How I treat catastrophic thrombotic syndromes

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Short title for running head: How I Treat Thrombotic Storm
ABSTRACT

Catastrophic thrombotic syndromes are characterized by rapid onset of multiple thromboembolic occlusions affecting diverse vascular beds. Patients may have multiple events on presentation, or develop them rapidly over days to weeks. Several disorders can present with this extreme clinical phenotype, including catastrophic antiphospholipid syndrome (APS), atypical presentations of thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT), and Trousseau’s syndrome, but some patients present with multiple thrombotic events in the absence of associated prothrombotic disorders. Diagnostic workup must rapidly determine which, if any, of these syndromes are present, since therapeutic management is driven by the underlying disorder. With the exception of atypical presentations of TTP, which are treated with plasma exchange, anticoagulation is the most important therapeutic intervention in these patients. Effective anticoagulation may require laboratory confirmation with anti-factor Xa levels in patients treated with heparin, especially if the baseline (pre-treatment) aPTT is prolonged. Patients with catastrophic APS also benefit from immunosuppressive therapy and/or plasma exchange, whereas patients with HIT need an alternative anticoagulant to replace heparin. Progressive thrombotic events despite therapeutic anticoagulation may necessitate an alternative therapeutic strategy. If the thrombotic process can be controlled, these patients can recover, but indefinite anticoagulant therapy may be appropriate to prevent recurrent events.
A 14 year-old, previously healthy young man developed progressive headaches, nausea and vomiting, culminating in a tonic-clonic seizure several days following a minor knee injury sustained while playing soccer. He was found to have extensive dural sinus thrombosis and started on anticoagulant therapy, but disseminated intravascular coagulation (DIC) and thrombocytopenia developed, limiting efforts to treat him with anticoagulants. Testing for antiphospholipid antibodies and heparin-induced thrombocytopenia (HIT) was negative, and heparin was restarted as the coagulopathy resolved. Despite aggressive efforts, severe brain swelling with herniation developed, and efforts to save him were withdrawn after documenting lack of blood flow above the internal carotid arteries. At autopsy, he had bilateral pulmonary emboli and iliac vein occlusions in addition to extensive intracranial venous thrombosis.

INTRODUCTION

Patients presenting with multiple thromboembolic events affecting diverse vascular beds are uncommon and management in the acute setting can be extremely difficult. Affected individuals are often younger, thrombotic events occur simultaneously or within days to weeks, and thrombosis frequently involves unusual sites\textsuperscript{1-3}. Therapeutic management may be complicated by the concomitant presence of hemorrhagic risk factors (e.g., thrombocytopenia, DIC) or the need for surgical intervention. Kitchens first referred to this clinical presentation as “thrombotic storm” in 1998, identifying the following characteristic features: 1) an underlying hypercoagulable state is frequently present; 2) a provocative factor, or “trigger”, is frequently associated with initiation of the thrombotic process; 3) new thromboembolic events develop rapidly, particularly if appropriate treatment is delayed; 4) prompt initiation of antithrombotic therapy is essential to achieve a successful outcome; and 5) long-term prognosis is good, if the cycle of thrombosis is interrupted early\textsuperscript{1}.
These catastrophic clinical presentations may occur in patients with a known prothrombotic disorder (e.g., antiphospholipid syndrome [APS], cancer) or in a previously healthy individual, as described above. Appropriate clinical management requires rapid identification of any associated hypercoagulable states, however, as treatment strategies vary and an incorrect decision can delay initiation of appropriate therapy, increasing the risk for serious adverse outcomes for the individual patient. The purpose of this article is to discuss the diagnosis and management of patients presenting with multiple, rapidly progressive thromboembolic events.

WHAT ARE THE “CATASTROPHIC THROMBOTIC SYNDROMES”?

Patients with several distinct disorders can present with this clinical phenotype. It is instructive to briefly review these disorders, since the initial clinical presentation can be similar, but treatment approaches differ if one of these diseases is identified (Table 1).

Catastrophic Antiphospholipid Syndrome. APS is defined as the combination of venous or arterial thrombotic events, and/or recurrent pregnancy morbidity, in association with persistent antiphospholipid antibodies (aPL). A catastrophic variant of APS was first proposed by Asherson in 1992, based on ten cases from the literature4. These patients presented with multiple vascular occlusive events, usually affecting small vessels supplying various internal organs, especially the brain, lungs, and kidneys, and presenting over a relatively short period of time. A subsequent review of 50 patients with catastrophic APS confirmed the microvascular thrombotic events, but also found that a significant number exhibited venous thromboembolism (VTE; 30%), peripheral arterial occlusions (12%), cerebral infarction (18%), and other large vessel occlusions5. A precipitating factor, or ‘trigger’, often preceded development of the syndrome, including infections, medication changes, surgical procedures, and anticoagulation
withdrawal\textsuperscript{5}. Larger studies have confirmed that this catastrophic variant is rare, occurring in ~1\% of patients with APS\textsuperscript{5}.

An international registry of patients with catastrophic APS, known as the CAPS Registry, was formed by the European Forum on Antiphospholipid Antibodies in 2000\textsuperscript{7}. Classification criteria were subsequently developed to identify patients with catastrophic APS (Table 2). Pediatric patients exhibit a similar clinical phenotype as adults, but with a higher prevalence of thrombotic events involving the peripheral vasculature\textsuperscript{8}. Almost half of all patients with catastrophic APS, and more than 85\% of pediatric patients, present with the catastrophic event as their first manifestation of APS\textsuperscript{8,9}. Patients with catastrophic APS frequently also manifest thrombocytopenia and hemolytic anemia\textsuperscript{10}. For patients without a prior diagnosis of APS or systemic lupus erythematosus (SLE), distinguishing catastrophic APS from a non-APS-related disorder can be difficult\textsuperscript{11,12}.

Treatment of catastrophic APS is not standardized, but commonly includes a combination of anticoagulation, corticosteroids, and plasma exchange\textsuperscript{7}. Other therapies that have been used include intravenous immunoglobulin, cyclophosphamide, rituximab, and eculizumab\textsuperscript{13-15}.

Atypical Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathies. Patients with thrombotic thrombocytopenic purpura (TTP) and other thrombotic microangiopathies typically exhibit schistocytes, thrombocytopenia, and organ injury secondary to arteriole and capillary thrombosis\textsuperscript{16}. Atypical presentations of TTP have been reported, however, that include patients with macrovascular occlusions, such as acute thromboembolic stroke\textsuperscript{17-19} and acute coronary syndromes\textsuperscript{18,20,21}. Confounding the issue further, some of these patients do not exhibit the characteristic laboratory findings of a thrombotic microangiopathy initially, which may develop days to weeks after the initial symptomatic presentation\textsuperscript{17,21}. Approximately two-thirds of these patients have been previously diagnosed with TTP or a thrombotic microangiopathy.
Importantly, the delay in appearance of thrombocytopenia and/or the presence of schistocytes can lead to delays in initiating therapy with plasma exchange and corticosteroids.

Occasionally, patients with SLE may present with TTP\textsuperscript{20,22}, which can be similar to catastrophic APS. The treatment differs, however, in that anticoagulant therapy is not typically administered in patients with SLE and TTP. Although most patients do not have a specific precipitating event, TTP has been reported to occur after infections\textsuperscript{23}, surgical procedures\textsuperscript{24}, and in patients with pancreatitis\textsuperscript{25}. The pattern of thrombotic events and laboratory findings help distinguish TTP from the other catastrophic thrombotic disorders (Table 1).

**Heparin-Induced Thrombocytopenia and Thrombosis.** HIT is a transient, immune-mediated prothrombotic disorder caused by antibodies that bind to platelet factor 4 (PF4) in complex with heparin or low-molecular weight heparin (LMWH)\textsuperscript{26}. Thrombotic complications in patients with HIT typically affect large vessels, with VTE occurring more frequently than arterial events\textsuperscript{27}. Multiple thrombotic events are not uncommon\textsuperscript{27}, and patients with catastrophic outcomes involving multiple vascular beds have been reported\textsuperscript{28,29}. Although HIT most often presents with macrovascular thrombosis, severe HIT complicated by DIC can be associated with limb ischemia and microvascular thrombosis, even in the absence of DVT or treatment with warfarin\textsuperscript{30,31}. In addition, patients with acute HIT who are treated with warfarin can develop warfarin-induced skin necrosis\textsuperscript{32} and/or venous limb gangrene\textsuperscript{33}, due to microvascular occlusions secondary to acquired deficiency of protein C.

Recently, several reports have described patients with an entity referred to as ‘spontaneous’ HIT\textsuperscript{34-38}. These patients present with venous and/or arterial thromboembolic events and may be thrombocytopenic at the time of presentation\textsuperscript{34,39}, or rapidly develop thrombocytopenia once heparin is administered to treat the thrombotic event(s)\textsuperscript{38,40}. Several of these patients presented with multiple events, or with the development of new thromboembolic occlusions over a brief
period of time. Antecedent events, have been reported, including surgical procedures (without evident exposure to heparin)\textsuperscript{36,37} and infections\textsuperscript{35}. Testing for antibodies to PF4/heparin is positive, and platelet activating antibodies can be demonstrated by the serotonin release assay\textsuperscript{39}. Many of these patients have antibodies capable of activating platelets in the absence of added heparin, but platelet activation is suppressed with excess heparin, consistent with a heparin-dependent antibody\textsuperscript{39}.

The primary treatment for patients with HIT is to stop all heparin exposure and start a non-heparin parenteral anticoagulant, such as argatroban or bivalirudin. Even in patients with profound thrombocytopenia, these patients can be treated with anticoagulants without hemorrhagic manifestations, although achieving a therapeutic level of anticoagulation with aPTT-adjusted therapies is challenging if concomitant DIC results in baseline (pre-treatment) elevation of the aPTT. Plasma exchange and rituximab have been used as adjunctive therapies in patients with refractory HIT with thrombosis\textsuperscript{41}.

\textbf{Cancer-associated thrombosis.} Patients with cancer have an increased risk for VTE\textsuperscript{42} as well as a greater likelihood to have recurrent thrombotic events despite appropriate therapy\textsuperscript{43}. Although thromboembolism is a leading cause of death in patients with cancer\textsuperscript{44}, most of these patients do not present with a catastrophic thrombotic phenotype. Trousseau’s syndrome, however, can be more aggressive, characterized by migratory thrombotic events in association with an underlying malignancy\textsuperscript{45}. Thromboembolic events may involve deep or superficial veins or the arterial circulation, and may be associated with non-bacterial thrombotic endocarditis (particularly arterial events) and DIC, which can complicate anticoagulant therapy\textsuperscript{46}. The primary treatment for patients with cancer-associated thrombosis consists of anticoagulant therapy with LMWH, but patients with multiple, particularly recurrent, events may benefit from an increased dose with consideration given to measure anti-factor Xa levels to tailor therapy\textsuperscript{47}. Warfarin may be ineffective in patients with severe Trousseau’s syndrome\textsuperscript{48}, and has been
associated with venous limb gangrene in patients with cancer and thrombosis, similar to patients with HIT\textsuperscript{49-51}. Rivaroxaban has also been associated with venous limb gangrene in a patient with acute cancer-associated thrombosis\textsuperscript{52}.

Patients with malignancy who develop catastrophic APS have been reported\textsuperscript{53}, and 9\% of patients reported in the CAPS registry had cancer\textsuperscript{54}. Patients with malignancy and catastrophic APS should be treated similar to non-cancer patients with catastrophic APS, with anticoagulation, steroids, and plasma exchange\textsuperscript{54}. Cancer patients may also develop a microangiopathic hemolytic anemia which is usually not responsive to plasma exchange or anticoagulant therapy\textsuperscript{55}.

Other disorders. Catastrophic thrombotic events have been described in patients with idiopathic hypereosinophilic syndrome\textsuperscript{56,57}, Kimura disease\textsuperscript{58}, inflammatory bowel disease\textsuperscript{2,59}, and Behçet’s disease\textsuperscript{60,61}. Behçet’s disease is associated with an increased risk for VTE, and, to a lesser extent, arterial occlusions and aneurysms\textsuperscript{62}. The most common thrombotic complication in patients with Behçets disease is DVT, and patients frequently have recurrent events. Different types of vascular involvement tend to cluster, such as dural sinus thrombosis and pulmonary artery thrombosis\textsuperscript{63}. Anticoagulant therapy is the primary initial intervention in these patients. Homozygous deficiency of protein C or protein S is associated with neonatal purpura fulminans, which, in some cases, includes large vessel occlusions\textsuperscript{64,65}. Catastrophic venous thrombosis in a young adult with protein C deficiency has also been reported\textsuperscript{66}. Management includes replacement of the deficient natural anticoagulant with fresh frozen plasma or protein C concentrates.

“Idiopathic” catastrophic thromboembolism. A subset of patients presenting with multiple thrombotic events will have none of the above disorders. Thrombotic complications include VTE, but these patients also sustain thrombotic events in unusual locations, including the
hepatic veins, portal vein, inferior vena cava (IVC), and cerebral venous sinuses\textsuperscript{2,3}. The arterial circulation is frequently involved, including myocardial infarction, stroke, transient ischemic attacks, and peripheral arterial embolism. A thrombotic microangiopathy may occur, including purpura fulminans and microvascular occlusions affecting internal organs; bilateral adrenal apoplexy has also been described\textsuperscript{1}. Multiple thrombotic events may present simultaneously or rapidly progress despite adequate anticoagulation, a clinical course we have referred to as thrombotic storm\textsuperscript{1,2}.

The patient described at the beginning of this article had no known hypercoagulable disorder, and all laboratory testing during the event was negative. Although it is possible that testing simply missed a hypercoagulable state because of his fulminant coagulopathy, he is best described as having “idiopathic” catastrophic thromboembolism.

DIAGNOSTIC APPROACH TO THE PATIENT PRESENTING WITH CATASTROPHIC THROMBOSIS

Initial diagnostic evaluation of a patient presenting with multifocal, or rapidly progressive, thrombotic events includes a thorough history and physical examination, relevant imaging studies, and clinical laboratory data (Figure 1). The history needs to cover symptoms associated with the acute thrombotic event(s), including timing, location, pace of progression, response, if any, to initial (or ongoing) therapies, prior thrombotic events, and prior diagnosis of APS or aPL, or TTP. Potential precipitating events should be identified, including recent illnesses, procedures, minor trauma, and medication changes, including recent heparin exposure. For women of reproductive age, use of oral contraceptives or the possibility of pregnancy needs to be considered. For pregnant women, recent changes need to be reviewed (e.g., new hypertension, urinary protein levels). Prior personal or family history of thrombosis
would suggest an inherited thrombophilia might be present. A thorough review of symptoms helps determine whether one needs to consider searching for an underlying malignancy or rheumatologic disorder.

The physical examination needs to assess the location and extent of thrombotic events, to guide decisions about imaging studies, determine the need for urgent intervention, and provide a baseline examination to assess response to therapy. Identification of lymphadenopathy, palpable masses or organomegaly, jaundice, or other unexpected findings should prompt evaluation for an underlying malignancy.

Imaging studies are needed to confirm the location, distribution, and overall burden of thrombosis. An echocardiogram is useful for identifying cardiac valvular disease, intracardiac thrombosis, inter-atrial shunts in patients with arterial thromboembolism, and right heart compromise in patients with pulmonary embolism. Imaging for an occult malignancy is not recommended in the absence of clinical symptoms or findings.

The initial laboratory findings are important to confirm the diagnosis and guide management decisions (Figure 1). Thrombocytopenia may be seen with any of these conditions, but the concomitant presence of schistocytes and an elevated LDH would favor a thrombotic microangiopathy. Catastrophic APS can also have laboratory evidence for a microangiopathic process, however, and, in the absence of a prior history of APS or SLE, a patient with catastrophic APS can appear very similar to a patient with TTP.

Isolated thrombocytopenia on presentation may be seen in patients with spontaneous (or delayed) HIT (Figure 1), but these patients may also present with a normal platelet count that drops rapidly with the initiation of heparin therapy. Coagulation studies are normal for some of these patients, but others present with or rapidly develop abnormal studies. A prolonged aPTT may signify the presence of a lupus anticoagulant, which is seen in >80% of patients with
catastrophic APS\textsuperscript{10}. A prolonged PT and/or aPTT should prompt evaluation for DIC. Abnormal renal or liver function studies may identify affected organs that can impact the choice of anticoagulant agent.

Several additional laboratory studies can be helpful in the management of these patients (Table 1). An ADAMTS13 level, which is typically low in patients with TTP\textsuperscript{16}, should be sent prior to initiating plasmapheresis. Positive results for a lupus anticoagulant, moderate-to-high titer anticardiolipin antibodies, and/or moderate-to-high titer anti-\(\beta\)2-glycoprotein I antibodies are suggestive of catastrophic APS. Patients with thrombocytopenia should be evaluated for anti-PF4/heparin antibodies, first by ELISA, and, if positive, confirmed by a functional assay\textsuperscript{39}. Decisions concerning anticoagulant therapy must not wait on any of these results, however, since delays in initiating appropriate therapy can be rapidly fatal. These laboratory studies may provide critical information that impacts management decisions after the first 24 to 48 hours, however, and should be obtained depending on clinical concern.

Our patient’s initial laboratory studies were unremarkable, but he subsequently developed DIC with marked hypofibrinogenemia and thrombocytopenia. He did not have notable microangiopathic changes, however.

THERAPEUTIC MANAGEMENT OF PATIENTS PRESENTING WITH CATASTROPHIC THROMBOSIS

Given the lack of clinical trials defining the optimal therapeutic approach for patients with catastrophic thrombotic disorders, the following recommendations are empiric and based on review of available data and the authors’ collective experiences. Prospective studies are needed, but the logistical difficulties of conducting such studies in these rare disorders are significant.
For patients presenting with multiple thrombotic events, several fundamental principles should be followed to provide the best chance for a good outcome. First, therapeutic anticoagulation, without interruption, is the most critical component in the management of these patients. Second, additional therapies, such as plasmapheresis and/or immunomodulatory agents, should be instituted promptly if catastrophic APS or atypical TTP is suspected. Third, ongoing management requires daily oversight and review of the patient’s response to therapy and development of new complications. Fourth, management of these patients frequently requires the collaborative involvement of specialists from several areas. This team must work together to provide a coordinated strategy and manage the diverse complications that may develop, including perioperative treatment, management of concomitant hemorrhagic complications, and integration of multiple therapeutic modalities. An early approach to management based on initial laboratory data is presented in Table 3.

**Antithrombotic Therapy.** The importance of continuous, therapeutic anticoagulation is underscored by the thrombotic complications that developed in patients when anticoagulant therapy was held, even briefly, in the report by Kitchens¹. Unfractionated heparin is an effective anticoagulant in this setting, given the ability to titrate dose, familiarity with management in the peri-procedural setting, and availability of a reversal agent, which should be reserved for cases of disastrous hemorrhagic complications only. If the baseline aPTT is prolonged, adequacy of heparin anticoagulation should be confirmed with an anti-factor Xa assay (targeting the upper end of the recommended heparin level of 0.3 to 0.7 anti-factor Xa units/mL), given the high frequency of lupus anticoagulants in this population. In addition, fibrinogen and D-dimer levels should be checked if the aPTT (and/or PT) is prolonged, to evaluate for DIC. Depending on the cause of the prolonged aPTT, using the aPTT alone may lead to subtherapeutic levels of anticoagulation and increased risk for recurrent thromboembolism. LMWH could be substituted
for heparin, but it needs to be dose-adjusted in patients with renal insufficiency and can be more difficult to manage in the peri-procedural setting.

Rapidly achieving target therapeutic anticoagulant levels is critical in these patients. In certain situations, patients may require unusually high doses of intravenous heparin to achieve a therapeutic aPTT (e.g., >25 Units/kg/hour), a phenomenon referred to as “heparin resistance”. Several potential mechanisms have been identified for heparin resistance, including high levels of factor VIII, fibrinogen, and other heparin-binding acute phase reactants, and decreased levels of antithrombin. Measuring anti-factor Xa levels can help with patient management, although we recommend interpreting these levels in the context of an aPTT obtained concomitantly. Heparin resistance due to antithrombin deficiency has been reported in patients undergoing cardiac bypass surgery and during extracorporeal membrane oxygenation, and antithrombin supplementation has been used to achieve effective anticoagulation. The value of antithrombin supplementation remains unclear, however, and switching from heparin to a parenteral direct thrombin inhibitor is an alternative approach. Elevated factor VIII levels can potentially interfere with using the aPTT to monitor argatroban, which should be suspected in patients who appear to exhibit ‘argatroban resistance’.

Patients with thrombocytopenia on presentation, or who develop thrombocytopenia shortly after starting heparin, should be considered as potentially having spontaneous HIT (or delayed HIT, if recently exposed to heparin). We recommend checking the anti-PF4/heparin antibody level and simultaneously switching the patient to argatroban or bivalirudin. Alternatively, fondaparinux could be used if renal function is acceptable and no acute interventional procedures are planned. If the anti-PF4/heparin antibody ELISA returns negative, the patient could be switched back to heparin or LMWH. Given the high likelihood of false-positive results with the immunoassays, particularly with low-positive results, we recommend confirming positive immunoassay results with a functional assay (e.g., serotonin release assay).
Thrombolytic therapy should be considered for patients who present with massive PE or extensive DVT. Thrombolytic therapy may also be considered in patients who present with acute stroke or peripheral arterial occlusion. Catheter-directed thrombolytic therapy is preferred for certain events, such as extensive DVT, if expertise is available. Mechanical thrombectomy and stent placement may be helpful in certain patients, including those with extensive iliofemoral thrombosis.\textsuperscript{74,75}

Antiplatelet therapy may be used in addition to anticoagulant therapy, particularly for patients with arterial thromboembolic events. We would not recommend replacing anticoagulant therapy with antiplatelet therapy in the acute setting, however. Dual antiplatelet therapy may be desired for patients having a stent placed; we would still recommend incorporating anticoagulation as part of the patient’s regimen, depending on the spectrum of events.

A subset of patients will have progressive thrombotic events despite apparently therapeutic, or even supra-therapeutic, levels of anticoagulation. We first confirm the degree of anticoagulation by laboratory testing, and then either increase the dose of the anticoagulant (if not supra-therapeutic) or switch to an alternative anticoagulant. Depending on the situation, one could also consider adding an antiplatelet agent or an immunomodulatory agent.

\textit{Anticoagulant therapy with heparin was re-initiated once his DIC began to improve. Anti-factor Xa levels were used initially given the abnormal aPTT results. Testing for HIT, prompted by his thrombocytopenia, was negative.}

\textbf{Inferior vena cava filter.} An IVC filter may be considered in some patients with catastrophic thrombotic syndromes, particularly if significant hemorrhagic complications develop or in the setting of a massive PE, cardiac compromise, and residual DVT. In general, we strongly recommend avoiding IVC filters in the acute setting, as these devices can be associated with a variety of adverse events, including IVC thrombosis and PE.\textsuperscript{76} IVC filter placement in patients
with HIT can exacerbate thrombotic complications\textsuperscript{77}, even in the setting of appropriate anticoagulant therapy\textsuperscript{78}. If an IVC filter is placed, we recommend use of a retrievable filter, concomitant use of anticoagulant therapy, if possible, and filter retrieval as soon as possible.

**Plasma Exchange.** Plasma exchange is frequently used in patients with catastrophic APS, and is the primary treatment for patients with TTP. For patients presenting with a catastrophic thrombotic syndrome, we consider plasma exchange in those who appear to have catastrophic APS and a prominent TTP-like presentation, in addition to anticoagulation. We recommend sending an ADAMTS13 level prior to initiating plasma exchange, to help establish the diagnosis. Decisions concerning how long to continue plasma exchange are based on clinical response to the procedure (e.g., normalization of platelet count, absence of schistocytes on the blood film).

**Immunomodulatory Agents.** Immunomodulatory therapies are essential for the successful treatment of patients with catastrophic APS\textsuperscript{79}. In addition to anticoagulant therapy and plasma exchange, prednisone and intravenous immunoglobulin are most commonly used. Less frequently, these patients have been treated with cyclophosphamide\textsuperscript{79}, azathioprine\textsuperscript{79}, rituximab\textsuperscript{80}, and eculizumab\textsuperscript{15}. Immunomodulatory therapies, particularly prednisone and rituximab, are also frequently used for TTP, but typically not for the other catastrophic thrombotic disorders.

**Surgical Procedures.** Surgical thromboembolectomy may be necessary in patients with massive PE, particularly with cardiac compromise, or in patients with acute peripheral arterial occlusions. Amputation of infarcted limbs resulted in the remission of catastrophic APS in two cases, presumably related to removal of chronic leg ulcers. These patients are at extremely high risk for thrombosis during interventional and surgical procedures. For required procedures, medical and surgical teams need to collectively devise a plan to minimize thrombotic as well as hemorrhagic risks\textsuperscript{91}.
Catastrophic Thrombotic Syndromes During Pregnancy. Catastrophic APS has been described in patients who were pregnant or in the peripartum period, including patients with known APS during transition from warfarin to LMWH initiated because of pregnancy\textsuperscript{82,83}. Patients without APS or other disorders can also develop a severe thrombotic syndrome during pregnancy or in the early post-partum setting\textsuperscript{2,84}. Presentation may overlap with other pregnancy-related syndromes, including HELLP, pre-eclampsia, and eclampsia\textsuperscript{83}.

Anticoagulant therapy is essential, using LMWH early in the pregnancy, and unfractionated heparin around the time of delivery. Steroids, plasma exchange, and/or intravenous immunoglobulins can be used in pregnant patients presenting with catastrophic APS. Early delivery may be necessary in certain situations, such as in the presence of HELLP or eclampsia as well as 'idiopathic' catastrophic thrombosis.

Platelet counts need to be followed closely in patients on heparin or LMWH during pregnancy, since thrombocytopenia may develop for several reasons, and HIT during pregnancy, although rare, has been reported. Historically, danaparoid was used in these patients, but this agent is no longer available in the U.S. Argatroban\textsuperscript{85} and fondaparinux\textsuperscript{86} have been used in this clinical setting. We recommend that these patients be managed at Thrombosis Centers with expertise in Hematology and high-risk Maternal-Fetal Medicine.

Long-term management. We generally recommend that patients with catastrophic macrovascular thrombotic events be treated with indefinite anticoagulant therapy. Although a provoking event may have triggered the initial thrombotic event, the outcome is atypical and extreme, and we consequently favor treating these patients with a long-term antithrombotic strategy.

Our patient’s thrombotic diathesis continued to progress during DIC and did not improve when heparin therapy was re-initiated. Abnormal coagulation studies not only raised concerns
about potential hemorrhagic risk, but also interfered with the management of his anticoagulant therapy. The extensive pulmonary emboli and deep vein thromboses were not identified prior to his death.

FUTURE DIRECTIONS

A better understanding of the catastrophic thrombotic syndromes, including what precipitates them and what drives the extensive, multicentric thrombotic process, is essential. The Thrombotic Storm Study Group was formed in 2009 (http://hihg.med.miami.edu/thromboticstorm), in response to the untimely and unexpected death of the patient presented in this article. The primary objective of this group is to investigate and characterize genetic and acquired risk factors associated with these catastrophic thrombotic disorders, in order to elucidate the basis of the extreme prothrombotic state, and to develop novel strategies to halt thrombotic progression.
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The authors wish to thank their colleagues in the Thrombotic Storm Study Group, the providers who have contacted us with questions and referrals of these complex patients, and the patients who have participated in research studies to better understand this disorder. The authors welcome any inquiries concerning patients with catastrophic thrombotic syndromes.

AUTHORSHIP

T.L.O., D.E., and C.S.K. all contributed to the writing and review of the manuscript.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflicts of interest relevant to the topic or content of this manuscript.
References


Table 1. Comparison of catastrophic thromboembolic disorders*

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<thead>
<tr>
<th>Catastrophic APS</th>
<th>Atypical TTP</th>
<th>Cancer-Associated Thrombosis</th>
<th>Delayed or Spontaneous HIT</th>
<th>“Idiopathic” Catastrophic Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical precipitating events/clinical conditions</strong></td>
<td>Infection, surgery, trauma, pregnancy</td>
<td>Pancreatitis, surgery, infection, pregnancy</td>
<td>Cancer (known or unknown at presentation)</td>
<td>Surgery, infections; recent prior heparin exposure with delayed HIT</td>
</tr>
<tr>
<td><strong>Thrombotic phenotype</strong></td>
<td>Microvascular events dominate; large vessel occlusions also occur</td>
<td>Arterial events may precede hematologic findings</td>
<td>Superficial and deep venous thrombosis; arterial thrombosis</td>
<td>Arterial and venous thrombotic events</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td>Lupus anticoagulant, anticardiolipin antibodies, anti-β2glycoprotein I antibodies</td>
<td>Decreased ADAMTS13 level; schistocytes; thrombocytopenia</td>
<td>Associated with DIC; cancer-specific markers may be present</td>
<td>Platelet-activating antibodies to PF4/heparin; thrombocytopenia</td>
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<tr>
<td><strong>Primary therapy</strong></td>
<td>Anticoagulation, plasma exchange, corticosteroids</td>
<td>Plasma exchange</td>
<td>Anticoagulation, especially LMWH</td>
<td>Anticoagulation with non-heparin agents</td>
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<tr>
<td><strong>Alternative/additional therapies</strong></td>
<td>Cyclophosphamide, rituximab, IVIG</td>
<td>Immunosuppression</td>
<td>Therapy for the underlying malignancy</td>
<td>Plasma exchange has been used for “refractory” HIT</td>
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Abbreviations used: APS, antiphospholipid syndrome; TTP, thrombotic thrombocytopenic purpura; HIT, heparin-induced thrombocytopenia; DIC, disseminated intravascular coagulation; PF4, platelet factor 4; LMWH, low-molecular weight heparin; IVIG, intravenous immunoglobulin.
Table 2. Classification criteria for catastrophic APS (from reference\textsuperscript{79})

1. Evidence of involvement of three or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion\textsuperscript{*}
4. Laboratory confirmation of antiphospholipid antibodies\textsuperscript{†}

Definite catastrophic APS

i. All four criteria present

Probable catastrophic APS

i. All four criteria, except only two organs, systems, and/or tissues involved

ii. All four criteria, except for the absence of laboratory confirmation of antiphospholipid antibodies

iii. Diagnostic criteria 1, 2, and 4

iv. Diagnostic criteria 1, 3, and 4, with the development of a third event more than one week but within one month of presentation, despite anticoagulation

\textsuperscript{*} Vasculitis may coexist, but significant thrombosis must be present as well.

\textsuperscript{†} Laboratory detection requires evidence of a lupus anticoagulant, medium-high titer anticardiolipin antibodies, or medium-high titer anti-β\textsubscript{2}-glycoprotein I antibodies on two occasions at least 12 weeks apart (Our recommendation for medium-to-high titer is >40 Units/L).
Table 3. Initial management strategies in a patient with a catastrophic thrombotic presentation*.

**Normal PT, aPTT, and platelet count**

<table>
<thead>
<tr>
<th>Initial intervention</th>
<th>Initial results</th>
<th>Subsequent management</th>
</tr>
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<tbody>
<tr>
<td>Start UFH</td>
<td>• Target aPTT achieved</td>
<td>• Follow aPTT, platelet counts, and clinical course</td>
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<td>• Unable to achieve target aPTT (i.e., subtherapeutic results)</td>
<td>• Check anti-factor Xa level (confirm heparin present)</td>
</tr>
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<td>• Check factor VIII and fibrinogen levels (evaluate for acute phase response)</td>
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<td>• Check antithrombin level (evaluate for acquired deficiency) and consider supplementation if low</td>
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<td>• Continue to escalate UFH dose or consider an alternative anticoagulant (e.g., LMWH, argatroban, bivalirudin)</td>
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<tr>
<td>Development of thrombocytopenia</td>
<td></td>
<td>• Re-check PT, fibrinogen, and D-dimer (evaluate for DIC)</td>
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<tr>
<td></td>
<td></td>
<td>• Re-evaluate blood film (evaluate for MAHA)</td>
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<tr>
<td></td>
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<td>• Check anti-PF4/heparin immunoassay (evaluate for HIT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider changing from UFH to an alternative anticoagulant if HIT is strongly suspected</td>
</tr>
<tr>
<td>New thrombotic event (“anticoagulant failure”)</td>
<td></td>
<td>• Re-check aPTT, anti-factor Xa level (assess drug effect)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider alternative treatment strategies (e.g., alternative anticoagulant, thrombolytic therapy, initiation of plasma exchange or immunomodulatory therapy)</td>
</tr>
</tbody>
</table>
### Normal PT and platelet count, prolonged aPTT

<table>
<thead>
<tr>
<th>Initial intervention</th>
<th>Initial results</th>
<th>Subsequent management</th>
</tr>
</thead>
</table>
| Obtain/review additional laboratory tests, including baseline and serial fibrinogen and D-dimer levels | • Results consistent with, or suggestive of, a LA | • Obtain ELISA testing for antiphospholipid antibody (aPL) (aCL, aβ2GPI)  
• Start UFH, use anti-factor Xa levels adjust heparin dose; alternatively, if renal function is normal and an operation or invasive procedure is unlikely, therapeutic LMWH or fondaparinux could be used  
• Results suggestive of factor deficiency or possible consumptive state | • Assess hemorrhagic risk and safety of anticoagulant therapy  
• If hemorrhagic risk is excessive†, or active bleeding, consider mechanical interventions (e.g., IVC filter, thrombectomy)  
• Frequent re-evaluation and initiation of anticoagulant therapy as soon as hemorrhagic risk is not excessive |

### Normal PT and aPTT, low platelet count (e.g., <100 x 10⁹/L)

<table>
<thead>
<tr>
<th>Initial intervention</th>
<th>Initial results</th>
<th>Subsequent management</th>
</tr>
</thead>
</table>
| Obtain/review additional laboratory tests, including baseline and serial fibrinogen and D-dimer levels | • Results consistent with MAHA | • Obtain/review laboratory testing for aPL (LA, aCL, aβ2GPI) and ADAMTS13  
• If TTP is suspected, consider initiation of plasma exchange, corticosteroids, rituximab  
• If catastrophic APS is suspected, initiate anticoagulant therapy |
dimer levels | with UFH and corticosteroids, +/- plasma exchange and/or IVIG
---|---
- Isolated thrombocytopenia, no other abnormalities noted |
- If low platelet count is new (i.e., prior platelet counts normal) and confirmed by repeat testing, consider sending testing for anti-PF4/heparin antibodies and initiating anticoagulant therapy with argatroban or bivalirudin if HIT is strongly suspected

| Prolonged PT and/or aPTT, low platelet count (e.g., <100 x 10⁹/L) |
|---|---|---|
| **Initial intervention** | **Initial results** | **Subsequent management** |
| Obtain/review additional laboratory tests, including baseline and serial fibrinogen and D-dimer levels | Results consistent with DIC | Assess hemorrhagic risk to determine whether anticoagulant therapy can be safely administered or alternative strategies need to be considered |
| | | - Frequent follow-up of laboratory testing to assess progress |
| | | - Initiate anticoagulant therapy with UFH as soon as hemorrhagic risk is acceptable, and monitor with anti-factor Xa levels if aPTT is abnormal |

* Initial laboratory data obtained in the absence of any anticoagulant therapy. Abbreviations used: PT, prothrombin time; aPTT, activated partial thromboplastin time; UFH, unfractionated heparin; LMWH, low-molecular weight heparin; DIC, disseminated
intravascular coagulation; MAHA, microangiopathic hemolytic anemia; HIT, heparin induced thrombocytopenia; IVC, inferior vena cava; APS, antiphospholipid syndrome; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; αβ2GPI, anti-beta-2-glycoprotein I antibodies.

† The hemorrhagic risk for an individual patient needs to be determined based on clinical criteria, including recent procedures, trauma, or evidence for bleeding, and laboratory parameters, including the platelet count, fibrinogen level, etc. For the patient described in the text, the presence of DIC, severe thrombocytopenia, and extensive dural sinus thrombosis was felt to represent an excessive hemorrhagic risk and hindered initial attempts at anticoagulant therapy.
Figure 1. Diagnostic approach to the patient with a catastrophic thrombotic presentation. The presenting history and physical examination, initial imaging studies, and laboratory studies are used to determine the most likely etiology of the patient’s thrombotic diathesis. Initial laboratory studies should include a complete blood count and blood film, a comprehensive metabolic panel (including blood urea nitrogen, creatinine, and liver function studies), an LDH, a prothrombin time, partial thromboplastin time, fibrinogen, and D-dimer, and testing for antiphospholipid antibodies. Additional diagnostic laboratory studies that might be obtained in selected subsets of these patients would include testing for anti-platelet factor 4/heparin antibodies (to evaluate for HIT), an ADAMTS13 level (to evaluate for an atypical presentation of TTP), additional testing for antiphospholipid antibodies (to evaluate for catastrophic APS), and selected additional tests that may direct or alter therapy (e.g., antithrombin level). There can be considerable overlap between these disorders, particularly at initial presentation. Abbreviations include: MAHA, microangiopathic hemolytic anemia; TP, thrombocytopenia; TTP, thrombotic thrombocytopenic purpura; TMA, thrombotic microangiopathy; CAPS, catastrophic antiphospholipid syndrome; TE, thromboembolism; HITT, heparin-induced thrombocytopenia with thrombosis; aPL, antiphospholipid antibodies.
Acute onset multiple thromboembolic events

History and physical examination, diagnostic imaging, and initial laboratory studies

Clinical data not suggestive of malignancy

Additional diagnostic laboratory studies

MAHA, TP, ↑LDH

TTP or other TMA

aPL, ±TP

Catastrophic APS

Normal

“Idiopathic” catastrophic TE

TP

HITT

Data suggestive of malignancy

Additional diagnostic evaluation

Positive

Cancer/Trousseau’s Syndrome

Negative
How I treat catastrophic thrombotic syndromes

Thomas L. Ortel, Doruk Erkan and Craig S. Kitchens

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