC; PNH 20 years later.
2‡	30	F	No	Pregnant	Yes	No	DVT, PE, CVT	OAC	No recurrences.
3‡	20	F	No	Postpartum	Transient	No	CVT, DVT	OAC	PF 17 years later; prolonged OAC
4	17	F	No	OC	Yes	No	ATE, PE	LT, BKA	DVT 1 yr later, when noncompliant with OAC
5	16	M	No	No	Yes	No	Recurrent DVT	OAC	Chronic LMWH
6	14	M	No	Injury	No	No	CVT, PE, DVT	OAC	Died
7	29	F	PE	Pregnant	Yes	No	Hepatic infarcts; TIA	OAC, steroids; D&E for IUFD	Chronic OAC
8	20	F	No	Infection	No	No	Multiple ATE	BEA, BKA, OAC	Chronic OAC
9	29	F	Yes	Infection	Yes	FVL	DVT, PE, CVA	OAC, rituximab	Chronic LMWH
10	34	F	RSA	Pregnant	Maybe	No	Eclampsia, DVT	OAC	Chronic OAC

Abbreviations: aPL = antiphospholipid antibody; APS = antiphospholipid syndrome; ATE = arterial thromboembolic event; BC = Budd-Chiari; BEA = below-elbow amputation; BKA = below-knee amputation; CD = cesarean delivery; CVT = cerebral vein thrombosis; D&E = dilatation and evacuation; DVT = deep venous thrombosis; F = female; FVL = factor V Leiden; HELLP = hemolysis, elevated liver enzymes, and low platelets; IUFD = intrauterine fetal demise; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; LT = lytic therapy; M = male; OAC = oral anticoagulation; OC = oral contraceptives; PE = pulmonary embolism; PF = purpura fulminans; PNH = paroxysmal nocturnal hemoglobinuria; PVT = portal vein thrombosis; RSA = recurrent spontaneous abortions; TE = thromboembolism; TIA = transient ischemic attack.

*Subacute to chronic therapy following acute use of parenteral anticoagulant therapy (see text).

†Case initially presented in Kitchens et al.¹

‡Case initially presented in Moreb and Kitchens.²⁶

without interruption of heparin therapy. When seen in follow-up, her levels of protein S and protein C were normal and her laboratory evidence for lupus anticoagulant had disappeared. Seventeen years later she and other family members developed acute food poisoning. She was the only one to deteriorate, developing full-blown purpura fulminans requiring several amputations. All coagulation studies including free protein S were normal. She has been treated with fondaparinux for the last 3 years.

Case 4 – Arterial and Venous Thromboemboli in the Setting of Antiphospholipid Syndrome

A 17-year old woman was admitted with pain and numbness of her toes, cold right leg, and barely palpable dorsalis pedis pulses. One week before admission she was placed on standard oral contraceptive (Kelnor [Barr Pharmaceuticals, Montvale, NJ], containing 35 µg ethinyl estradiol). She was found to have an anticardiolipin immunoglobulin G (IgG) antibody level elevated 3 times normal and positive assays for lupus anticoagulant and D-dimer. Heparin therapy was initiated and local infusional intra-arterial thrombolysis was attempted twice, yet she required below-knee amputation. A computed tomography scan of the chest showed pulmonary

embolism. Progressive infarction of the right leg necessitated an above-the-knee amputation.

Case 5 – Thrombotic Recurrences in a Teenager with Lupus and Antiphospholipid Syndrome

A 16-year-old boy of Eastern Indian descent presented with history of nontraumatic left leg swelling due to extensive deep vein thrombosis. He manifested findings suggestive of systemic lupus erythematosus, including a prolonged partial thromboplastin time, a positive lupus anticoagulant test, and sustained high levels of anticardiolipin antibodies. A year later, an asymptomatic proximal extension to his common iliac vein was documented; his target international normalized ratio was increased from 2.5 to 3.5. Regardless, subsequent imaging obtained 3 months later revealed a new symptomatic thrombus progression. Seven months later he presented with a third thrombus extension, when his international normalized ratio was documented to be 2.0. Subsequently therapy was switched to tinzaparin, and he has had no further documented thrombus progression.

Case 6 – Intracranial Venous Sinus Thrombosis Complicated by Disseminated Intravascular Coagulation in a Teenager Following Knee Injury

Following a sports-related knee injury, this 14-year old boy subsequently developed progressive headaches, nausea and vomiting, confusion, and a seizure. Magnetic resonance imaging revealed thrombosis of the sagittal, right transverse, and sigmoid sinuses. Heparin therapy was started, in addition to anticonvulsants. Disseminated intravascular coagulation developed, with fibrinogen levels decreasing to 131 mg/dL and platelet counts to 66,000/ μ L. Pentobarbital coma was induced and hypothermia initiated. Testing for HIT was negative. Further hypercoagulable work-up was negative to include analysis for antiphospholipid antibodies. Disseminated intravascular coagulation resolved over the second week. Subsequent studies showed no blood flow above the intracranial carotids, and severe brain swelling with herniation. In addition to the extensive intracranial thromboses, bilateral pulmonary emboli and bilateral pelvic vein thromboses were identified at autopsy.

Case 7 – Hepatic Infarctions and Transient Ischemic Attacks Complicating Intrauterine Fetal Demise and HELLP

A 29-year-old woman with a known history of systemic lupus erythematosus and antiphospholipid syndrome was admitted at 14 weeks gestation with HELLP and intrauterine fetal demise. She had been administered therapeutic enoxaparin during the course of her pregnancy. Abdominal imaging revealed multifocal hepatic infarctions. A suction dilatation and evacuation was performed, but the patient subsequently developed acute bilateral vision changes, but without evidence for an infarct. Her platelet count reached a nadir of 38,000/ μ L. Glucocorticoid infusions and plasmapheresis were initiated. Testing for HIT was negative and she was continued on heparin therapy. Her platelet count returned to normal, as did her liver function tests.

Case 8 – Multiple Arterial and Venous Occlusions in a Patient with Crohn Disease

A 20-year old woman with a history of Crohn disease and a prior repair procedure of a degenerative mitral valve developed fever, leukocytosis, acute renal insufficiency, and hypotension followed by mental status changes, respiratory distress, and progressive infarction, and necrosis of her right arm and both legs below the knees. Steroid therapy, heparin infusion, and plasma exchange therapy were initiated for possible microvascular thrombi involving her limbs. Antiphospholipid antibody testing was negative, and evaluation for other hypercoagulable states revealed only a transiently decreased antithrombin III level. The aortic arch and right arm vessels were normal, but the radial artery tapered to complete occlusion in the right mid-forearm. She eventually underwent amputations of both legs and the right arm

below the elbow; widespread venous and arterial thromboses were found. She has been maintained on chronic anticoagulant therapy without recurrence.

Case 9 – Recurrent Arterial and Venous Thromboembolism in a Patient with Antiphospholipid Syndrome and Prior Deep Vein Thrombosis

A 29-year-old woman with persistent lupus anticoagulant, anticardiolipin IgG and IgM levels between 40 and 80 U, and anti- β_2 -glycoprotein-1 IgG and IgM antibody levels above 80 units initially presented with deep vein thrombosis and pulmonary embolism 8 years ago. She was heterozygous for the factor V Leiden mutation. She sustained a second deep vein thrombosis for which she was treated with low-molecular-weight heparin (LMWH). Eight years later, chest X-ray study revealed bilateral pulmonary infiltrates, and an echocardiogram demonstrated an ejection fraction of 22%. Femoral vein deep venous thrombosis and right upper lobe pulmonary embolism were found. Therapy with LMWH was initially stopped, and she was treated with intravenous heparin for 5 days. When LMWH therapy was restarted, she sustained an acute stroke in the right middle cerebral artery distribution, and argatroban therapy was started. A cardiac computed tomography angiogram revealed normal coronary arteries but severe hypokinesis of the left ventricular walls. She was then treated with plasma exchange, intravenous immunoglobulin, glucocorticosteroid therapy, hydroxychloroquine, and a course of rituximab.

Case 10 – Ovarian Vein Thrombosis, Right Atrial Thrombus, in a Patient with Eclampsia

A 34-year-old woman had had one prior normal pregnancy and 2 spontaneous abortions. Laboratory evaluation showed that she had positive anticardiolipin antibodies. She then became pregnant again with twins and was treated with aspirin 81 mg/day. Near term she rapidly developed eclampsia and underwent an emergency cesarean delivery with bilateral tubal ligation. Her liver function tests were normal at that time, as was her platelet count. No schistocytes were seen. She had bilateral thromboses of her ovarian veins, extending up into the inferior vena cava (IVC), causing functional obstruction of the renal veins. An IVC filter was placed. Transesophageal echocardiography showed thrombus in her right atrium traversing a patent foramen ovale into her left atrium. She was fully anticoagulated with intravenous heparin. Repeat echocardiography performed after 8 hours of full therapeutic dose heparin now failed to reveal left atrial thrombus. Daily plasma heparin levels of 0.6-0.8 units/mL were documented. After a year, her retrievable IVC filter was removed. The patent foramen ovale was left alone and she remains on warfarin therapy indefinitely.

Table 2 Clinical Characteristics of Our Patients with Thrombotic Storm

Typically encountered characteristics

Younger age *plus* 2 or more of the following criteria:

Acute, 2 or more arterial or venous thromboemboli, with or without thrombotic microangiopathy,* typically in a compressed period of time (1-2 weeks) yet may recur from time to time over years.

Unusual location†

Progressive/recent unexplained recurrence

Refractory to acute therapy or atypical response to therapy

Exacerbated by inadequate or interrupted treatment (eg, subtherapeutic anticoagulation)

Frequently preceded by an initiating event (“trigger”)‡

Characteristics usually not encountered

Cancer (excluding minor skin cancers)

Myocardial infarction in the setting of advanced coronary artery disease

Cocaine use associated with symptom onset

Expected thrombotic complications associated with intravascular devices

Known paroxysmal nocturnal hemoglobinuria or myeloproliferative disorder

Multi-trauma/severe trauma (eg, multiple limb injury)

Premorbid clinical status before development of thrombotic complications

*Thrombotic microangiopathy defined as microvascular thrombosis (arteriole, venule, capillary) on tissue pathology.

†Unusual locations would include thromboembolic complications other than pulmonary embolism, lower extremity deep venous thrombosis, myocardial infarction, and stroke such as thrombosis of hepatic, cerebral, portal, or renal veins, skin (purpura fulminans), and adrenal glands.

‡Such as pregnancy, surgery, trauma, infections, and inflammatory states.

DISCUSSION

We have preliminarily developed a list of certain clinical characteristics that occur frequently enough from our collected experiences to support a working diagnosis of thrombotic storm (Table 2). These are not unique to thrombotic storm, nor, taken individually, are they different from more commonly occurring thromboses. Rather, we argue that the pace of events, the combination of events, multiple thromboses at unusual sites, and the overall “gestalt” seems to describe this group of patients. Thrombotic storm might be regarded as an extreme continuum of thrombotic events rather than a distinct free-standing entity. The purpose of employing these characteristics is to enhance our chances of discovery by focusing on a group of patients at the more vigorous end of the spectrum of phenotypic manifestations. Similarly, we have tentatively excluded certain other clinical conditions that, although they might well be associated with more routine thrombotic events in other clinical settings, they were neither characteristic of nor seemingly required in our cases (Table 2). Our patients tended to be younger than typical patients with “hypercoagulability”; our

oldest was 38 years old. We have agreed that an arbitrarily selected age cut-off of 40-50 years be used to minimize the chances of including patients with an undiscovered malignancy. We currently cannot explain why 8 of our 10 presented patients are female.

The clinical phenotype of these 10 patients is profoundly more severe and rapidly progressive than characteristically seen in patients with most hypercoagulable states. Antiphospholipid antibodies were detected in some but not all individuals. One patient was diagnosed with paroxysmal nocturnal hemoglobinuria 10 years after her presentation with thrombotic storm (Case 1). Near-total absence of protein S was transiently noted in 2 of the patients, yet corrected with resolution of the thrombotic storm (Cases 2 and 3). A temporary and more complex process (“a perfect storm”), or yet-to-be-determined novel additional hypercoagulable disorders, is postulated. Candidate second and third provocations include infection, inflammation, pregnancy, surgery, trauma, and medications (Tables 1, 2).

Thrombotic storm may explosively exacerbate with cessation of anticoagulant therapy in patients being adequately treated for a fresh thrombosis. Fresh clots are known to contain and exude thrombin and thus, should effective therapy be held, can propagate the process.²⁷

A trigger might lead to the development of circulating microparticles originating from different cellular origins and promoting a prothrombotic environment.²⁸⁻³¹ Another possible contributor might be acquired disorders of “a disintegrin and metalloproteinase with thrombospondin components” (ADAMTS-13), differing from the ADAMTS-13 pattern associated with classic thrombotic thrombocytopenic purpura, as has been described in disseminated intravascular coagulation,^{32,33} HELLP syndrome,¹⁵ and inflammation.³⁴ Pregnancy, injury, inflammation, and particularly, sepsis, affect the endothelium, causing an outpouring of unusually large von Willebrand factor, and such patients can diminish their native supply of ADAMTS-13. Such a hypothesis is compatible with the oft-observed salubrious effect of therapeutic plasma exchange in this syndrome and may be, in large part, due to the replenishment of ADAMTS-13 during therapeutic plasma exchange.^{34,35}

In keeping with the centrality of thrombosis and its likely curtailment by aggressive continuous anticoagulant therapy, published reviews of CAPS suggest that anticoagulant therapy is a key component in the therapeutic management of these patients.⁶ Whereas most patients with CAPS also are treated with various immunosuppressive strategies (most commonly glucocorticosteroids), anticoagulant therapy remains the fulcrum in one’s therapeutic approach.

FUTURE PLANS

We will exploit recent advances in genomic technology to study a limited number of patients. As an example of this technology used in a similar situation, sequencing of the whole exome, or the coding region of the genome, in a limited number of affected individuals, followed by a fil-

Table 3 Potential Findings from this Study

Potential new disorders may be discovered by genomic analysis of registrants' DNA
 Patients may manifest a previously undiagnosed disorder over time, thus revealing more information than was initially known
 Patterns of events/risk factors may be disclosed
 Centrality of stimulus (infection, pregnancy, trauma, or surgery) may become more clear
 Roles of underanticoagulation and interrupted anticoagulation will be examined
 Explore the roles of ADAMTS-13, UL-VWF, and microparticles in genesis of thrombotic storm

ADAMTS-13 = a disintegrin and metalloproteinase with thrombospondin components; UL-VWF = unusually large von Willebrand factor.

tering approach to select those genes most likely to be implicated in the disorder, has been shown to be an efficient strategy to search for alleles underlying rare mendelian disorders. Using this approach, a single candidate gene was identified from a total of only 2 individuals in one kindred, and one unrelated kindred affected with Miller syndrome, a rare disorder characterized by multiple malformations.³⁶

In an effort to better characterize and define this extreme phenotype, we have formed the Thrombotic Storm Study Group. Collaborating investigators from adult and pediatric hematology, rheumatology, maternal-fetal medicine, and human genetics form the core clinical study team. A primary objective of the Study Group is to recruit and enroll patients with thrombotic storm (either at the time of the event, or subsequently) into a patient registry to better define the clinical characteristics of thrombotic storm. Given the rarity of the syndrome, we are promoting the study through colleagues, professional organizations, patient advocacy groups, and other strategies. With time, we hope to construct validated inclusion and exclusion criteria to support the diagnosis of thrombotic storm.

We also will develop a sample repository for serum, plasma, genomic DNA, and RNA, which will be used to investigate potential genetic risk factors that may predispose individuals to this syndrome. Possible outcomes from these analyses are summarized in Table 3.

References

- Kitchens CS. Thrombotic storm: when thrombosis begets thrombosis. *Am J Med.* 1998;104:381-385.
- Erkan D, Asherson RA, Espinosa G, et al. Long term outcome of catastrophic antiphospholipid syndrome survivors. *Ann Rheum Dis.* 2003;62:530-533.
- Greisman SG, Thayaparan R-S, Godwin TA, Lockshin MD. Occlusive vasculopathy in systemic lupus erythematosus. Association with anticardiolipin antibody. *Arch Intern Med.* 1991;151:389-392.
- Ingram SB, Goodnight SH Jr, Bennett RM. An unusual syndrome of a devastating noninflammatory vasculopathy associated with anticardiolipin antibodies: report of two cases. *Arthritis Rheum.* 1987;30:1167-1172.
- Asherson RA, Piette J-C. The catastrophic antiphospholipid syndrome 1996. Acute multi-organ failure associated with antiphospholipid antibodies: a review of 31 patients. *Lupus.* 1996;5:414-417.
- Cervera R, Bucciarelli S, Plasín MA, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the "CAPS Registry". *J Autoimmun.* 2009;32:240-245.
- Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics.* 2008;122:e1100-e1107.
- Baxter JK, Weinstein L. HELLP syndrome: the state of the art. *Obstet Gynecol Surv.* 2004;59:838-845.
- Sibai BM, Ramadan MK, Usta I, et al. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol.* 1993;169:1000-1006.
- Minakami H, Oka N, Sato T, et al. Preeclampsia: a microvesicular fat disease of the liver? *Am J Obstet Gynecol.* 1988;159:1043-1047.
- Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science.* 2005;308:1592-1594.
- Sibai BM. Imitators of severe pre-eclampsia. *Semin Perinatol.* 2009;33:196-205.
- Smulian J, Shen-Schwarz S, Scorza W, et al. A clinicohistopathologic comparison between HELLP syndrome and severe preeclampsia. *J Matern Fetal Neonatal Med.* 2004;16:287-293.
- Hulstein JJ, Rison CN, Kappers-Klunne MC, et al. Activity loss of Von Willebrand factor cleaving protein (ADAMTS-13) is diagnostic for primary and pregnancy-related thrombotic thrombocytopenic purpura [Dutch]. *Ned Tijdschr Geneesk.* 2004;148:1972-1976.
- Lattunda A, Rossi E, Calzarossa C, et al. Mild to moderate reduction of a von Willebrand factor cleaving protease (ADAMTS-13) in pregnant women with HELLP microangiopathic syndrome. *Haematologica.* 2003;88:1029-1034.
- Le Thi Thuong D, Tieulie N, Costedoat N, et al. The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. *Ann Rheum Dis.* 2005;64:273-278.
- Clark EA, Silver RM, Branch DW. Do antiphospholipid antibodies cause preeclampsia and HELLP syndrome? *Curr Rheumatol Rep.* 2007;9:219-225.
- Moake JL. Thrombotic microangiopathies. *N Engl J Med.* 2002;347:589-600.
- Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. *Blood.* 2008;112:11-18.
- Loirat C, Girma JP, Desconclois C, et al. Thrombotic thrombocytopenic purpura related to severe ADAMTS13 deficiency in children. *Pediatr Nephrol.* 2009;24:19-29.
- Rangel-Frausto MS, Pittet D, Costigan M, et al. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA.* 1995;273:117-123.
- Levi M, Schouten M, van der Poll T. Sepsis, coagulation, and anti-thrombin: old lessons and new insights. *Semin Thromb Hemost.* 2008;34:742-746.
- Bhatia M, He M, Zhang H, Mochhala S. Sepsis as a model of SIRS. *Front Biosci.* 2009;14:4703-4711.
- Warkenton TE, Makris M, Jay RM, Kelton JG. A spontaneous prothrombotic disorder resembling heparin-induced thrombocytopenia. *Am J Med.* 2008;121:632-636.
- Erkan D, Cervera R, Asherson RA. Catastrophic antiphospholipid syndrome: where do we stand? *Arthritis Rheum.* 2003;48:3320-3327.
- Moreb J, Kitchens CS. Acquired functional protein S deficiency, cerebral venous thrombosis, and coumarin skin necrosis in association with antiphospholipid syndrome: report of two cases. *Am J Med.* 1989;87:207-210.
- Mutch NH, Robbie LA, Booth NA. Human thrombi contain an abundance of active thrombin. *Thromb Haemost.* 2001;86:1028-1034.
- Hughes M, Hayward CP, Warkenton TE, et al. Morphological analysis of microparticle generation in heparin-induced thrombocytopenia. *Blood.* 2000;96:188-194.
- Dignat-George F, Camoin-Jau L, Sabatier F, et al. Endothelial microparticles: a potential contribution to the thrombotic complications of the antiphospholipid syndrome. *Thromb Haemost.* 2004;91:667-673.
- Piccin A, Murphy WG, Smith OP. Circulating microparticles: pathophysiology and clinical implications. *Blood Rev.* 2007;21:157-171.

31. Alijotas-Reig J, Palacio-Garcia C, Vilardell-Tarres M. Circulating microparticles, lupus anticoagulant and recurrent miscarriages. *Eur J Obstet Gynecol Reprod Biol.* 2009;145:22-26.
32. Ono T, Mimuro J, Madiowa S, et al. Severe secondary deficiency of von Willebrand factor-cleaving protease (ADAMTS13) in patients with sepsis-induced disseminated intravascular coagulation: its correlation with development of renal failure. *Blood.* 2006;107:528-534.
33. Lam JK, Chion CK, Zanardelli S, et al. Further characterization of ADAMTS-13 inactivation by thrombin. *J Thromb Haemost.* 2007;5:1010-1018.
34. Claus RA, Bockmeyer CL, Budde U, et al. Variations in the ratio between von Willebrand factor and its cleaving protease during systemic inflammation and association with severity and prognosis of organ failure. *Thromb Haemost.* 2009;101:239-247.
35. Bortolati M, Marson P, Fabris F, et al. Recovery from catastrophic antiphospholipid syndrome by a plasma exchange procedure: report of four cases and review of the literature. *Autoimmun Rev.* 2009;8:297-301.
36. Ng SB, Buckingham KJ, Lee C, et al. Exome sequencing identifies the cause of a Mendelian disorder. *Nat Genet.* 2010;42:30-36.